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A THERMODYNAMIC AND KINETIC APPROACH TO DECOMPRESSION SICKNESS

by

B. A. HILLS

M.A. (*Cantab.*), *B.Sc.* (*Adelaide*), *Dip.Chem.Eng.* (*London*).

Senior Lecturer in Thermodynamics, Department of Chemical Engineering,

The University of Adelaide.

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STATEMENT

This is to certify that all ideas and results presented in this thesis are products of the writer's own work except where due reference is given.

The thesis contains no material previously submitted by the author for a degree in this University or any other.

B.A. Hills
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Summary

A THERMODYNAMIC AND KINETIC APPROACH TO DECOMPRESSION SICKNESS

An hypothesis has been developed to explain the mechanism and kinetics of the occurrence of marginal symptoms of decompression sickness. The approach is essentially quantitative, all expressions being derived from fundamental physical and physiological parameters.

The hypothesis attempts to offer a more comprehensive mechanism for processes leading to the onset of pain than do existing theories. It deviates widely from the latter on several major issues by including postulations of:-

1. Random nucleation for gas phase separation in tissue. This is adopted in preference to the concept of a metastable limit to the supersaturation of tissue by gases which is effectively implied by conventional methods of calculation. Experimental evidence is provided for the random nature of cavitation at liquid-liquid interfaces.
2. Tissue as a two-phase system of irregular internal boundaries. This has provided a satisfactory transport model for describing the transient uptake of gases which is consistent with histological considerations. Data for assessment has been obtained experimentally from the exchange of inert substances in the same tissue both with and without circulation. The relevant model for predicting the occurrence of symptoms is taken as the 'worst possible case'. This refers to considerations of both the random geometry of tissue and the statistical thermodynamics of phase separation.
3. Diffusion as the rate-limiting process in this particular 'worst possible' case.
4. The driving force for inert gas elimination following phase separation to be an 'inherent unsaturation' arising in tissue by virtue of metabolism and the physico-chemical properties of blood.

Experimental evidence is provided for the existence of this 'inherent unsaturation', and its predicted tendency to increase with either oxygen enrichment of inhaled gas or with increased pressure. The latter is the chief source of deviation from existing predictions of the optimal decompression format. Much deeper staging of a diver is suggested. This is shown to be consistent with the purely empirical format devised by pearl divers operating in Australian coastal waters.

The same expressions provide a better quantitative correlation of fifteen different sets of published practical data than do the existing theories. Data analysed include aerial decompressions, repetitive dives, and dives where there is oxygen enrichment, helium inhalation, titrated staging, no staging, working conditions, resting conditions, an effectively infinite exposure, etc

The hypothesis also appears to be qualitatively more consistent with some twenty-three essentially different aspects of decompression sickness.

A pneumatic analogue has been devised to analyse dives according to the hypothesis. It can simulate radial diffusion and can automatically account for the effects of a phase change upon inert gas transport. Excessive mathematical complexity has been similarly avoided by using a thermal analogue to predict the optimal deployment of decompression time.

These optimisations have shown a saving of at least 35% in the decompression time for equal safety following a dive of 40 minutes at 150 feet, relative to standard tables tested concurrently in vivo. These comparative trials offer the strongest support for the reality of the mathematical expression and synthesis of the hypothesis.

NOTATION

The following symbols retain one meaning throughout the text, others being defined locally:-

a - capillary radius.
A - surface area of a cell.
A_1, A_2 ... etc. - coefficients as defined in text.
b - radius of volume receiving gas from one capillary.
B - blood perfusion rate.
C_1, C_2, C_i - gas capacities per unit tension - see fig. 5.
C_{o_2}, C_{co_2} - concentrations of O_2 and CO_2 at an arbitrary extravascular point.
C'_{o_2}, C'_{co_2} - concentrations of O_2 and CO_2 in the serum of venous blood.
D - diffusion coefficient of inert gas in cellular material.
D_w - diffusion coefficient of inert gas in water.
D' - diffusion coefficient of helium in cytoplasm.
E - energy.
F - volume fraction of separated gas in extravascular tissue.
F_c - critical value of F for the occurrence of symptoms.
g - inert gas entering unit volume of extravascular tissue upon compression.
g' - inert gas eliminated from unit volume of extravascular tissue.
G - total inert gas traversing unit length of capillary wall upon compression.
G' - inert gas eliminated per unit length of capillary.
H - depth, whose maximum value for a dive is H_b.
I_n, J_n, K_n - Bessel and modified Bessel functions defined by Watson (1944).
k - time constant.
K - bulk modulus of the critical tissue type.
L - thickness of tissue section.
p - inert gas tension at an arbitrary point in tissue.
p_A, p_V, p_T - arterial, venous and mean tissue tensions of the inert gas.
p_{co_2}, p_{o_2} - CO_2 and O_2 tensions at an arbitrary point in tissue.
p'_{co_2}, p'_{o_2} - venous CO_2 and O_2 tensions.
p_o, p_c, p_w - mean extravascular O_2, CO_2 and water vapour tensions.
P - absolute pressure.
P_o - standard atmospheric pressure.
P_b - absolute pressure at maximum depth of a dive.
P'_o - arterial oxygen tension.
Q - blood flow (volume per unit time).

$\dot{Q}_A$, $\dot{Q}_V$ - arterial and venous blood flow rates (volume per unit time).

$\dot{Q}_L$ - lymph drainage rate (volume per unit time).

Q_A, Q_V - arterial and venous oxygen capacities, volume O_2 per unit volume of blood.

r - radial co-ordinate.

R - decompression ratio.

R_1, R_2 - coefficients defined in text.

s - tissue:blood partition coefficient for inert gas.

s' - peri-capillary filtrate:blood partition coefficient for inert gas.

S, S_{O_2}, S_{CO_2} - net solubilities of inert gas, O_2 and CO_2 in cellular material.

S_p - solubility of oxygen in serum.

t - time.

T_1, T_2, T_i - fundamental half-times of isolated processes.

v - volume of gas separated in tissue volume V.

V - tissue volume.

x - mole fraction of inert gas.

g - bubble radius.

Y_n - Neumann functions - see Watson (1944).

z - linear co-ordinate.

α_n - roots of equation.

β_1, β_2, β_i - inert gas capacity ratios.

γ - surface tension.

Γ - a general intensive parameter.

δ - pressure of bubble relative to tissue.

δ' - critical value of δ' for just causing pain.

θ_1, θ_2, θ_3 - experimental half-times of response components.

θ - exposure time at maximum depth.

Θ - temperature.

τ_m - time spent at the m^{th} stage.

CHAPTER 1

INTRODUCTION

INTRODUCTION

1.1 PERSPECTIVE

1.11 General

Decompression sickness arises through subjection of the human body to excessive pressure variation, and is one of many examples illustrating the limitations of subjecting man to unnatural environments. While its manifestations may take many forms and degrees of severity, their avoidance has proven far more expedient than their 'cure'.

Hence research has been directed largely towards attaining sufficient understanding of the syndrome to enable the possible occurrence of symptoms to be predicted under any circumstances. The ultimate goal of hyperbaric investigations is the application of such conclusions to enable a diver to be returned safely to the surface at the fastest rate, minimising the wearisome time spent suspended in the ocean during ascent. This implies a carefully calculated depth-time relationship for each decompression.

The limitations of such optimisations must therefore depend upon the ability to recognize the predominating mechanisms and to describe the system in a precise yet realistic mathematical form. Decompression sickness is thus one aspect of Medicine where the practical value of any new concept is greatly enhanced if capable of exact quantitative expression.

1.12 The Project

Decompression sickness features a vast literature in which the number of independent quantitative approaches are few by comparison with the wealth of excellent pathological, histological and physiological theory and recorded experimentation. The latter provides a host of evidence upon which to judge the merits of any comprehensive hypothesis, the information ranging from at least twenty of the most varied qualitative facts to many sets of decompression data requiring detailed mathematical correlation.

Despite much attention from the Navies of the world, the published quantitative approaches have tended to be mostly semi-empirical in origin and restricted in application. Their shortcomings have been well illustrated for long, deep or repetitive dives in recent Royal Naval articles (Hempleman, 1960 and 1962) which tend to confirm earlier suggestions that the recognised theories contain at least one fundamental error - probably physical rather than physiological in nature. Such conclusions are corroborated by observations of the Aeromedical Unit (Adelaide) whose recordings (Appendix I) of the extreme exposures to pressure experienced by native pearl divers in the Torres Strait indicate the existence of some means of decompressing the human body far faster than advocated by standard tables. Moreover, the deviations of such data are far too great to be attributable to any approximation made in deriving the conventional equations.

The writer therefore, decided to analyse rigorously the many facets of decompression sickness according to the basic concepts of mass transfer and thermodynamics, irrespective of the mathematical complexity imposed by tissue constitution.

1.13 Australian problem

A further reason for undertaking this project is the unique opportunity for studying this subject afforded by living in Australia. Around the Northern coast of the continent, both types of diving most likely to deviate from conventional theory are performed regularly. These vary from long exposures in the deep tidal channels of the Torres Strait to repetitive submersions in the shallow waters around Broome.

Despite the amazing success of local decompression techniques, empirically derived at the initial cost of many lives, unforeseen circumstances still incur symptoms and a few fatalities. Reduction of the latter would be greatly aided by adjustments to their method based upon a realistic quantitative theory, although these would be accepted only if the overall ascent times suggested proved as economical as their present techniques. Such a solution should thus prove of value to the divers supplying the oysters essential for culture pearl farming which is one of the few profitable industries providing native employment and helping to retain population in the far North of Australia.

1.2 MANIFESTATIONS OF DECOMPRESSION SICKNESS

1.21 Symptoms

Decompression Sickness is the term given to the syndrome experienced by divers, pilots and caisson workers following decompression. The feature of its manifestation is the tremendous diversity of symptoms, Behnke (1951) claiming that in the 55 cases investigated by Masland (1943) "on no single point do all cases agree".

This is further illustrated by the following list, as quoted in order of decreasing preponderance by Duffner et al (1946):-

1. Localised pain (bends 70-92%)
2. Numbness
3. Muscular weakness
4. Rash
5. Visual disturbances (5%) (diplopia 1.3%)
6. Vertigo
7. Aphasia (0.3-1%)
8. Headache
9. Unconsciousness
10. Chokes (1.6-6%)
11. Nausea

Any of these may be transitory to the more serious effects of hemiplegia, paralysis or, ultimately, death.

Figures in parentheses refer to the incidence rate quoted by Haymaker (1957) summarising the details of 7,000 cases published by various authors. Approaching decompression sickness from a pathological angle, he estimated spinal cord involvement as 0.6-21%.

Duffner et al (1946) found that two symptoms occurred simultaneously in 26% of cases, more than two in 4.4%, and confirmed the overwhelming predominance of bends, pain failing to occur in only 5.3%.

1.22 The bends

Behnke (1951) defined the symptom of bends as "a dull throbbing type of pain, progressive and shifting in character, and frequently felt in the joints, or deeply in muscles and bones". This may be preceded by paresthesia, often described as numbness or just an awareness that "something is not right".

1.23 Location of bends

Bends seem to be strictly limited to those parts of the body primarily concerned with locomotion. Ferris et al (1943a), have shown that the pain can be markedly influenced by differential exercise, bends occurring only in those regions selectively exercised. Such conclusions

are corroborated by the results of similar decompression chamber tests performed by Anthony et al (1943a), Henry et al (1945a) and many sources of diving information. Most pearl divers confirm this finding.

Dissimilar body movements, required by the nature of their work, may thus account for any difference in the location of pain experienced by divers and caisson workers.

1.24 Pain and occupation

While a preponderance of bends in the lower extremities of caisson workers is claimed, Behnke's report (1951) on the analysis of 131 Naval dives, showed 70% occurrence of painful symptoms in the upper extremities - particularly the shoulder. However, reversal of the latter findings for 17 'saturation' exposures supports the general opinion that there is no definite rule for predicting pain location.

Bends, essentially identical in character to those described by divers, are experienced by pilots, Behnke (1942b) reported that men with mild symptoms were unable to distinguish between pain induced in a low-pressure chamber and that following diving. The relative rareness of spinal cord involvement with aerial decompression, and more rapid amelioration of symptoms upon recompression, indicate that any difference is essentially one of degree. The absolute value of atmospheric pressure appears to limit the severity of the manifestations of decompression sickness experienced by pilots (Piccard, 1941).

1.25 Time of onset

For all three occupations, the time of onset of symptoms and the rate of bends propagation are variable - as illustrated by the following table for caisson workers.

TIME OF ONSET OF SYMPTOMS

IN CAISSON WORKERS

Time of onset	Number of cases	
First hour	64.2%	60%
Second	17.7%	35%
Third	6.9%	3%
Fourth	3.2%	
Fifth - eighteenth	7.6%	
After twelfth		2%
Total cases	280	300
Source of data	Levy (1922)	Thorne (1941)

TABLE 1

Heller et al (1900) analysed the time of death of 92 fatal cases recorded in the literature, quoting the following figures for divers - 28 immediately upon surfacing, 13 within 2 hours, 18 after 2-4 hours, 13 after 2-14 days, 5 after 2-4 weeks, 10 after 1-3 months, etc. Keays (1909) reported 85.1% of symptoms occurring within 1 hour in 3,692 cases studied.

Similar distributions appear to apply aerially, Ferris and Engel (1951) stating that pain generally reaches unbearable intensity after 15 minutes at 35,000 feet, while it rarely develops after 90 minutes.

In the writer's opinion, there are two salient features about onset time arising from the vast quantity of data available - largely collected by the U.S. Air Force during World War II. The first is the marked decrease in induction period with increased exercise following decompression. Cook (1951) described an experiment upon 474 men where a change from 1 to 2 sets of 10 x 9" 'step-ups' every 30 seconds reduced the average onset time from 42.4 to 33.8 minutes at 30,000 feet, and from 29.0 to 19.4 minutes at 38,000 feet.

The above experiment also illustrates the second feature which is the decrease of induction period with increased decompression - a trend confirmed by many sets of data from diving and aerial records. Thus the more rapid onset of symptoms seems to be favoured by conditions most likely to enhance the severity of any pain eventually developed.

1.26 Severity of symptoms

Throughout the literature there would appear to be unanimous agreement with the statement that, above certain threshold limits, more severe symptoms are generally incurred by any increase in either the extent of decompression or the exposure time at the higher pressure. A more quantitative approach towards severity seems hardly justified on account of the arbitrary means available for its estimation. These usually depend upon individual ability to withstand pain or a personal description of its intensity.

1.27 Feasibility of a quantitative approach

The foregoing objections do not apply to use of the body senses as a detector of marginal symptoms, these providing a well-defined 'titration point' for determining the threshold conditions. It is this sharp demarcation of limits which renders any mathematical approach feasible. The significance is emphasized by Behnke (1951) in describing any contingencies as "perhaps 5 feet in diving depth and several thousand feet in altitude ascent separating injury from a state of well-being". Moreover, when prevention is so much more effective than the treatment of decompression

sickness, the need for advanced programming in avoiding any manifestations provides ample justification for any quantitative approach.

The problem thus resolves itself into one of determining the pressure vs. time relationships which enables the human body to avoid marginal symptoms during optimal decompression or at any subsequent time.

However, before attempting to express such conditions quantitatively, a mention should be made of the influence of parameters related to the individual.

1.3 FACTORS INFLUENCING SUSCEPTIBILITY OF INDIVIDUALS

1.31 Susceptibility range

Henry and Ivy (1951), who were primarily concerned with the development of pilot preselection tests, describe a day-to-day variation in men about a fairly stable mean. Ferris and Engel (1951) state that the reason for this, and the larger variation between individuals, is unknown. In the writer's opinion the best quantitative assessment of susceptibility distribution is afforded by the frequency of symptoms observed with increasing decompression following an effectively infinite exposure to the higher pressure.

After plotting the data of Gray (1943b), Ferris et al (1944), Cook et al (1944b) and Webb et al (1944a), Nims (1951) found a linear increase in the incidence of aerial bends with the extent of decompression from ambient pressure.

While Gray (1944b) found that 1% of a particular group developed symptoms at 23,000 feet, on the results of 6,000 man-runs, Cook (1951) has put the lower level at 22,000 feet. The latter author claims that cases below 25,000 feet are rare. The same description would also seem to fit the 38ft. of sea water quoted by Behnke (1951) as the minimum depth needed to induce decompression sickness. Such values probably refer to professional pilots and divers preselected for their natural tolerance. According to Duffner et al (1959), Van der Aue quoted a critical pressure of 33 feet (w.g.) for the 'weakest' divers as a result of extensive trials by the United States Navy.

Royal Naval figures for both men and goats are quoted in table 2.

DISTRIBUTION OF INDIVIDUALS ACCORDING TO MINIMUM DEPTH FOR INCURRING SYMPTOMS

Number of cases showing even mild symptoms										
Depth (feet)	<27	27-29	29-31	31-33	33-35	35-37	37-39	39-41	>41	Total
Men (Crocker; 1951)	0	0	2	0	3	2	2	2	4	15
Goats (Davidson; 1950)	2	0	3	2	0	1	2	0	1	11

TABLE 2

Gray (1951) has correlated group susceptibility with constitutional factors, finding it possible only in times of national emergency to assemble sufficient data to establish the less obvious trends.

1.32 **Age**

From this World War II aerial data, Gray (1951) has shown a roughly linear advance of susceptibility with age, expressing the relationship as:-

Relative susceptibility $\propto$ Age (in years) - 13.4

This expression represents the culmination of many qualitative reports indicating the same trend in divers and caisson workers, dating back to Catsaras (1890), Snell (1896), Heller et al (1900) and later corroborated by Hill (1912), Boycott et al (1908a) and many others.

1.33 Water balance

Cook (1944c), after summarising altitude tests, claimed that men with a naturally high fluid turnover were less susceptible to bends, although no appreciable effect was noticed following a forced increase in imbibed liquid.

1.34 Fitness

Karpovich (1943) found no correlation between susceptibility at altitude and the scores from physical fitness tests taken by 197 A.A.F. cadets; although Motley (1945) estimated that severe symptoms occurred in 4.7% of caucasians compared with 3% for negroes out of 4,600 American subjects similarly decompressed.

Ferris and Engel (1951) report a slight correlation between bends incidence and lung clearance from data recorded by Henry (1945b) and Stevens et al (1943 and 1947), although this may not be relevant to fitness. A more definite trend is claimed by Jones et al (1942) who found a decrease in susceptibility with increased elimination rate of a radioactive inert gas from the body. While largely substantiated by Henry (1943a, b), the correlation is still described as "poor" by Henry and Ivy (1951). The latter claim that the uptake of radioactive krypton by a hand shows "more promise".

1.35 Obesity

Boycott et al (1908a) and Vernon (1907) describe the increased susceptibility of obese caisson workers while, as early as 1868, de Mericourt recommended that no corpulent individual be employed as a sponge fisherman.

Many attempts have been made to correlate obesity and bends incidence quantitatively. Fraser (1942) indicated a linear variation between corporeal density (body weight/surface area) and susceptibility, while Gray (1951) claimed relationships with linear density (weight/height) and ponderal index (weight/height^3). The trends have been confirmed qualitatively by Welham et al (1944) and Swann and Rosenthal (1944), but seem typical of many correlations with body features - rendered vague by considerable random scatter. Such statistical characteristics are in direct contrast to the influences of externally controllable parameters.

1.4 EXTERNAL PARAMETERS DETERMINING INCIDENCE

1.41 Exposure

Apart from pressure and time which are the two predominating parameters determining exposure, other externally imposed factors which can influence the incidence of symptoms include:-

1.42 Time of day

Henry et al (1943b), after carefully standardising their aerial decompressions, found a slight yet distinct increase in symptoms occurring in morning compared with afternoon trials. This

increase coincided with a reverse trend in the measured metabolic rate of the same subjects. Gray (1943b) found that this diurnal bends effect increased with altitude, the number of forced recompressions reaching 70 (morning) compared with 40 (afternoon) at 38,000 feet.

1.43 Temperature

Both Nims (1951) and Cook (1951) summarise the effects of increased temperature for which all results tend to show a slight drop in the occurrence of symptoms. This has been particularly well demonstrated by Tobias et al (1943) who found a lower incidence of bends in locally heated regions than in those on the opposite side of the body.

1.44 Inhaled gas composition

Respiration is practical at depth provided the necessary mechanical balance is maintained between hydrostatic and inhaled gas pressures. The latter must equal the sum of the partial pressures of each molecular species present. The effects of these gases upon the system may be classified according to the types most likely encountered under operating conditions, namely:-

a. inert gases - chemically unreactive in the body,

b. a possible accumulation of exhaled CO_2,

c. oxygen necessary for tissue metabolism.

While nitrogen has been the inert gas inhaled by subjects in the data quoted hitherto, its replacement by helium is desirable under certain circumstances if cost permits (see section 1.52).

The literature contains much theoretical speculation concerning carbon dioxide. Gray (1944a), after recording every detail of all symptoms which developed at 38,000 feet in 204 subjects breathing 100% O_2 and another 204 simultaneously decompressed and breathing 88% O_2 + 12% CO_2, found that "in no single respect was there any difference between the groups of even moderate statistical significance". Thus Cook (1951) would appear well justified in stating that "carbon dioxide has no effect whatsoever upon decompression sickness".

The literature presents undisputed agreement that any increase in the oxygen mole fraction of inhaled gas tends to reduce the incidence of symptoms. Preventive measures based upon this trend take the following forms:-

a. preoxygenation of pilots prior to decompression,

b. increased O_2 partial pressure supplied to divers,

c. therapeutic treatment before or after the development of symptoms.

However, the application of these methods is limited by effects which may develop at pressure, each of the principal constituents of air being capable of producing undesirable reactions.

1.45 Compression limits imposed by gas composition

Excessive exposure to increased oxygen partial pressures may cause loss of consciousness while nitrogen can sometimes exert a narcotic effect upon a diver rapidly lowered to depths in excess of 130 feet (Behnke, 1951) to 180 feet (Miles, 1960). Behnke et al (1935b) quoted 428 mm.

mercury as the irritant level for prolonged oxygen breating, and claimed that 100% O_2 at atmospheric pressure can prove toxic after 12 hours. The time needed to produce these toxic effects is reduced to 3 hours at 3 atmospheres and to 15 mins. at 4 atmospheres partial pressure of oxygen. A 3-fold increase in consumption with pedalling a bicycle may produce signs after only 10 mins. at 3 atmos.

Both nitrogen narcosis and oxygen 'blackout' are enhanced by increased CO_2 content. It must be emphasized that neither are symptoms of decompression sickness, although similarly provoked by exercise.

1.46 Exercise

Apart from the effects upon onset time and pain location outlined previously, exercise has a considerable influence upon the incidence of bends and other symptoms. The many articles upon this aspect of the subject seem somewhat conflicting at first, but it would appear that the outcome of any physical exertion depends upon the stage of the dive, or decompression, at which it is undertaken, i.e. whether:-

a. before decompression,

b. during decompression,

c. following decompression, or

d. during any pre-oxygenation.

Many references can be cited which illustrate the increased incidence of symptoms with exercise at depth, Behnke (1951) quoting 25 mins. as the safe working time at 100 feet followed by non-stop surfacing compared with a maximum exposure of 34.5 mins. in the resting condition.

There is similar unanimous agreement upon the effects of muscular activity following decompression - as shown by Van der Aue et al (1936) and many others for diving. Quantitatively, Gray (1943b and 1944c) comes to the general conclusion that exercise taken aerially may reduce a man's bends-free altitude by as much as 5,000 feet over the range 26,000 - 38,000 feet. This trend is supported by comprehensive records compiled from U.S. and Canadian Air Force data by Cook (1951).

The effects of exercise during decompression seem quite controversial with Van der Aue et al, showing a definite increase in susceptibility when the standard U.S. Navy decompression tables (1943) are used. On the other hand, Behnke (1951) quotes Bornstein (1910), and others, who point out the theoretical advantages of men working during ascent to the surface. Japp (1909) found no deleterious effects in letting caisson workers walk through a tunnel during decompression. However, it is interesting to note that his men exercised at pressures greater than advocated for ascent by standard Naval procedures.

While Robinson (1943) could find no improvement with working during pre-oxygenation, a similar claim by Gray (1942) seems based upon results which indicate a slight fall in bends incidence from 12.7% to 11.4%. Webb et al (1944b) recorded 18 forced recompressions among 39 men for 1 hour on oxygen before decompression, compared with 26 for the same men resting during that period. Finally Evelyn (1941) claims that 30 mins. pre-oxygenation with muscular activity is equivalent to 60-90 mins. of the same treatment resting.

1.5 PREVENTIVE MEASURES

1.51 Cause of symptoms

Since the work of J.S. Haldane (1908), there has been no dispute that symptoms of decompression sickness are manifestations of the presence of bubbles somewhere within the body, the term "extricated air" having been used as early as 1855 by Littleton to explain the deaths of several Cornish caisson workers. However, at this stage, any further eluciation as to the site, conditions for appearance, mechanism of formation, kinetics of growth or composition of the separated gas would only serve to emphasize that the etiology of this syndrome is one of the most controversial in the literature.

1.52 Change of inert gas

The appreciable contribution to the bubble content generally attributed to the inhaled inert gas would suggest the replacement of nitrogen by one less soluble in tissue. The use of helium has thus enabled decompression times to be reduced for dives of long duration at maximum pressure. Helium has lower absolute solubilities in fat and water than nitrogen and a more favourable blood:tissue partition coefficient (Ikels, 1964).

Taking an arbitrary depth of 200 feet, the U.S.N. Diving Manual (1954), indicates a saving in total ascent time for any exposure exceeding 35 mins. However, the fact that the reverse is true for shorter durations suggests the more rapid assimilation of helium by the body despite its lower solubility in blood. This observation indicates that diffusion may play a major role in controlling tissue permeability.

1.53 Increased oxygen

An alternative means of avoiding the gradual accumulation at depth of an excessive tissue concentration of volatile substances can be provided by partially replacing the inhaled inert gas by one continuously consumed by metabolism (Gersh and Catchpole, 1951). Thus, by increasing the partial pressure of oxygen to 1.6-1.8 Kgm. cm.$^{-2}$, the Microperi company (Pellegrini, 1962) have enabled men to surface directly and safely after working at 82 feet for as long as 7 hours - compared with 67 mins. permitted by the U.S.N. air tables. Limits for the substitution of O_2 for an inert gas are ultimately set by those described in section 1.45.

In avoiding such dangers, and their provocation by exercise, the breathing of oxygen-enriched air may be delayed until a predetermined safe period of rest immediately preceding decompression. Using 8 divers in a 'wet' pressure tank, Hawkins et al (1935) have shown that breathing 100% O_2 for 2 mins. before direct ascent, at a simulated 50 feet /min., enables the duration at depth to be extended considerably (table 3).

A COMPARISON OF EXPOSURE TIMES WITH AND WITHOUT 2 MINS. BREATHING 100% O_2

Maximum exposure for direct ascent (mins.)			
Depth (feet)	2 mins. on O_2 * before ascent	air decompressions	
		U.S.N. tables (1954)	safe limits+
100	42	25	26
150	27½	15	11
167	16½	5	8
185	13½	5	7
200	13	-	6

TABLE 3.

*Data from Hawkins et al (1935). +Data from Miles (1962).

Similarly, the desaturation of tissues by inhaling pure oxygen before ascent to altitude has invariably tended to reduce the incidence of symptoms in pilots (Bateman, 1951).

1.54 Pre-oxygenation

Quantitative assessment of the undisputed protection afforded pilots by breathing 100% O_2 prior to decompression is rendered difficult by a large random scatter of results. While the literature is primarily concerned with the increased onset time relevant to flying combat missions, Bateman (1951) has plotted the incidence of mild and severe symptoms versus duration of pre-oxygenation. These data, taken from several sources, are summarised in table 4.

REDUCTION IN AERIAL SYMPTOMS WITH PRE-OXYGENATION

(Data from Bateman, 1951)

Source of data - Author	Cases as percentage of those without pre-oxygenation							
	Numbers involved		Conditions		Mild symptoms		Severe bends	
	men	trials	Exercise level	Altitude (feet)	1 hour pre-ox.	2 hours pre-ox.	1 hour pre-ox.	2 hours pre-ox.
Ferris et al (1943b)	-	41	working	35,000	90-35%	45-50%	67-72%	25-28%
Clarke et al (1945)	15	44	working	38,000	50-55%	17-19%	48-53%	13-15%
Henry et al (1944)	-	52	working	38,000	20-22%	13-15%	20-25%	8-9%
Gray et al (1942)	80	-	resting	38,000	4.8-5.1%	< 1%	1.2-1.6%	<0.1%

TABLE 4

The results of pre-oxygenation during ascent are again well summarised by Bateman (1951) who concludes that breathing oxygen is more effective at lower altitudes. He quotes Fraser's trial ascents (1943)

to 35,000 feet in which the number of cases of moderate and severe symptoms was reduced from 45% to 21% by administering 100% O_2 for 1 hour at 20,000 feet, and finally to 12% for the same time at 10,000 feet. Gray (1944c) has found oxygen inhalation at 'pre-bends' altitudes of 20,000-28,000 feet to be $\frac{1}{2}$-$\frac{3}{4}$ as effective as at sea level. More recent work reported by Fryer (1962) has been rather more specific in selecting 25,000 feet as the lower pressure limit for gaining any advantage from pre-oxygenation. The rapid onset of symptoms with further decompression, following a 3 hour stop at 25,000 feet, indicates that decompression sickness is already "pre-established" at this altitude. Akin to these observations are those of Houston (1946) who found that repetitive decompressions lowered the minimum altitude for marginal symptoms from 22,000-23,000 feet (section 1.31) to 17,000-18,000 feet, despite the victims breathing 100% O_2 during each ascent.

1.55 Treatment of developed symptoms

Bends, and most other symptoms, eventually disappear if no treatment is applied, divers with a slight pain usually deciding to "sit it out". This indicates a decay factor in severity which has been quantitative combined with a growth term by Lawrence and Hamilton (1945) in their successful empirical expression for the rate of production of aerial symptoms, viz:-

$$\frac{d}{dt}(N_s/N) = A_1 \exp(-k_1 t) - A_2 \exp(-k_2 t) \qquad (2)$$

where N_s is the number of cases, N is the total number of subjects, A_1, A_2, k_1 and k_2 are constants and t represents time.

The failure of drugs to be effective in decompression sickness has been well summarised by Cook (1951) who classified them as follows:-

1. Vasodilator drugs, which can open up capillaries, have been effective in accelerating the elimination of inert gas from dogs, but have proven of little use in preventing symptoms during altitude tests.

2. Certain drugs, such as morphine, enable the victim to tolerate a greater pain level, but represent no real cure.

3. CO_2 has been suggested as a tonic influence on the cardio-vascular system, but any advantage has been completely dispelled by Gray (section 1.44).

While the administration of oxygen has proven helpful in ameliorating the more serious symptoms of decompression sickness (Behnke et al, 1937 and Workman, 1964), no therapeutic treatment has proven more effective than recompression.

1.56 Recompression

Provided excessive time has not elapsed since the development of symptoms, these usually disappear completely upon full recompression. Often pressures far lower than the original working depth suffice, Behnke (1951) quoting a general value of 100 feet (water gauge) for alleviating the majority of 'mild' bends pains.

Return to ground level almost invariably rids pilots of any symptoms - except in a few rare instances where they have occurred

following recompression, the subject having experienced no ill effects at altitude. The latter has been termed 'post decompression sickness', cases having been reported by Haymaker, (1957) LeMessurier and Baxter (1963), while Masland (1943) has commented upon the danger of such delayed manifestation.

A feature of the bends is its reversible nature, almost certainly stemming from the mechanical effect of hydrostatic pressure upon the volume of gas separated from solution in the pain-provoking tissue. A second decompression, soon after recompression, causes the pain to re-occur immediately in the original site. Many authors have reported this effect, whose prominence decreases with the duration of recompression, but which may persist for 3-4 hours (Cook et al, 1944b) or even as long as 6 hours (Blankenhorn et al, 1942 and 1944) following the return of pilots to ground level. Behnke (1951) quotes periods of the order of days for the pressure treatment of severe symptoms in divers.

These facts support the general opinion that manifestations of decompression sickness are relatively difficult to cure when once established. To avoid such a condition the potential treatment time may be considerably reduced if the successive recompressions are effectively incorporated into the initial decompression by returning the diver to the surface in a series of stages.

* 1.57 Staging

Staging has been universally employed for decompressing divers since its introduction by Haldane and co-workers in 1908. The various methods are usually published in the form of tables which prescribe times to be spent at various depths. These stops in the ascent conventionally differ by intervals of 10' after the first "pull" towards the surface.

At altitude significant protection against aerial symptoms by staging at 12,000' has been reported by Marotta et al (1961) whose subjects were breathing air.

The published decompression tables are based mainly upon empirical modifications of various quantitative theoretical approaches whose deviation from experience for long and deep or repetitive dives (Hempleman, 1960 and 1962) would suggest their critical review.

1.6 CRITICAL REVIEW OF THEORIES

1.61 Historical

Theoretical discussions of decompression sickness date back to the first cases of 'compressed-air illness' reported by Triger in 1841, their early development being well summarised by Goodman (1961).

However, the publication of "La Pression Barometrique" by Paul Bert in 1878 is regarded by many as the genesis of present knowledge on the effects of pressure variation upon biological systems. Indeed, the subsequent emphasis upon the inert gas distribution emanates from the preponderance of nitrogen found by his analysis of the bubbles whose presence he demonstrated in decompressed animals.

Quantitative approaches effectively commenced with the appointment of a deep diving committee by the Admiralty in 1906 under the guidance of the celebrated physiologist J.S. Haldane. Publication of their resulting theory (Boycott et al, 1908a,b) led to the compilation of the first set of decompression tables whose influence upon present techniques is still most pronounced - in fact comparison with current Naval procedures supports the claim that they have undergone little more than semi-empirical modification.

1.62 The Haldane rule

The Haldane principle forms the basis upon which most decompression tables are founded and is, perhaps, best introduced by the following extract from the classical textbook by Haldane and Priestley (1935a):-

> "The formation of bubbles depends, evidently, on the existence of a state of supersaturation of the body fluids with nitrogen. Nevertheless, there was abundant evidence that when the excess of atmospheric pressure does not exceed about 1¼ atmospheres, there is complete immunity from symptoms due to bubbles, however rapid the decompression. Thus bubbles of nitrogen are not liberated within the body unless the supersaturation corresponds to more than a decompression from a total pressure of 2¼ atmospheres. Now the volume of nitrogen which would tend to be liberated is the same when the total pressure is halved, whether that pressure be high or low. Hence Haldane thought it probable that it would be just as safe to diminish the pressure rapidly from 4 atmospheres to 2, or 6 atmospheres to 3, as from 2 atmospheres to 1".

Quantitatively this condition for safe decompression may be expressed as:-

$$(\Sigma p)/P < R = 2 \qquad (3)$$

where Σp is the total tissue tension, P is the absolute pressure and R is a constant of two termed the decompression ratio. Although not using the specific symbol Σp, it is uncertain from Haldane's text whether this critical

transient quantity is nitrogen or total gas tension, both terms being used. However, he estimates Σp from a simple exponential format which may be expressed quantitatively for a general tissue (i) as:-

$$(\Sigma p)_i = P_o + (P_1 - P_o)(1 - \exp(-k_i t)) \qquad (4)$$

for a step change in absolute pressure defined by:-

$P = P_o$ for $t \leq 0$, to $P = P_1$ for $t > 0$, where k_i is the appropriate time constant. The theoretical basis for the linear response implied by equation 4 is discussed in sections 5.23 and 5.24.

The writer can raise no fundamental objection to the verbal description of the principle by Haldane and Priestley. However, the ultimate use of equation 4 for estimating Σp assumes that the tissue has an uptake response for the metabolisable gases identical to that for the inert gas, and that air may be effectively regarded as 100% N_2 for calculation purposes. Moreover, the equation implies that a tissue will eventually obtain true saturation with respect to the inhaled atmosphere.

> These basic assumptions have been perpetuated by many later authors and partially concealed by such tension units as a "footsworth" of gas (Rashbass, 1955a) in which gas composition is not specified. It is this quantitative implication of a direct proportionality between absolute pressure and the total tissue tension eventually attained which forms the theme for later discussion (section 5.6).

1.63 Tables based upon supersaturation theories

For calculation purposes most authors represent a dive, and any subsequent staging, as the closest rectangular pressure-time profile (fig. 1). Time spent moving between stages is normally apportioned equally between those levels. If the dive is of duration θ at a 'bottom' depth (absolute pressure P_b) followed by staging comprising times $\tau_1, \tau_2 \ldots\ldots \tau_m$

at absolute pressures:- P_1, P_2, ...P_m respectively, the net tension of the i^{th} tissue at time t from the start of compression is obtained from equation 4 using the principle of superposition, i.e.

$$(\Sigma p)_i = P_o + (P_b - P_o)(1-\exp(-k_i t)) - (P_b - P)\left[1-\exp(-k_i(t-\theta))\right]$$
$$-\sum (P_m - P_{m+1})\left[1-\exp\left(-k_i\left(t-\theta-\sum_1^m \tau_m\right)\right)\right] \qquad (5)$$

Tables are calculated by selecting the highest value of $(\Sigma p)_i$ for the i tissues considered relevant and applying the ratio rule (equation 3) to determine the next staging pressure P_{m+1} as:-

$$((\Sigma p)_i)_{max}/P_{m+1} = R(\leq 2).$$

In practice the convention has been adopted of determining the staging time (τ_m) for arbitrary 10 foot intervals, i.e. $P_{m+1} - P_m = 10$ feet until $P_m = P_o$ where P_o is the absolute pressure at the surface. Decompression tables can thus be compiled by repeating the computations for various exposures (θ) and 'bottom' pressures (P_b).

In compiling the original Haldane tables the tissues regarded as likely to provoke symptoms were assigned half-saturation times ($= 0.693/k_i$) of 5, 10, 20, 40 and 75 mins. (Haldane and Priestley, 1935a).

While the procedure advocated by Boycott et al (1908a,b) probably represents the greatest single advance in avoiding decompression sickness, the value of R = 2 has been shown to be dangerous for long exposures or depths in excess of 120' - Behnke (1951). Hawkins et al (1935) allotted different ratios to the different tissues considered important, varying from R = 5.5 for the fastest to R = 1.7 for the slowest.

A HALDANE-TYPE DETERMINATION OF A STAGED DECOMPRESSION

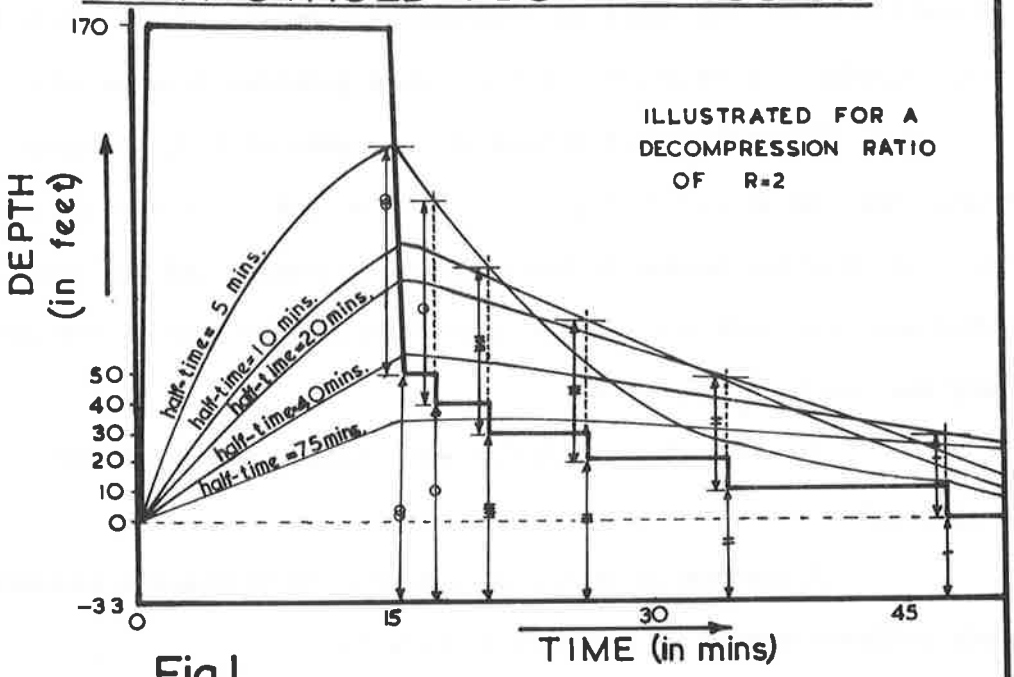


Fig.1

TRANSIENT TENSION DISTRIBUTION IN A FLAT SLAB OF TISSUE

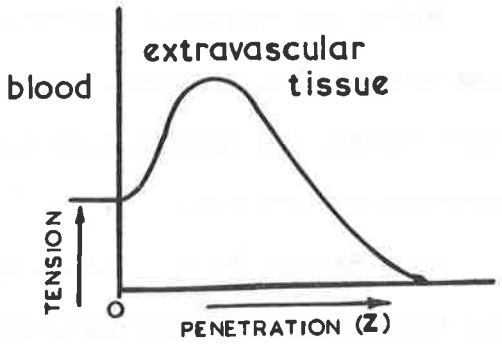


Fig.2

Similar modifications were advocated by Yarborough and Behnke (1939). More recently Dwyer (1956) has selected four tissues of half saturation times 20, 40, 80 and 120 mins. for which he recommended R values of 2.5, 2.3, 2.1 and 2.0 respectively as a reasonable fit for data gathered from experience.

Reverting to R values of the order of 1.7, Molumphy (1950) retains the use of 5, 10, 20, 30, 40, 50, 60 and 70 minute tissues in modifying the original helium tables compiled by Momsen and Wheland. The U.S.N. (1964) advocate direct surfacing after breathing oxygen at the 40' stage of any dive on He/O_2 mixtures.

Current standard tables are based upon such semi-empirical approaches.

Illustration of the design of a decompression assuming an arbitrary 5-tissue system is provided in fig. 1.

1.64 Fundamental interpretations

While the foregoing empirical modifications by the U.S. Navy to the Haldane method of calculation have reduced the staging times of the original British tables, the authors have been very cautious in offering any fundamental explanation.

Thus Behnke (1951), with many years of experience, admitted that "what appears to be a supersaturation tolerance could well prove to be an index of the degree of embolism which the body can tolerate". This alternative explanation for a constant ratio, first advanced by Haldane, has been discussed by Piccard (1941). It is based upon the simple deduction that decompression of a solution, saturated at P_1, and decompressed to a lower absolute pressure P_2, liberates equal volumes of the same gas whatever P_1 -

provided P_1/P_2 is constant, assuming surface tension effects can be ignored.

The above concept of a ratio as the relevant parameter in describing the limit of supersaturation is in direct contrast to the constant pressure difference (ΔP) advanced by Harvey (1951a). His biological evidence for such a conclusion is discussed later in considerable detail (section 4.3).

Concerning the uptake of the inert gas within the body, Behnke (1951) has measured a man's nitrogen elimination (G) in relation to the time following a sudden change to breathing 100% O_2 at atmospheric pressure. Such 'oxygen washout curves' have been analysed into the form:-

$$G = G_\infty \left[1 - \Sigma R_j \exp(-k_j . t) \right] \qquad (6)$$

where $G = G_\infty$ for $t = \infty$.

This format has proven expedient in analysing the inert gas elimination data of many workers including Jones et al (1945b). However, the use of experimental time constants (k_j in equation 6) has proven no more successful in correlating diving data than the empirical values.

Equation 6 has often been quoted in support of the existence of individual tissue types, each exhibiting a simple exponential response to changes in alveolar partial pressures. However, such reasoning supposes that each of the hypothetical tissue types, designated as an "i" term in equation 5, contributes to no more than one of the "j" terms in equation 6. Practical evidence for doubting that each tissue response can be described by a single exponential term is provided by Eggleton et al (1945) who have found that, for cats,

$$G \propto \sqrt{t} \qquad (7)$$

for small values of t.

These authors strongly criticised Behnke's model attributing each of the exponential terms comprising the elimination curve to specific tissues - all in parallel with each other and in series with the same blood supply.

Physically, the simple exponential equation(4) implies one of at least two alternative Mathematical models including:-

(1) That venous blood leaves in equilibrium with tissue, the blood-tissue exchange rate being totally circulation-controlled, or

(2) That each tissue (i) is equivalent to a fully-stirred pot separated from blood by a membrane which embodies all resistance to mass transfer, its geometric dimensions and gas permeability determining k_i.

The derivation of the exponential form (equation 4), for both cases, is included in the overall discussion of transport (sections 5.23 and 5.24).

Thus if the linear tissue response assumed in deriving equation 4 were valid, the expression would hold whether the rate-limiting process were diffusion or circulation. Behnke emphasized the former and Workman (1964) implied the latter, while the issue is considered of secondary importance to those content with expressing blood:tissue exchange by this simple mathematical form. The U.S. Naval authors have concentrated more upon empirically modifying tissue time constants (k_i) and decompression ratios (R) than seeking fundamental explanations.

1.65 Diffusion Theories

Contrary to the foregoing approaches, Hempleman (1952) introduced the concept that a single tissue type may be responsible for marginal symptoms whatever the decompression format. Moreover, he disputed the assumption that extravascular tissue may be regarded as a fully-stirred fluid. Assuming that blood circulation is not rate-contributing, he selected a linear bulk diffusion model for calculating the uptake of inert gas by tissue. Elucidation of the rate-controlling transport process is considered in great detail later (section 5.2).

Hempleman adopted the approach of A.V. Hill (1928) in regarding extravascular tissue as a flat parallel-sided slab, of infinite area, bathed on both sides by well-stirred blood at arterial tension. He derived the transient tension distribution as an error function whose form implies that infinite slab thickness had been assumed (section 2.1). Applying Fick's law to the blood-tissue boundary, Hempleman obtained an expression whose approximation for short time exposures (θ) would give the conditions for non-stop surfacing from depth (H) as:-

$$H\sqrt{\theta} = \text{constant} \qquad (8)$$

This form has proven more successful than any multiple-tissue single-exponential approach for values of θ not exceeding 40 minutes on air. Examples of the relative success of this method is given by Duffner et al (1959) for no-stage dives on both air and He/O_2 mixtures. Duffner et al found that, upon rewriting equation 8 as a general power function of $H\,\theta^{\mu}$ = constant, no single value of μ gave an adequate correlation with the experimental results. Empirically he selected:-

$\mu = 0.38$ for $0 < \theta < 30$ mins.

$\mu = 0.85$ for $30 < \theta < 50$ mins.

$\mu = 0.76$ for $50 < \theta < \infty$

The form suggested by equation 8 has been extended by Crocker and Taylor (1952) to staged dives. This has again resulted in a better correlation of bends incidence for dives of short duration, 25 minutes at 180 feet being the greatest exposure tested.

Attempting to correlate long exposures, the Hempleman model has been used by Rashbass (1955) who neglected all but the first three terms of the expression for linear bulk diffusion derived as a Fourier series (Appendix II). Quoting Harvey et al (1944a), Rashbass assumed the limit of supersaturation for the critical tissue to be a constant differential (ΔP) between absolute pressure and tissue tension (taking air as 100% N_2). Thus he derived the condition for no symptoms following decompression to P_2 from an exposure time (θ) at absolute pressure P as:-

$$\Delta P = (P_1 - P_2) - (P_1 - P_o)\frac{8}{\pi^2}\left[\exp(-k\theta) + \frac{\exp(-9k\theta)}{9} + \frac{\exp(-25k\theta)}{25}\right] \geq 30 \text{ feet} \quad (9)$$

for a dive defined by $P = P_o$ for $t \leq 0$, $P = P_1$ for $0 < t \leq \theta$, and $P = P_2$ for $t > \theta$.

While Rashbass draws many diagrams illustrating gas distribution perpendicular to the parallel faces of his 'slab' of tissue after partial decompression, his mathematics essentially represent an integral approach, i.e. he calculates net gas traversing the blood-tissue interface. If the nucleation of a supersaturated solution were the trigger

point indicated, then surely the maximum local concentration, or peak tension, is a more relevant parameter. This is described quantitatively in Appendix II, and illustrated in fig. 2.

While the Rashbass approach provided the best correlation for the overall depth vs. time relationship representing the limits of no-stage diving for both air and He/O_2 mixtures (Duffner et al, 1959), sea trials of the staged dives were disappointing - producing a 1% bends incidence.

Despite expounding a diffusion model, neither Hempleman nor Rashbass calculated a diffusion coefficient. However, taking their empirical value of $k = 0.00792 = \pi D/4b^2$, (Appendix II), where 2b is the thickness of the slab, $D/b^2 = 0.0101\ min^{-1}$, i.e. a value of D many orders less than water for (2b) values in range of published inter-capillary distances (see section 5.49).

The writer could find no discussion by these authors of their implied contradiction of the popular belief that blood perfusion is the process limiting the rate of tissue permeability.

While the Hempleman concept of linear diffusion has the above-mentioned flaws, his approach would seem to represent a considerable advance in theoretical thinking - both conceptual and in practice.

1.66 Semi-empirical approaches

Crocker (1957), after expressing disappointment at the sea trials of the Rashbass staging procedures, retained the same method of calculation as "a convenient mathematical instrument", but claimed no fundamental significance in its use. Although not stated, the integral

nature of equation 9 would seem more appropriate to Crocker's acceptance of the existence of "silent bubbles", i.e. bubbles not of sufficient size to have become manifest in the clinical sense.

Modifying the Rashbass conditions to fit the practical case, he introduces a "bubble regression factor" as an overall exponential in equation 9 to help accommodate the difference.

The net effect is one of increasing staging time for the longer and deeper dives, the resulting tables closely resembling other semi-empirical sets derived by the U.S. Navy. In the sea trials 246 submersions produced 14 cases of decompression sickness. However, it would appear most significant that the recommended decompressions of the offending dives were modified by increasing the time spent on the last stage only, i.e. at 10 feet. Thus the deeper stagings advocated by most tables seem to have changed little and represent a legacy of the original Haldane approach.

An alternative to the U.S.N. or Crocker methods of empirically increasing staging time from deep dives, is provided by Albano (1961). The latter considered a single tissue of exponential response with a time base inversely proportional to the diver's maximum depth (P_1) i.e. $\propto k/P_1$. Thus Albano proposed that the condition for safety was:-

$$D_{pc} = (P'/P_o)^{\frac{1}{3}}\left(760-251.\exp(-k.\Delta P.t/P_1)\right) \text{ mm.Hg} < \text{constant} \qquad (10)$$

where ΔP is the decompression, P_o is the absolute pressure prior to compression (760 mm.Hg for diving) and P' is that corresponding to the threshold altitude for symptoms which Albano takes as 9,000 m. i.e. $P' = 230$ mm.Hg.

The last equation gives a good correlation for his recordings of 1,729 non-stage dives performed by 9 men but, unfortunately, his exposure range terminated at 43 minutes which is just in the region where Hempleman's $\sqrt{\theta}$ relationship starts to display an appreciable discrepancy.

His critical parameter for symptoms, D_{pc}, he defined as:-

D_{pc} = True bubble pressure - absolute external pressure (P).

Since he did not measure D_{pc} directly his statement to the effect that his transport equation was determined empirically as

$$D_{pc} = 760 - 251 \exp(-k.\Delta P.t/P_1)$$

must imply that equation 10 is also empirical.

Referring to Harvey's evidence for very small free gaseous masses or nuclei in tissue, Albano's theory (1960) is based upon the existence of pre-formed nuclei. The origin of these is better described in his own words as:-

> "les mouvements, l'activité fonctionelle des différents systèmes, l'existence de cavités très hydrophobiques dans les tissus permettent la formation et la stabilité des noyaux".

The theme seems to be that nuclei form, or that pre-formed nuclei do not grow until the diver is decompressed to the absolute external pressure (P") at which the critical tissue is saturated. These micro-bubbles are then postulated to expand from their initial volume (V") to a final volume (V_2) at the final pressure (P_2).

Writing Boyle's law as $P".V_2 = P_2V"$, but correcting it in later steps to be $P"V" = P_2V_2$,

Albano:-

(1) Considered growth of each nucleus by mechanical expansion only, thereby assuming that no more gas molecules were acquired with decompression beyond equilibrium, despite the increasing supersaturation surrounding an established gas phase.

(2) Ignored surface tension in applying Boyle's law, despite his argument resting on the condition that $D_{pc} = 2\gamma/y_c$ where γ is the surface tension and y_c is the critical bubble radius for provoking symptoms.

This omission is made all the worse by his determination of D_{pc} as 509 mm.Hg whose neglect relative to such absolute pressure as 760 mm.Hg and 230 mm.Hg , in deriving constants from aerial data suggests that his theoretical attempts to explain a good empirical equation (10) are an arithmetic fabrication. The writer can find no author who has quoted Albano's work.

An approach with similar emphasis upon surface tension has been recently described by Degner et al (1965). Primarily concerned with determining the optimal pressures and gas compositions for spacecraft, and suits for the transfer of astronauts in orbit, they postulate the model of small seed bubbles coalescing intravascularly. Furthering the theme of Piccard, (1941) they derived the volume of blood (B) from which a bubble of critical radius (y_c) may be formed as:-

$$B = \frac{P_2}{P_1} \cdot \frac{T_1}{T_2} \cdot \frac{4\pi}{3V_g} \left(\frac{2\gamma}{P_1 + P_e - P_2} \right)^3$$

where P_2 and T_2 are the final absolute pressure and temperature respectively, V_g is the nitrogen available from venous blood at pressure P_1 and temperature T_1, and P_e is a term to account for the exercise level.

In view of the importance which Degner et al attribute to surface tension by stating:-

$$P_1 + P_e - P_2 = 2\gamma/y_c,$$

it would seem a gross oversight to omit the contribution of such terms to bubble gas pressure in applying Boyle's law as P_2/P_1. Another objection similar to those levied at Albano is the neglect of the additional moles of gas available for bubble formation by virtue of decompression from P_1 to P_2, i.e. a further increase in V_g beyond that predicted by their transient expression:-

$$V_g = C_1(1-\exp(-\lambda_1 t)) + C_2(1-\exp(-\lambda_2 t))$$

where C_1 and C_2 are capacity terms and λ_1 and λ_2 are the respective time constants determined experimentally for the claimed bimodal response of nitrogen concentration in postcaval blood.

Degner et al did not mention the potentially greater effect of surface tension upon their postulated initial seed bubbles and consequent influence upon the position of phase equilibrium by virtue of the increased partial pressure of the separated gases. Moreover, in advancing the concept of symptoms arising through intravascular bubbles lodging in capillary loops, they offer no explanation for the well-known fact that bends pain usually re-appears at the same site following an insufficient period of recompression. This is discussed in detail later (section 3.35).

1.67 Bubble growth

"Silent bubble" theories with more realistic physical bases have been proposed by Nims (1951) and Bateman (1951) who are among the few to express, quantitatively, their belief that the rate of mass transfer across the gas-tissue boundary influences the time of onset of symptoms. They consider that the manifestations of decompression sickness are a matter of the position and size of bubbles whose initiation is not a limiting, or even rate-contributing, factor. In justification of this assumption, Harris et al (1945b), Harvey (1945) and Whitaker et al (1945) are quoted as having observed cavitation in animals provoked by exercise without a change of external pressure.

Nims and Bateman assumed a model of bubbles growing in a supersaturated extravascular fluid of tension presumably uniform - as inferred by the quantitative expression that its response to alveolar partial pressure is a simple exponential (equation 4).

However, Nims took the rate of accumulation of the inert gas by the bubble as:-

Rate $\propto$ surface area (tissue tension - bubble tension)

This simple linear relationship is incongruous with the above model in view of the absence of any resistance specific to the interface, as originally expressed by "invasion coefficients" (e.g. Krogh, 1918a), but now rendered obsolete by a revision of absorption theory. It is current practice to assume complete equilibration at the phase boundary (Whitman, 1923). The only resistance to the growth of a bubble in a supersaturated solution can be afforded by the establishment of a concentration gradient

in the liquid extending radially beyond the interface - in which case diffusion in the fluid is rate-controlling. Should the latter impose the appreciable time lag implied by the whole approach, then extravascular diffusion must apply equally to the uptake of inert gas from the blood, in which case, a single exponential term for each tissue type can no longer describe the latter process adequately.

This objection is circumvented, to some extent, by Bateman whose whole argument seems to rest upon the assumption that extravascular tissue may be regarded as a fully-stirred fluid. Incorporating the growth equation determined experimentally in vitro by Bateman and Lang (1945) for agitated solutions of various gases, he derived the condition for symptoms as:-

$$\frac{(P_{No}+P_o+62-P)}{(P+30)\sqrt{t}} \cdot \frac{(P_{No}-P_{N\infty})(1-10^{-k't})}{k} - \left[(P-P_{N\infty}-P_o-63)t \right] > \chi$$

expressing all pressures in mm.Hg where P_{No} and $P_{N\infty}$ are the nitrogen partial pressures for $t = 0$ and $t = \infty$ respectively, P is the absolute pressure for which $P = P_o$ for $t = 0$. k and k' are constants. $\chi = 650$ taking 44' as the depth for non-stop decompression of a diver.

Since Bateman and Lang essentially measured the overall expansion of decompressed solutions dilatometrically, their growth equation must be a function of nucleation in addition to gas transfer across the phase boundary. Moreover, the relative magnitudes of these effects could be far different to that in vivo.

Bateman's analysis of threshold altitudes for various periods of pre-oxygenation is as good as the very random scatter of experimental values permits. However, his attempts to explain the staging

of a diver by his theory completely break down leading to his very honest admission that his equations "have been painstakingly examined only to be completely demolished by the final demonstration of fundamental inadequacy". Bateman concluded from analysis of his aerial results that, although his quantitative expression may not be the answer, stable bubbles can be formed without necessarily producing symptoms.

In the writer's opinion, one of the most serious quantitative omissions by both Nims and Bateman is their failure to complete a transient mass balance for the inert gas in tissue. Thus the phase separation is, in effect, assumed by both to have no influence upon desaturation via the capillaries. This omission cannot be excused as of negligible effect when one considers Behnke's value (1945a) of 0.0127 c.c. N_2/c.c. H_2O atmos. for the solubility of nitrogen in water. The formation of a bubble of this inert gas would require complete desaturation of about 79 times its volume of surrounding fluid at the same tension. A more recent figure given by Ikels (1964) is 0.01206 c.c. N_2/c.c. atmos. - equivalent to 83 times its volume of surrounding fluid.

Nims adopts what is probably the most realistic parameter of any theory by determining the development of a deformation pressure (δ), or the differential between bubble and hydrostatic pressures likely to distort nerve endings and give pain. The fundamental nature of this concept is emphasized by Roth (1959).

Quoting the experience of Inman and Saunders (see section 4.12) who found a threshold mechanical pressure (δ') for inducing pain identical to bends by injecting buffered isotonic Ringer's solution,

Nims proposes the following relationship for defining the severity (W) of symptoms as:-

$$W = K(\delta - \delta')$$ where K is a constant.

Nims then admits his greatest assumption in stating that the rate at which members of a group develop symptoms is proportional to W, expressing the result as:-

$$\frac{d}{dt}(N_W/N) = K(P_N - P'_N)$$

where P_N is the nitrogen tissue tension and $P_N = P'_N$ for $\delta = \delta'$.

This appears to be a step of Mathematical expediency designed to arrive at a final expression in agreement with that derived empirically by Lawrence and Hamilton (equation 2), Nims quoting

$$\frac{P_N}{{}_oP_t} = (\frac{k_2}{k_1} - 1)(\exp(-k_1 t) - \exp(-\beta' k_1 t)) + (y_o + k_1 t)\exp(-k_1 t)$$

where $\beta' = k_B \cdot {}_oP_t/k_1$, k_1 and k_2 are empirical time constants and $y_o = {}_oP_N/{}_oP_t$ where ${}_oP_t$ is defined as the tissue tension at zero time.

In relating the deformation pressure (δ) to bubble tensions P_{N_2}, P_{CO_2}, P_{O_2} and P_{H_2O}, absolute external pressure (P) and surface tension (γ), Nims quotes

$$\delta = P_{N_2} + P_{CO_2} + P_{O_2} + P_{H_2O} - P - 2\gamma/r$$

where r is the bubble radius.

However, in the final integration for the development of deformation pressure with time, the surface dimensions of the bubble are assumed constant and the transient action of the elastic properties

of the tissue is ignored. Moreover, the bulk modulus is introduced, only after integration.

The mathematics seem unrealistic in view of the practical fact that a bubble must change dimensions as its internal pressure increases relative to the hydrostatic.

In conclusion to this review of the published theories, it was felt that the greatest criticism of most approaches lay in the interpretation of plausible models into quantitative terms, i.e. in the application of mathematics rather than any shortcomings in the manipulation of equations.

CHAPTER 2

OUTLINE OF THE PROJECT

2.1 The Object

2.2 Preliminary Calculations

2.3 The Vital Issues

OUTLINE OF THE PROJECT

2.1 THE OBJECT

The object of this research is the elucidation of the predominating physical and chemical processes involved in provoking marginal symptoms of decompression sickness. For any appreciable contribution to be made in this field, it is felt that the emphasis must be quantitative, any hypothesis derived needing to be based upon fundamental physical and physiological parameters.

The ultimate product of the work should thus take the form of mathematical expressions which determine whether present techniques are optimal and, if not, the decompression format to be followed to enable a diver to be returned to the surface in the shortest time guaranteeing safety.

The approach envisaged may be arbitrarily divided into the following phases:-

1. Collection of the vast mass of literature on decompression sickness and development of a theme for its classification according to a basic set of phenomena which range from some simple qualitative observations to many sets of data requiring exacting mathematical analysis.

2. A critical review of this material from a quantitative standpoint. Many papers seem to have discrepancies between the written concepts and the mathematical expression of these concepts. In too many cases, mathematical manipulation would seem to be the unfortunate limitation to sound theoretical reasoning.

3. The derivation of an hypothesis, its correlation with the many qualitative facets of decompression sickness, and its rigorous testing using the large amount of data available upon practical diving experience recorded in the literature.

2.2 PRELIMINARY CALCULATIONS

Many of the criticisms of the existing theories stem from restricted mathematical analyses of ideas which sound plausible. Consequently, prior to attempting to develop an independent approach, the following modifications to published quantitative expressions were tried:-

1. Assuming an infinite spectrum of tissue half-saturation times in the original Haldane approach requires putting $k = k'$ in equation 4 for the worst case under any conditions where

$$\left(\frac{\partial p}{\partial k}\right)_{k=k'} = 0, \text{ for which } \left(\frac{\partial^2 p}{\partial k^2}\right)_{k=k'} < 0$$

The resulting power equation defines the envelope curve to the individual tension vs. time relationships conventionally plotted for selected half-saturation times. No improvement over the Haldane method could be detected.

2. Reversion to the original error function derived but not used by Hempleman. Such functions are tabulated (Jahnke et al, 1960) and need not be approximated to $\sqrt{t}$, i.e.

$$\frac{\Sigma p - P_o}{(P_1 - P_o)} = \text{erf}\left(\frac{z}{2\sqrt{Dt}}\right)$$

where $P = P_o$ for $t < 0$ and $P = P_1$ for $t > 0$ as derived later (Appendix II).

This has been used to describe the transient tension distribution perpendicular to the parallel face (z-direction) of Hempleman's tissue slab which his quantitative expressions imply is of infinite thickness. Only slight improvement in predicting conditions for non-stage dives were obtained.

3. Modification of the Hempleman approach to account for finite slab thickness (2b) has been effected, the resulting equation also enabling the peak total gas tension ($\Sigma p'$) to be determined from:-

$$\frac{2(\Sigma p' - P_o)}{(P - P_o)} = \text{erf}\left(\frac{b - z'}{2\sqrt{Dt}}\right) + \text{erf}\left(\frac{b + z'}{2\sqrt{Dt}}\right)$$

for $P = P_o$ for $t < 0$ and $P = P_1$ for $t > 0$, where the peak tension is located at z' given by:-

$$\left(\frac{\partial p}{\partial z}\right)_{z=z'} = 0, \text{ for which } \left(\frac{\partial^2 p}{\partial z^2}\right)_{z=z'} < 0$$

Error functions are defined in Appendix II.

However, no ratio ($\Sigma p/P$) of the peak tension ($\Sigma p'$) to the absolute pressure (P), or fixed differential ($\Sigma p' - P$), could be found which gave any correlation for non-stage dives in any way superior to that afforded by the Rashbass equation (9). This modification still retains the basic assumption that all gas behaves the same as the inert gas.

4. Reversion to a radial diffusion model (section 5.54) has resulted in similar failure to improve correlation upon the supersaturation concept. Radial peak tensions ($\Sigma p'$) can be derived (section 5.94) as:-

$$\frac{(\Sigma p' - P_o)}{(P - P_o)} = 1 - \pi \sum_{n=1}^{\infty} \frac{(J_o(r'\alpha_n)Y_o(a\alpha_n) - Y_o(r'\alpha_n)J_o(a\alpha_n))\exp(-\alpha_n^2 Dt)}{(J_o(a\alpha_n)/J_1(b\alpha_n))^2 - 1}$$

where $\left(\frac{\partial p}{\partial r}\right)_{r=r'} = 0$, for which $\left(\frac{\partial^2 p}{\partial r^2}\right)_{r=r'} < 0$,

and the roots $\pm\alpha_n$ are defined in equation VIII.

The above analyses proved most time-consuming and the negative results disappointing.

2.3 THE VITAL ISSUES

The failure to obtain any comprehensive correlation of diving data according to the published theories, or the preceding modifications eliminating some of the more obvious objections, indicates that at least one fundamental physical principle has been misapplied or remains unrecognised. This would indicate the need for a thorough survey of the many facets of decompression sickness and related physiological features.

Moreover, the foregoing review of published approaches would indicate that the derivation of any theory of decompression sickness, capable of quantitative interpretation, must raise the following issues:-

SITE

1. The number of tissue types involved.
2. The site of symptom-provoking bubbles within a tissue type, e.g. intra- or extravascular, intra- or extracellular etc.

MECHANISM

3. The physical mechanisms controlling separation of the gas phase.

4. A physical mechanism for forming gas emboli and their mode of provoking symptoms.

5. The critical parameter best selected for predicting the onset of such symptoms e.g. tension, bubble radius etc.

TRANSPORT

6. The driving forces behind the transport of each gas within the body.

7. The process limiting the permeability of tissues to each gas i.e. diffusion or blood perfusion or both.

8. Transport following decompression.

9. Any influences of capillary and cellular geometry, or the chemical composition of tissue, in determining the transport model.

QUANTITATIVE THEORY

10. A final comprehensive set of expressions relating fundamental parameters of the model to the external conditions.

11. Use of practical data to determine constants incapable of direct measurement.

CHAPTER 3

THE SITE OF BUBBLES PROVOKING MARGINAL SYMPTOMS

3.1 Quantitative Decisions

3.11 Symptomatology and pathology

3.12 Issues vital to any quantitative approach

3.2 The Number of Tissue Types Involved

3.21 Autopsies

3.22 Bubbles in sacrificed animals

3.33 Physiological elimination

3.24 Selection of single tissue concept

3.3 Intra-vs. Extravascular Sites

3.31 General review of opinions

3.32 Circulation in decompressed animals

3.33 Pathological evidence

3.34 Origin of bubbles

3.35 Selection of extravascular site

THE SITE OF BUBBLES PROVOKING MARGINAL SYMPTOMS

3.1 QUANTITATIVE DECISIONS

3.11 Symptomatology and pathology

Perhaps the most surprising feature in undertaking a quantitative approach to decompression sickness is the remarkably limited assistance afforded by the symptomatology and pathology of this syndrome, despite the excellence and popularity of such studies. Behnke (1951) states that "the mechanism by which intravascular and possibly extravascular bubbles produce symptoms is yet to be determined". In a very carefully compiled summary of the etiology, Ferris and Engel (1951) emphasized the association of bends with the locomotor system, indicating that pain is essentially physical in origin. This mechanical distortion of tissue by bubbles may induce traumatic effects which cause secondary vascular reactions in either contiguous or distal sites, thus accounting for the other symptoms.

The pathological approaches have been most comprehensively reviewed by Haymaker (1957), from which "vast mass of material", he admits that "nothing really pertinent to establishing a model or mechanism can be extracted".

While there is seldom any doubt about the cause of death and serious symptoms, any conclusions drawn from observations of separated gas in animals killed subsequent to decompression would appear to suffer from one extreme disadvantage. This is the uncertainty in knowing which bubbles produced pain, and in which of their many sites, they could provoke marginal symptoms under threshold conditions.

Bubble size and frequency could be far outweighed by such tissue factors as elastic modulus and the preponderance of nerve endings in their ability to produce clinical manifestations.

3.12 Issues vital to any quantitative approach

The first essential in deriving a quantitative theory for decompression sickness would seem to be the elucidation of the number of tissue types, any one of which can be solely responsible for producing marginal symptoms over a particular range of practical exposure to pressure. This fixes the number of independent time and pressure functions to be considered when forecasting limiting safety conditions.

The next decision in the formulation of a mathematical model is whether bubbles provoking marginal symptoms occur intra- or extra-vascularly and, if the latter, their probable location relative to cell boundaries. The wide diversity in the selection of bubble sites and number of critical tissue types adopted in the published theories, (section 1.6), provides ample evidence that the solutions to these issues are by no means obvious. However, it is felt that a detailed comparison of the many qualitative biological facts and opinions with the more quantitative aspects may reduce the extent of speculation.

3.2 THE NUMBER OF TISSUE TYPES INVOLVED

3.21 Autopsies

When decompression sickness is the cause of death, autopsies seem to reveal bubbles in vessels and all except the highly vascularised tissues. Their presence in the pial vessels of the spinal cord, medulla and cerebrum of dead divers, was recorded as early as 1879 by Leyden, 1900 by Heller et al and 1907 by Zografidi. Involvement of the

central nervous system would appear to be the undoubted cause of death - as shown by Haymaker (1957) whose review includes a summary of the reports of post mortem examinations upon 12 fatal cases of aerial decompression.

3.22 Bubbles in sacrificed animals

Gas bubbles can be generally seen in most of the less vascularised regions of animals sacrificed just before or after decompression, explosive rates having been found necessary to produce lesions in such well-perfused organs as lungs, brain and heart (Hitchcock, 1951).

Gersh et al (1944, 1945a, 1946a) have preserved the sites of bubbles by freeze-drying the carcasses of rats and guinea pigs as soon as possible after killing them upon return to ambient pressure. They have demonstrated the presence of gas in aqueous tissue, but have found a preponderance of bubbles in fat. Hill and Greenwood (1910) have described the appearance of such lipid regions as "a foam". Gersh et al (1944) found a marked increase in bubble preponderance in fatter animals and decrease in the survival rate of the fatter guinea pigs following decompression. This supports similar findings in goats reported by Boycott et al (1908a). However, applying the χ^2 test to decompressed cats, Harvey (1951b) reports no significant correlation of bubble appearance with body weight, sex, total fat or the lipid content of peritoneal, omental, popliteal or subcutaneous regions.

Gersh (1945b) reported bubbles in bone marrow following severe decompression, corroborating much earlier observations by Twynam (1888) of bone necrosis in caisson workers whose high incidence of chronic arthritus has been attributed to repeated embolic injury (Bornstein and Plate, 1911).

After decompressing excised rat tissue to 110 mm.Hg , Harvey(1951a), has observed bubbles in connective tissue, dorsal aorta, sciatic nerve, brain, liver and in all other tissues examined with the important exception of muscle. This corroborates the earlier reports of Boycott et al (1908a) who could find no evidence for their presence in skeletal muscle, although Bert (1943) had previously observed them in intermuscular fascia.

Gersh et al (1944) could find no significant change in muscle, liver, nerve, or blood from the heart when trying to detect gas by density variation. Simultaneous microscopic examination revealed no bubbles in these tissues apart from a few in "some large accumulation of fat cells in a fascial plane" of muscle. However, a marked density change was observed in tendon - an effect which Gersh and co-workers related to the lipid content which was found to vary from 9.0% for lean to an average of 13.1% for fat guinea pigs. In a later article,Gersh (1945b) described finding gas bubbles prominently displayed in the long tendon near the ankle joint. Gersh (1946b) found that those occurring in fat and connective tissue were indistinguishable when he attempted to locate bubbles in decompressed guinea pigs by X-rays.

While many more references could be quoted in support of the above trends, special attention has been paid to the work of Gersh and co-workers whose practical technique tends to delay the formation of bubbles by putrefaction. This uncertainty cannot be overlooked in view of the rapid rise in the CO_2 concentration of tissue after death - as demonstrated in frogs by Blinks et al (1951), and in rats by Harris et al (1945a).

3.23 Physiological elimination

Several physiological features can be invoked to reduce the foregoing list of anatomical sites of observed bubbles to those where marginal symptoms may be initiated.

Considering depot fat, Behnke (1951) described the improvement in decompression limitations upon changing from nitrogen to helium, for long dives, as far less than would be suggested by the corresponding 5:1 reduction in lipid solubility. The data recorded by Duffner et al (1959) indicated that the minimum depths for contracting symptoms are of the order of 33' for air to 42' for breathing 80% He + 20% O_2. While much attention has been paid to muscle, despite the repeated failures to detect bubbles in such areas, another reason for discounting such tissue is provided by Whitely and McElroy (1946). They have shown that muscle desaturates with exercise during pre-oxygenation far faster than the rate of protection against aerial symptoms would suggest.

The remaining tissue types are thus tendon, connective tissue and intermuscular fascia, all recurring in reasonably close proximity to each other at various parts of the body associated with the locomotor system.

Tendon has a structure of collagen fibrils whose high elastic moduli would give the greatest local pressure differential for the same quantity of separated gas, and whose structure would permit movement of such entrained gas under mechanical stimulus. This could account for the common experience that bends pain can often be transferred to an adjacent site by massage (Lund et al,.1945).

Although providing a strong indication, the above discussion does not positively identify any one particular tissue type as responsible for marginal symptoms.

3.24 Selection of single tissue concept.

While Rashbass (1955a) has given the theoretical basis for a diving experiment to distinguish between a single and multi-tissue theory, its execution upon goats by Hempleman (1961) proved inconclusive. Detailed discussion of their findings is seriously curtailed by omission of the vital graphs, but failure to reach a decision upon this most difficult issue seems to stem from the uncertainty in knowing the best mathematical expression to describe the response of any single tissue.

The writer takes the view that whenever one tissue supersedes another as the closest to its respective threshold for provoking marginal symptoms, there should be a discontinuity in the parameters defining safe decompression limits. Since each tissue must have its own time response to be effectively different from the others, a change of the one most critical must result in a transition point in the plot of experimentally determined conditions for minimum safety. Selecting pressure and time as the two parameters most sensitive in determining proximity to marginal symptoms, no discontinuity could be detected in the plot of the limits of depth versus exposure time for safe non-stage decompressions. Such plots investigated include the diving data recorded by Van der Aue (1951) and Albano (1960) for air, and by Duffner et al (1959) for He/O_2 mixtures.

In the apparent absence of any more convincing evidence to the contrary, the writer has therefore decided to adopt the concept of attributing marginal symptoms to the bubbles present in ONE tissue type only. However, the ultimate assessment of the validity of this decision can only be obtained from the correlation attained in the final analysis of practical data upon such a basis.

3.3 INTRA-vs. EXTRAVASCULAR SITES

3.31 General review of opinions

The next step in devising a realistic mathematical model is the determination of the site of the separated gas provoking marginal symptoms. The clinical significance of such a finding is well expressed by Behnke (1951) who states that "the matter of bubble location is of the greatest importance since, if bubbles form extravascularly in nervous tissue, any decompression holds the probability of serious consequences".

The first question to be answered would seem to be whether such potentially dangerous bubbles originate within the cardiovascular system. Diving and aeromedical authorities seem to be roughly evenly divided upon this issue, to which the symptomatology offers no immediate solution. Thus Ferris and Engel (1951), describing the development of bends from their considerable experience, state that "pain begins in periarticular tissues, gradually radiating and extending distally along the shaft of a bone, generally it appears to follow neither nerves nor arteries". However, observing 16,293 exposures of 6,566 men to an altitude of 35,000'

Stewart et al (1943) claim to have found some evidence for pain following a particular vascularity in certain instances.

Many experiments have been devised to try to settle the question by examining the circulating blood of decompressed living animals using such techniques as the lucite calvaria, as described by Sheldon and Pudenz (1944), for observing the cerebral blood vessels of decompressed monkeys.

3.32 Circulation in decompressed animals

The first bubble observed in a living animal was probably that seen in the eye of a viper decompressed by Robert Boyle in 1670, using his newly-invented vacuum pump.

Soon after the realization of decompression sickness, Hoppe-Seyler (1857) recorded that bubbles were more commonly, and sometimes exclusively, seen in veins rather than arteries. Bert (1943), making similar observations upon animals, attributed this to the lower hydrostatic pressure of venous blood. More recently Whitely and McElroy (1946) have again demonstrated that bubbles are most abundant in veins - especially those from muscle. A greater preponderance in vessels draining muscle were the sites from which Blinks et al (1951) recorded the sudden appearance of bubbles, after a variable induction period, following the decompression of rats or rabbits to a pressure simulating an altitude of 50,000'.

Behnke et al (1935b), describing the events succeeding the rapid decompression of dogs from 60 p.s.i., have first noted bubbles circulating rapidly through cutaneous arteries and veins, and gradually increasing in size with simultaneous slowing of the circulation until it eventually stops. A similar movement of bubbles has been noted in the pial

blood vessels of cats by Wagner (1944), while bubbles in the vena cava of 4 out of 11 of them decompressed to 110 mm.Hg in the anaesthetised state are recorded by Harvey (1951b). The latter author reported the occasional occurrence of bubbles in the humour of the eye, cerebrospinal fluid and amniotic fluid of resting, deeply-narcotised rats, cats and dogs returned to ambient pressure from 103 p.s.i. (gauge).

The initial appearance of bubbles in the veins draining tissues associated with the locomotor system would seem significant in view of their greatly increased prevalence and reduced time of appearance with exercise. This has been well demonstrated by the correlation of intravascular bubble appearance in bull frogs and rats with the extent of muscular activity - as induced by the 2-6 volt electrodes used by Whitaker et al (1945).

Although bubbles have been frequently observed in the vascular system this does not settle the question of their origin. If their genesis occurred extravascularly, lesions in the vessel walls should be revealed under careful microscopic examination of the dead tissue.

3.33 Pathological Evidence

The autopsies of divers in which decompression sickness was the cause of death usually reveal bubbles present both extra-and intra-vascularly (Hill, 1912). Such bubbles in blood, following circulatory collapse, have been attributed by Romano et al (1943) to stagnation, their presence in peripheral vessels being a secondary or late manifestation of decompression sickness.

Examinations of sacrificed animals have tended to show similar findings for decompressions with less severe consequences. Since the early demonstrations of bubbles by Hoppe-Seyler (1857) and Bert, the greater ease of observing intravascular bubbles, particularly in living animals, has tended to favour such sites. The term "aeroembolism" was thus introduced by Armstrong (1939) to indicate that the origin of high altitude symptoms is the occlusion of blood vessels by bubble emboli. His observations have revealed no change in rabbits but many bubbles on both sides of the capillary walls of sacrificed goats. Similar findings in guinea pigs were described by Gersh and Catchpole (1951) for decompression from positive gauge pressures.

Blinks et al (1951), dissecting electrocuted rats whose carcasses had been subjected to a simulated altitude of 50,000' for 10 mins., found that 4 were free of vascular bubbles. These were found in only the venous system of the remaining 6 out of 10 animals resting before death. Violently exercising 12 rats before electrocution, they found only one to be free while the other 11 had bubbles in arteries, veins and heart - often profuse. Such findings are somewhat contrary to Harvey's failure (1951a) to detect bubbles in the vascular systems of 8 cats decompressed from 6-8 to 2-3 atmospheres.

Boycott et al (1908a) concluded that areas of necrosis in the spinal cord were caused by extravascular bubbles originating from the release of excess lipid-soluble gas.

Reverting to the question of whether the genesis of intravascular bubbles is extravascular, autopsies of dead rats performed by Blinks et al (1951) have indicated that they originate in appendages

or vessel walls. However, pulmonary haemorrhage has been reported by Gersh and Catchpole (1 951) as occurring irregularly with decompression in rabbits but regularly in other animals - particularly with explosive decompression (Berg et al, 1 943, and Smith, 1 942). This supports the view of Leyden (1 879) who postulated that expanding extravascular bubbles may cause vascular congestion resulting in haemorrhage. This has been actually observed by Chase (1 934) and Tureen and Devine (1 936). The haemorrhage and vascular distention frequently associated with extravascular gas, has been reported by Gersh and Catchpole (1 951) who mention the alternative explanation that intravascular bubbles may be responsible for the rupture of blood vessels.

3.34 Origin of bubbles

The theory of bubbles of extravascular origin appearing in intravascular sites by the laceration of cell walls is certainly consistent with their decreased time of appearance with exercise as recorded by Harvey (1 951 b), Harris et al (1 945) and Blinks et al (1 951). More conclusive support for this theme is provided by the considerable increase in rapidity of observing bubbles where tissue is likely to have suffered mechanical damage. The latter has included applying a tourniquet (Blinks et al, 1 951) or freezing one leg of a frog (Berg et al, 1 945), crushing the legs of cats (McElroy et al, 1 944a) and forcibly stretching, pounding or vigorously jerking a cat's hindleg (Harvey, 1 951 b).

More significant than any evidence described hitherto would seem to be the experiment conducted by Behnke and Shaw (1 937). Decompressing from 60 p.s.i. (gauge) they found that dogs were really

sick, displaying rapid shallow breathing and halting circulation, by the time that bubbles were seen moving through cutaneous arteries and veins. Thus it would appear that symptoms become manifest long before the bubbles attain sufficient size to rupture vessel walls. Moreover, Behnke(1945a) describes numerous experiments in which quantities of air have been intravenously introduced into dogs without any ill effects - showing that bubbles can exist in the blood stream without causing symptoms.

3.35 Selection of extravascular site

While the foregoing discussion would tend to favour bubbles originating in extravascular tissue, more conclusive proof is provided by the following points listed by Ferris and Engel (1951).

1. Cases with marginal symptoms of decompression sickness show no signs of local cyanosis, pallor, or temperature change suggestive of defective blood supply resulting from the occlusion of vessels by bubbles.
2. Bends are quite unlike anoxic pain which is most acute during recovery.
3. The symptoms produced by injecting sufficient air into veins are very different to those of decompression sickness.
4. X-ray studies reveal that gas seldom follows a vascular distribution.
5. Local recompression of a bends area will relieve pain - even at pressures high enough to occlude blood flow.

6. Pain can re-occur in the same site up to 4-6 hours after recompression, indicating that bubbles have not been swept away by the circulation despite their reduced size.

The latter would appear to be the most conclusive piece of evidence considering the observations of Chase (1934) who found that bubbles were only able to penetrate beyond the arterioles of greater diameter. A decision being necessary at this juncture, the writer considers that the evidence indicates that phase separation does not originate in the cardio-vascular system.

The single-tissue mathematical model thus progresses to one in which the bubbles provoking marginal symptoms are located in extravascular sites.

CHAPTER 4

MECHANISM OF DEVELOPING SYMPTOMS

MECHANISM OF DEVELOPING SYMPTOMS

4.1 THE MARGINAL CONDITION

4.11 General

Since this work is aimed at providing a more realistic quantitative definition of conditions for marginal symptoms, it would appear desirable to elucidate this critical state in more detail before discussing the possible physical mechanisms involved.

The data quoted in section 1.21 illustrate the overwhelming predominance of bends as the major clinical manifestation of decompression sickness. While much attention has been paid to the etiology of other symptoms, it would seem reasonable to presume that the critical state, or titration point of dives, coincides with the threshold for pain.

4.12 Physical interpretation of pain

There would seem to be unanimous agreement in the literature that the pain associated with decompression sickness, and indeed many other syndromes, originates from the bending or some other distortion of nerve endings. Whether such physical deformation occurs or not, there seems little doubt that pain is closely associated with the establishment of local stress whatever mechanical form it may take. Such stress would be created by formation of an extravascular embolism whose pressure differential relative to the surrounding tissue, would provide the motive force for deformation, and which would be retained by membranes preventing its dissipation by gas expanding into the cardiovascular system. The latter is compatible with data quoted in section 3.34 showing that appreciable

quantities of intravenous bubbles did not provoke symptoms. The possible expansion of extracellular bubbles by pressure transmission through the lymphatic system is discussed later.

The body can stand a very wide range of external pressure providing the hydraulic fluids can reach all surfaces including the middle ear and sinal cavities, Behnke (1951) stating "cerebrospinal fluid and blood pressures not changing by as much as 1 mm. Hg" in varying from an external 550 ft. s.w.g. to an equivalent altitude of 50,000 ft. On the other hand, a very small differential pressure can cause excruciating pain. Such pain has been induced by Inman (1944) and Saunders (1943) with as litttle as 35 cm. (w.g.) transmitted by isotonic Ringer's solution via a fine hypodermic needle. In 'tight' tissues they have just invoked pain by applying differential pressures as low as 15 cms. (w.g.) irrespective of the flow required to maintain those differentials.

4.13 Critical parameter

While most of the published theoretical approaches circumvent such basic issues, the foregoing discussion indicates that the most relevant parameter in determining the proximity to pain is the differential pressure (δ) of the embolism relative to the surrounding tissue. Symptoms should thus occur when δ exceeds a threshold value (δ'),

i.e. Bends if $\quad \delta > \delta' \qquad (I)$

reverting to Roman numerals to distinguish equations derived as intermediates to the final quantitative expression of the hypothesis developed in this project.

4.14 Pressure differential and tissue mechanics

The establishment of a pressure differential must be influenced by any mechanical interaction between the embolism and the surrounding material. This mutual adjustment is apparently ignored by all except Nims (1951) who states that "the importance of the elastic properties of the tissues to decompression sickness cannot be over-emphasized", a smaller bubble in a 'tight' tissue being capable of invoking the same pain as a larger bubble in a 'loose' tissue.

While, in full agreement with this statement, the writer disagrees with the subsequent development of the theme advanced by Nims for the reasons stated in section 1.67.

4.15 Quantitative development

If v is the volume of the embolism formed in a micro tissue region of volume V, then from the definition of bulk modulus (K),

$$\delta = \frac{Kv}{V} .$$

If K refers to the critical tissue type, combination with equation I indicates that pain should occur if:-

$$\frac{Kv}{V} > \delta' \qquad \text{(II)}$$

Since K decreases with ease of deformation the critical value of v must increase, equation II thus providing a quantitative re-iteration of the above statement comparing the susceptibility of 'tight' and 'loose' tissues.

Before proceeding further, it would seem wise to test the feasibility of this approach numerically. The critical value of v/V is derived from dive analyses in section 8.65 as $v/V = F_c = 0.00525$ for the most susceptible individuals. However, Inman and Saunders quote a range of 10-15 mm. Hg for the minimum pressure differential required to induce pain in various individuals by their fluid injection method (section 4.12). For the most susceptible individuals, this corresponds to $\delta' = 1.33 \times 10^4$ dyne cm^{-2}.

Hence equation II gives the bulk modulus as:-

$$K = \delta'/F_c = 2.53 \times 10^6 \text{ dyne cm}^{-2}.$$

Since tissue in limbs is essentially unbounded by rigid surfaces:- $K \approx M/3$

where M is the elastic (Young's) modulus.

Hence for the weakest individuals, $M \approx 7.6 \times 10^6$ dynes cm^{-2}.

Values of elastic moduli for tissues seem to be very scarce, but Abbot and Lowy (1958) quote a range of $3.5 \times 10^6 - 8 \times 10^6$ dynes cm^{-2}, for smooth muscle. Since higher moduli imply greater susceptibility it is regarded as most significant that, from data derived from the weakest divers, equation II should predict a value of M within 5% of the upper limit of the experimental range. However, the practical values refer to smooth muscle and need not coincide with those for the critical tissue type.

While the above calculations cannot be offered as quantitative proof of equation II, they illustrate that the approach is feasible numerically.

4.16 Variation in modulus

The uncertainty in knowing which is the critical tissue type renders it very difficult to obtain any practical correlation between bends incidence and critical tissue modulus. However, there is an indirect means which obviates the need for positive identification.

Hallock and Benson (1937), and several later groups, have found a marked increase in the Young's modulus of the human aorta with advancing age. The results of this would indicate a roughly linear relationship for stresses of the order of 15mm. Hg consistent with pain (section 4.15). If the same overall effect occurs elsewhere in the body, then equation II would predict increasing susceptibility to decompression sickness with advancing age - a relationship which would be linear if the last-quoted data are paralleled in the critical tissue type.

Such a prediction is in direct agreement with the practical data quoted in section 1.32. Moreover, Gray's linear relationship between bends incidence and age would tend to confirm the direct proportionality between δ' and K which forms the basis of equation II.

The latter expression would thus seem to represent a form for expressing the threshold of pain which is both dimensionally and numerically feasible.

While small differences in the mechanical properties of their critical tissue types can account for the differential susceptibility of otherwise identical individuals, equation II indicates that one of the major variables in determining proximity to pain is the volume of the embolism.

4.17 Formation of the embolism

Before attempting to express v in terms of measurable parameters, it would seem essential to determine the predominating mechanisms for its development. These may be any of the physical processes underlying the four possible stages of formation of an embolism at a point in the critical tissue during decompression or at any subsequent time. Postponing discussion of the secondary secular effects of gas transport in solution, such stages may include:-

A. Saturation, the hydrostatic pressure being lowered until it reaches the total tension of all volatile substances present at the point considered.

B. Supersaturation, by further decompression beyond this equilibrium state, until nucleation conditions are reached and phase separation is initiated.

C. Transfer of volatile substances in excess of saturation from solution into the gas phase.

D. Coalescence, or congregation, of the emerging gas with that separating at adjacent sites.

At this stage the writer is anxious to avoid the popular term of "bubble" which presumes a specific geometric form.

While 'A' is the undisputed first step in the development of pain, the above enumeration provided a convenient preliminary classification for the published theories reviewed in section 1.6. All published theoretical approaches incorporate 'B' - if only for the apparent mathematical necessity

of providing a driving force for inert gas ventilation after exceeding equilibrium conditions. However, the rate-limiting step is taken as 'C' by Nims and an experimental 'in vitro' combination of 'B' and 'C' by Bateman (section 1.67). 'D' does not seem to have received consideration.

In view of this overwhelming emphasis upon critical supersaturation (or nucleation) conditions as the "trigger point" to eventual symptoms, the first step in elucidating the true mechanism should thus be an analysis of the whole question of suspended transformation. This comprises all cases where there is a delay in the appearance of a new phase required for the system to revert to its most stable thermodynamic state.

4.2 SUSPENDED TRANSFORMATION IN VITRO

4.21 The Issue

The first vital issue is whether conditions for separation of the gas phase coincide with those for the thermodynamic equilibrium or not. While the quantitative expressions of the published theories make the implicit assumption that supersaturation can exist at all points within the critical tissue, relatively few have tried to provide experimental justification. Notable among such work are the much-quoted papers of E. Newton Harvey who was primarily concerned with the popular and controversial issue of defining the nucleation point quantitatively. This includes whether the limits of supersaturation in vivo are better described as the original Haldane ratio or a fixed tension excess - as used quantitatively by Rashbass (section 1.65).

However, the writer could find no reference in the literature upon decompression sickness to a third possibility that nucleation is random, the idea being presumably dismissed as irreconcilable with the conventional mathematical treatment of blood:tissue exchange.

It is this third alternative which would seem to warrant further pursuit in view of the statistical approach adopted by most disciplines concerned with the general phenomenon of suppressed transformation. The latter refers to any instance where a phase change may not occur immediately the transition point is reached, the reluctance of a system to revert to a more stable thermodynamic state tending to be greater when the required change involves a decrease of entropy. For example, water will seldom freeze without a finite degree of supercooling, while no report could be found of ice having been superheated to above $0^{\circ}C$ at atmospheric pressure.

Although the net energy requirement is included in the latent heat, there is a greater energy barrier associated with performing the work of orientation needed to increase the order of a system and thus decrease entropy. Such reasoning applies to bubble formation by decompression to the extent that gas phase separation partially seggregates volatile from non-volatile molecular species.

While the theories for initiating a phase change would constitute a most interesting digression, studies of decompression sickness are solely concerned with whether the new phase required by the most stable thermodynamic state is established or not - whatever the mechanism of formation.

Examples of suppressed transformation include:-

1. Solid-solid transitions, where the appearance of a more stable polymorphic form may be suspended almost indefinitely, e.g. allotropic changes in phosphorus with temperature.

2. Partially miscible liquids, where temperature change may cause the system to exceed the limits of miscibility.

3. Gas-liquid transitions include the superheating of liquids beyond their boiling point and supersaturation by decompression.

4. Liquid-solid transitions including both freezing of a pure liquid and crystallisation of a solute from solutions supersaturated by cooling or solvent evaporation.

Since the latter example was the first to receive extensive attention, its selection for initial consideration provides a suitable historical introduction of the terminology relevant to suppressed transformation.

4.22 Suspended appearance of a solid phase

Ostwald (1911) was probably the first to propose the existence of the three regions of concentration which constitute the basis of all "limited supersaturation" theories of decompression sickness. Primarily concerned with the supercooling of solutions of solids in liquids, he lists these regions as follows:-

1. An undersaturated region extending to the saturation limit in which no crystallisation can occur.

2. A metastable region on the other side of the saturation curve in which seeding is necessary for crystal deposition.

3. A labile region in which the phase change occurs spontaneously, being separated from the metastable region by a well-defined line known as the 'metastable limit'.

Miers (1927), summarising his earlier work with Isaac (1906,-7,-8), supports the existence of a metastable limit which he represents as a degree of supersaturation almost constant with respect to temperature. However, he found that careful protection against contamination or mechanical shock was necessary.

De Coppet (1911) strongly criticizes the theories of Ostwald and Miers on the basis of his own experimental results. These show that phase separation can occur within their postulated metastable region, the probability increasing with the degree of supersaturation.

Further discredit to the idea of a metastable limit is contained in the results of Young et al (1911, 1913) in their investigations of the effect of mechanical stimulus upon crystallisation. Supplying the appropriate amount of mechanical energy, they found that nucleation could be induced anywhere in the supersaturated region which they concluded to be effectively labile.

More recent work by Ting and McCabe (1934) and Preckshot and Brown (1952) show that nucleation occurs throughout the metastable region, even under static conditions, if sufficient time is allowed. The final statistical interpretation of nucleation is well illustrated by McCabe and Smith (1956) as a probability curve. Ross (1938) emphasizes the similarities between nucleation and chemical reaction, expressing the energy barrier for initiation of the solid phase as an activation energy.

The writer's overall conclusion is one of small yet finite probability of nucleation occurring within the postulated 'metastable' zone of liquid-solid systems. Similar conclusions are reached by Smoluchowski (1952) in his discussion of solid-solid transitions.

4.23 Some theoretical aspects of cavitation

Reverting to the suspended appearance of a vapour phase, a mechanical balance across the gas-liquid interface would indicate that a bubble is in equilibrium with the surrounding fluid if:-

$$p_s + p_g = P + 2\gamma/y \qquad (11)$$

where P is the absolute ambient pressure, p_s is the vapour pressure of the solvent at that temperature, p_g is the tension of the entrained gas in the solvent, γ is the surface tension of the solvent and y is the bubble radius.

If we now consider a small pressure fluctuation within the system, a small decrease in P would be enhanced by a corresponding decrease in $2\gamma/y$ and would result in the bubble being unsaturated with respect to the surrounding fluid. Growth by acquiring gas from solution would further reduce the value of $2\gamma/y$, increasing the tension differential between the phases and so promoting further growth. A bubble expanding in an infinite continuum of liquid would thus continue to grow indefinitely.

For an increase in P, relative to the equilibrium state defined by equation 11, the compression should cause y to decrease. This would further increase the tension excess $(P + 2\gamma/y - p_s - p_g)$ of internal vapours over the surrounding fluids and cause more gas to dissolve. The effect should 'snowball' resulting in the eventual disappearance of the bubble. This is described in more detail by Epstein and Plesset (1950).

A gas bubble in an infinite continuum of liquid is thus dynamically unstable, the critical radius (y_c) differentiating between disappearance or indefinite growth being derived by the application of Boyle's law to the vapour in the cavity. Eisenberg (1961) quotes:-

$$P - p_s = \frac{\text{const}}{y_c^3} - \frac{2\gamma}{y_c} \qquad (12)$$

Thus Dean (1944) calculates the critical radius for a bubble in water at 20°C as 1.42 microns.

It is felt that such a criterion is highly relevant to decompression sickness where it is important to know whether separated gas constitutes a stable phase or not.

However, discussing the mechanism of phase separation, Eisenberg (1961) states that "it is now the generally accepted view that the inception of cavitation in technical fluids is associated with the growth of nuclei (submicroscopic in size) containing vapour, undissolved gas, or both". In differentiating between the latter, Strasberg (1956) introduces the terms "vaporous" and "gaseous" cavitation, a nucleus which grows explosively containing mostly vapour. Lower rates of pressure change enable bubbles to grow by the slower diffusion of gas. Noltingk and Neppiras (1950-51), using ultrasonic techniques, showed that the true vaporous cavitation process has only a slight dependence upon the duration of decompression.

Quantitative theoretical treatments probably began with determinations of the fracture strength of fluids such as Frenkel's (1939) estimate of the force required for the simultaneous separation of all atomic bonds cutting a plane surface. However, these proved many orders of magnitude greater than those found experimentally.

Such hypotheses have tended to be superseded by those of a more statistical nature, a classical approach being that of Fürth (1941) who derives the probability distribution, $W(y)$, of hole size from an equation of state for liquids as:-

$$W(y)\,dy = C \exp(-U/kt)\,y^6\,dr$$

where the probability, W(y).dy, that the radius, y, of any hole lies between y and (y + dy) is a function of the energy of formation of the hole, U, its radius and the temperature. Equations of state used include those of Eyring (1936) and Lennard-Jones (1937) who regard liquids as disarranged solids.

The energy barrier to formation of a spherical hole in a liquid continuum, U, can be derived in terms of the work done against surface tension and external pressure. Circumventing a more detailed description of the Mathematics, such "hole theories" predict a labile region and a finite probability of nucleation occurring within the 'metastable' zone. This is commensurate with experience of solid-liquid systems as described previously, and covers the case most relevant to decompression sickness which is that of gaseous cavitation.

4.24 Condensation and vaporous cavitation

The formation of the liquid phase from vapour cooled to the boiling point, and below, is possible anywhere within the supersaturated region according to the general review of the subject by Pound (1952). The 'supercooling versus nucleation' probability curve given by Probstein (1955) for condensation is very similar to that for crystallisation. Moreover, most theories have a statistical basis, including the widely-accepted treatments of Volmer (1939) and Becker and Doering (1935) for steam.

The reverse process, suspended formation of the vapour phase, may be observed whenever the vapour pressure of a pure liquid exceeds the absolute hydrostatic pressure. This may be effected by either superheating, decompression, or both.

Using small clean capillaries, Kenrick et al (1924a) were able to heat water to 270°C at atmospheric pressure, the vapour pressure at this temperature being 54 atmospheres.

The alternative method of supersaturating by decompression, has enabled some remarkable negative pressures to be recorded. These are often designated 'tensile strengths', values having been obtained under both static and dynamic conditions by a wide variety of methods. They are listed in Table 4.

RECORDED 'TENSILE STRENGTHS' OF VARIOUS LIQUIDS

Tensile Strength	Liquid	Reference	Method
300 atmospheres	water	Bethelot (1850)*	static
4.8 "	water	Reynolds (1870)	dynamic
30 "	water	Meyer (1911)	static
40 "	ether	Meyer (1911)	static
150 "	water	Dixon (1914)	static
207 "	cell sap	Dixon (1914)	static
2.38 "	water	Vincent (1941)	static
2.94 "	mineral oil	Vincent (1941)	static
2.9-114 "	mineral oil	Vincent (1941)	static
100-1,000 "	water	Harvey (1944)	static
0.8 "	water	Dean (1944)	dynamic
100-200 "	water	Pease & Blinks (1947)	static
280 "	water (10°C)	Briggs (1947)	dynamic
20 "	water	Willard (1953)	ultrasonic
200 "	water	Galloway (1954)	ultrasonic
140 "	benzene	Galloway (1954)	ultrasonic

TABLE 4

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

The variation of the values quoted in Table 4 needs no comment. However, most authors tend to emphasize their highest reading, often making no mention of other runs failing to reach the maximum. While this would seem quite acceptable in attempting to determine the 'fracture strengths'

of liquids, their frequent quotation in support of limiting supersaturation theories of decompression sickness would seem of little value in deciding whether the implied metastable limit exists or not.

> The writer feels that any threshold for phase separation can be greatly influenced by the results one is prepared to discard as affected by chance contamination, the whole study of suspended transformation suffering from the extreme disadvantage of never knowing with certainty when this has occurred. The same drawback is particularly applicable to gaseous cavitation.

4.25 Gaseous cavitation

Fundamental approaches to gaseous cavitation have been similarly directed towards determining the probability of forming a nucleus of critical radius as a result of random thermal fluctuations within the gas solution. Such kinetic predictions have tended to agree with the maximum values of fracture strength recorded experimentally - Harvey (1951a), and Temperley and Chambers (1946).

These very high supersaturations may be attained by pressurising the solution, isolated from any gas phase, to well above the total tension of undissolved substances. The technique is well described by Pease and Blinks (1947), Harvey (1951a) finding 30 mins. at 16,000 p.s.i. most effective. Many authors, including Willard (1953), have attributed this 'memory' for past high pressures to the presence of undissolved bubbles in normal liquids. Quantitative expression is provided by the following hypothetical equation proposed by Strasberg (1956):-

$$P_c = i_1 \cdot p - i_2 \cdot P_u$$

where P_c is the critical pressure for cavitation, p is the gas tension, P_u is the maximum external pressure to which the liquid has been subjected, and

i_1 and i_2 are constants where $i_2 + 1 > i_1 > i_2 > 1$.

In all this work, extreme care must be taken against contamination or mechanical shock, the preparation of containing surfaces usually following the procedure originally outlined by Tomlinson (1867, 1873).

Kenrick et al (1924b) were able to saturate water with oxygen, nitrogen or carbon dioxide at 100 atmos. and then reduce the pressure to 1 atmosphere without producing bubbles. Decompressing by thermal contraction, Clare (1925) saturated water with carbon dioxide at 250 atmospheres and, upon decompression, sometimes obtained a cloud of fine bubbles.

Generating a 'nuclei-free' supersaturated solution of CO_2 by mixing ultra-centrifuged solutions of M.$NaHCO_3$ and M.HCl, Harvey (1951) admits that a few bubbles have been observed.

4.26 Random nucleation

In attempting to account for the general lack of reproducibility by performing each decompression twenty times, Strasberg (1956) found a linear relationship between dissolved air tension and the 'critical inception pressure' for cavitation in water. By extrapolating these results, and those of Blake (1949), to a system at one atmosphere absolute pressure, the mean tension for nucleation would be 1.65 atmos. of air. 1.65 is appreciably less than any value of the decompression ratio based upon air (R/x in section 1.6) quoted in the diving literature.

However, there is a wide scatter of the 30 points through which Strasberg draws his line, the worst deviation being 45% on a tension basis.

When it is realised that each of Strasberg's points represents twenty determinations, the distribution of the individual readings should be far greater. This would imply that the cavitation of dust-free water, without previous pressure treatment, is a very random process. Unfortunately Strasberg does not publish his individual readings.

Such details are available, however, for the work of Crump (1949) who records his results for pumping both fresh and sea water through a venturi nozzle. His graphical representation of several hundred readings, on the basis of air content vs. critical inception pressure, indicates that cavitation is a very random process indeed. For sea water, under such conditions, there is an appreciable probability of nucleation occurring for tension differentials below 90 mm. Hg. Crump found that average critical inception pressures dropped markedly with increased temperature, indicating that the Strasberg mean decompression ratio of 1.65 could be appreciably lower at blood temperature ($37^{\circ}C$).

However, when town water is run from a tap, or soda-water is uncorked, the bubbles form at the surface retaining the liquid. Hence it would seem essential to pursue the possible effect of phase interfaces in 'catalysing' nucleation.

4.27 Cavitation at phase interfaces

There are very few instances in which bubbles have been observed to form in the bulk of the fluid. The only cases seem to occur by extreme decompression such as recorded by Clare (1925), or by generating cavities ultrasonically, e.g., Wismer et al (1953).

While Kenrick et al (1924b) do not state the site, and Briggs (1952) could not be certain, Wismer (1922) reports that all bubbles are initiated at the walls of the containing vessel. Moreover, Pease and Blinks (1947) found it impossible to form bubbles in the bulk of the fluid, concluding that a solid surface is the separation point.

While the theoretical implications of the micro-geometry of the container walls has been discussed by Harvey (1951), the simple explanation that they retain small pockets of gas which act as the embryos for bubble growth, no longer seems adequate. Farncombe (1925) reports bubbles forming at the surface of solids deposited from the same solution as the gas, particularly upon those substances only wetted with difficulty by the solvent. Since such interfaces have never been exposed to any gas, these observations somewhat detract from the emphasis which the advocates of supersaturation theories of decompression sickness place upon the sealed environment of tissue fluids.

Harvey (1951) records that a paraffin surface always bubbles profusely in soda water however well it is cleaned. Apart from glass, or metal surfaces where galvanic action renders any findings irrelevant to this project, very little information could be found concerning cavitation at other phase boundaries.

In view of the finite lipid content of even the predominantly aqueous tissue types, (Widdowson et al, 1951), the fat-aqueous interface assumes greater importance. Although it is a rather moot point whether such direct interfaces exist in the body, any intervening membrane could well supply the "organic skin" which Fox and Herzfeld (1954) postulate as exerting such a vital role in stablising nuclei and hence promoting cavitation.

If direct contact of the liquid phases is discounted, the pertinent boundaries are again the surfaces of the retaining walls. However, a membrane may be regarded as a gel and thus intermediate between a solid and a liquid from both mechanical and chemical standpoints (Hills, 1962). Since a similar interpolation applies to its effect in promoting cavitation in an adjacent liquid phase, there should be little doubt of the response of a gel-liquid system to decompression if both liquid-liquid and solid-liquid cases behave similarly. While bubble formation in the latter system has been shown to be random, no published information could be found for the other limiting case.

Whether direct lipid-aqueous contact is postulated or not, the relevant behaviour would seem to be that of cavitation at liquid-liquid interfaces. The experimental programme described in section 6.2 has been undertaken to offset the apparent absence of published information upon this system, the results obtained leaving little leeway for alternative interpretation. They indicate that the formation of a stable gas phase at a liquid-liquid interface is a random process, there being a significant probability of the gas phase appearing for any significant degree of potential supersaturation.

Reverting to a more quantitative approach, the most relevant parameter is probably the energy barrier for phase separation at a hydrophobic surface, which may best be assessed from a thermodynamic analysis of the interface.

4.28 Thermodynamic considerations

At inception, the energy contained in a cavity by virtue of its surface may be far in excess of that contained in the very small volume of gas separating initially. The energy barrier to gas phase initiation would thus be determined by the free energy change in creating the new surface. The minimum activation energy per unit area of cleavage is thus given by:-

$$E = (\Delta F)_{aqueous} = 2.(\Delta F)_a$$

where $(\Delta F)_a$ is the Gibbs free energy change, per unit area, in creating a new interface between air and the aqueous phase.

If the plane of cleavage now coincides with an oil-air interface, the minimum activation energy E' per unit area now becomes:-

$$E' = (\Delta F)_{oil\text{-}aqueous} = (\Delta F)_o + (\Delta F)_a - (\Delta F)_{oa}$$

where $(\Delta F)_o$ and $(\Delta F)_{oa}$ are the free energies per unit area for the oil-air and oil-aqueous interfaces respectively.

The probability of gas phase separation occurring at the oil-aqueous interface should be greater than that of nucleation within the bulk of the aqueous phase if $E' < E$.

Continuing this argument parallel to the derivation by Davies and Rideal (1963) of the Antonoff relationship for determining whether one immiscible liquid will spread over another, the expression of free energies as measurable parameters reduces the foregoing equations to:-

$$E' \propto \gamma_a + \gamma_o - \gamma_{oa} \qquad (13)$$

$$E \propto 2\gamma_a \qquad (14)$$

i.e. $E' < E$ if $\gamma_a + \gamma_{oa} - \gamma_o > 0$

where γ_a, γ_{oa} and γ_o are the interfacial energies for the air-aqueous, oil-aqueous and oil-air system respectively.

Using the following values quoted by Glasstone (1954) for liquid paraffin and water:-

$$\gamma_a = 72.5 \text{ dyne cm}^{-1}$$

$$\gamma_o = 31.8 \quad " \quad "$$

$$\gamma_{oa} = 57.2 \quad " \quad " \quad ,$$

$$\gamma_a + \gamma_{oa} - \gamma_o = 97.9 \text{ dyne cm}^{-1}.$$

Equations 13 and 14 give:- $E \propto 145$ and $E' \propto 47.1$

More quantitative justification for this approach is given in section 6.27.

Hence the liquid paraffin/water interface offers a relatively low energy barrier for air separation from solution.

4.29 Conclusions

Whatever the mechanism of nucleation, or whether such a process exists, the experimental facts indicate that the conditions for reversion of a system in suspended transition to its equilibrium state can only be treated on a statistical basis. The separation of the gas phase from a solution supersaturated by decompression is a particularly random process, average values indicating that the transformation is more probable for the liquid components present in the body than for pure water. The latter becomes evident when replacing γ_a in section 4.28 by the value for serum which Geigy (1954) quotes as 47 dyne cm^{-1}.

Most exponents of theories of decompression sickness seem to have overlooked the vast wealth of cavitation research in many other fields when quoting little other than the work of Harvey. The latter has emphasized his work in vitro on the grounds that the endothelial lining is essentially hydrophobic. However, this presumes that nucleation occurs intravascularly which is contrary to the conclusions of section 3.3. His adherence to 'denucleated' systems is presumably based upon the fact that body fluids have been hermetically sealed by membranes since conception. In practice, they have undergone neither the extreme pressurisation nor the ultracentrifuging techniques employed by Harvey.

Even accepting his approach, there seems to be no true metastable limit for any aspect of suspended transformation, and no means of predicting the nucleation point on any particular occasion. The writer therefore regards the problem as transposed to one of deciding whether it is more realistic to programme a dive according to the behaviour of the statistical average or by choosing the worst possible micro-region of the critical tissue.

Since living tissue need not conform to the frequency distributions found for the above systems, the decision is better delayed until consideration has been given to the results of cavitation in vivo.

4.3 CAVITATION IN VIVO

4.31 Resting animals

Research in this aspect of decompression sickness has been largely directed towards determining the constant pressure ratio, or fixed differential, which describes the limits of the implied metastable zone

characteristic of living tissue. Such investigators, mostly quoting Harvey's work in vitro, almost invariably assume that supersaturation exists and that nucleation is the predominant mechanism in estimating proximity to marginal symptoms.

Most experimenters have searched for bubbles in animals killed immediately before or after decompression between various combinations of initial and final absolute pressures.

One of the most comprehensive programmes in this field employed cats, the results being recorded in a series of joint papers by Harvey (1944a, b, c), McElroy (1944a, b), Whiteley (1944), Warren, Pease, Cooper and Barnes. The results are summarised in table 5, and would seem to offer convincing evidence that cavitation in vivo is a random process.

BUBBLES OBSERVED IN RESTING CATS

Time at pressure (P_1)	Initial absolute pressure (P_1)	Final absolute pressure (P_2)	Number of cats in trial	Number displaying bubbles
∞	1 atmos.	0.14 atmos.	37	4
∞	1 "	"	11	1+2?
2 - 5 hrs.	3.5 "	1 "	18	9
	3.14 "	1 "	10	7
	2.64 "	0.14 "	10	4
	3 "	1 "	12	3
	2.5 "	1 "	6	0
	2.0 "	1 "	5	0
	9 "	2 "	10	4
	6.8 "	2-3 "	8	0

TABLE 5

Harvey waited 5,000 secs. before searching for bubbles in several tissue types.

The results in table 5 are in quite good agreement with the general findings of Boycott et al (1908b) using goats and guinea pigs.

Harvey (1951a) has reported bubbles in all isolated tissues decompressed to ambient pressure from 'saturation' at 40-80 atm. N_2. Employing his 'denucleation' technique of pressurising to 16,000 p.s.i. for 30 mins., yet not increasing gas concentration, the same author has still found bubbles in all principal tissue types except muscle upon decompressing to 110 mm. Hg.

Observations by Daly (1941), who has recorded occasional bubbles in the tissues of monkeys, rabbits, and guinea pigs decompressed to an equivalent altitude of 45,000', would again corroborate the random nature of the results in table 5. The need to treat such experimental data on a statistical basis is well illustrated by Harvey's use (1951a) of the χ^2 significance test in drawing correlations.

Results of the type recorded in table 5 would appear to be limited in interpretation, since it is impossible to observe every part of even one tissue type by microscope before autolysis sets in or the separated gas is dissipated by diffusion. Thus it seems impossible to ascertain whether animals in which no bubbles were recorded were truly free of cavities. Any justification for such doubts would tend to reduce the extent of protection conventionally attributed to supersaturation.

Such pressure differentials would appear to be reduced by stimulation, Harvey (1945) having found that it is difficult to demonstrate bubbles in any animal examined unless muscular movements have occurred. This is pertinent to decompression sickness since divers are seldom resting at depth.

4.32 Stimulated animals

Harvey (1951a), after applying 17 volt (60 c.p.s.) stimuli for 0.2 seconds every second for 1,000 seconds following decompression from ambient pressure to 110 mm. Hg , found that only 3 out of 26 cats failed to show bubbles. Similar results were obtained decompressing a further 11 cats to a simulated altitude of 35,000'.

By stimulating cats decompressed to ambient from positive pressures, Harvey found bubbles in each of 23 which had been held at 3.5 atmos., 9/12 held at 3 atmos., 17/23 held at 2.5 atmos. and 18/23 held at 2 atmos. Applying the χ^2 test, he found a slight correlation with fat content in resting cats, but nothing significant with respect to the extent of stimulation. This is corroborated by earlier work upon goats by Boycott et al (1908b).

Blinks et al (1951) describe the work of Harris et al (1945b) who have found bubbles in all of 31 bullfrogs exercised upon decompression to ambient following 1 hour at pressures ranging from 5-60 p.s.i. (gauge). Inducing muscular activity in rats by 5-15 volt (60 c.p.s.) A.C. stimuli, they record a threshold pressure of 3 p.s.i. (gauge) at which 2 out of 5 gave bubbles just large enough to be observed with difficulty.

This pressure differential is much smaller than any advocated in the semi-empirical methods conventionally employed for predicting marginal symptoms (section 1.6). Moreover, the random nature of detected bubble occurrence in both the resting and stimulated conditions, would suggest that there is an appreciable probability of gas separating from solution in tissue whenever equilibrium concentrations are exceeded.

4.33 Histological considerations

It has been shown in section 4.28 that aqueous-lipid interfaces are more conducive to cavitation on thermodynamic grounds. It is therefore, interesting to consider the more specific location of such sites within the body.

Both of the two tissue types, most likely to be responsible for marginal bends (section 3.3), have an appreciable content of lipoidal material. Gersh et al (1944) record values of 8-15% lipid content in the lean tendon of guinea pigs, while the presence of isolated fat cells in the predominantly-aqueous connective tissue is illustrated by Maximow and Bloom (1948a). The latter authors describe the increased preponderance of collagen in tendon implying a high elastic modulus and, hence, susceptibility to pain - equation II. Such deduction would depend, however, upon the preponderance of nerve endings and their deployment.

Sensory nerve endings in striated muscle "are always present in considerable numbers", according to Maximow and Bloom (1948b) - appearing in the muscular tissue, tendons or at musculo-tendon junctions. The latter are the locations for "palisade-like" terminal branches for nerve fibres which are present in both 'naked' and 'encapsulated' forms. "The physiological significance of the muscular and tendinous sensory apparatus" is summarised by Maximow and Bloom as "their responsiveness to various peripheral stimuli of general character, giving sensations of pain, pressure, and particularly of 'muscle sense'". From such qualitative descriptions there would seem to be adequate sensitivity to pressure differential in tendon and its junctions with muscle fibres or connective tissue.

Reverting to the search for likely phase boundaries, the myelin sheaths of the 'encapsulated' nerve fibres are predominantly lipoidal, comprising certain cerebrosides, phospholipins, fatty acids, but mainly cholesterol (Maximow and Bloom, 1948b). Haymaker (1957) in his review of the pathological evidence for decompression sickness, publishes photomicrographs displaying fenestration in the myelin sheaths of the white matter in the central nervous system. Fewer minute gas bubbles are recorded by Gersh and Catchpole (1951). They attribute these occurrences to the higher solubility of nitrogen in myelinated peripheral nerves.

It seems very difficult to ascertain whether the presence of lipoidal material in aqueous tissue implies a direct fat-water interface. However, such interfaces may occur within the membranes themselves. The basis for these postulates is the more rapid transmission of compounds with a higher fat-water partition coefficient as originally discovered by Overton and confirmed by many later workers including Staverman (1948) who defines a reflection factor for each compound.

This has led to many theories for the structure of cell membranes in which lipid is a major component. Thus Danielli (1935) postulates that the resistance to diffusion is provided by a bimolecular screen of lipoidal material orientated with polar groups facing outwards and sandwiched between monolayers of protein.

Since membranes have the mechanical consistency of a gel, gas separating from solution at the phase boundaries need not necessarily assume a spherical form at nucleation. Decompression could thus create films of gas following the contours of lipid/aqueous-gel interfaces. Experimental evidence for the formation of such films between olive oil and gelatin in vitro is provided later (section 62.3).

4.34 Conclusion to nucleation

While most authors expounding theories of decompression sickness quote Harvey, with particular reference to his results with denucleated solutions, there is an almost total absence of any reference to cavitation research in connection with fluid dynamics. The overall impression, reached in section 4.29, that suspended transformation in vitro is a random process seems equally applicable in vivo. Moreover, whether induced by the possible presence of thermodynamically-preferable nucleation sites or not, microscopic observations show that bubbles can be produced in animals by pressure differentials far smaller than empirical decompression ratios would imply if limited supersaturation were the critical mechanism.

The statistical nature of the evidence collected in this chapter would indicate that, while any tissue can probably retain considerable supersaturation over most of its mass, the probability of finding at least one highly nucleated micro-region is far too high to be ignored. If seeding was sufficiently dense over such an area, equilibrium would be established rapidly and maintained for the remainder of the decompression and for some time subsequently.

An isolated embolism formed from the gas in such a micro-region is likely to create a rather greater local pressure differential than might be expected from uniform nucleation throughout the whole tissue. Moreover, the loss of all supersaturation in such areas would reduce the rate of ventilation of gas to the capillaries since the driving force for desaturation via the blood is the concentration gradient of gas remaining in true physical solution.

The writer comes to the conclusion that it is safest to programme the decompression of the human body as though the critical tissue type contained at least one micro-region in which there was complete thermodynamic phase equilibration at all points for all times. This poses the problem of inert gas transport, which is so conveniently accommodated by postulating supersaturation, and implies that pain-provoking emboli are formed by the coalescence of separated gas.

4.4 COALESCENCE

4.41 Micro-bubble sites

Gas films following phase interfaces, or very small bubbles grown from finely dispersed nuclei, can only coalesce to form an embolism of pain-provoking dimensions if permitted to do so by the mechanical boundaries present. Since the latter would be the numerous membranes, it is important to know whether gas separates from solution in cells.

Blinks et al (1951) describe profuse intravascular bubble formation upon decompressing rats to a pressure equivalent to an altitude of 50,000 ft., Harris et al (1945a) reporting considerable numbers in the lymphatic system. The histological description of the latter system by Maximow and Bloom (1948c) would indicate that any embolism would have a better chance of expansion than if contained within the confines of a cell membrane.

Occasional bubbles in cells have been reported by Gersh et al (1944), while Harvey (1951a) reports finding them in fat but none in

predominantly aqueous cells. The latter author finds that whereas bubbles rarely occur on uninjured tissue surfaces decompressed to the water vapour pressure, they are common in cut connective tissue.

However, more significant to the writer, is a remark by Harvey to the effect that bubbles could be readily observed deep in most aqueous tissue if it were moved by a glass rod or the microscope objective. Harvey, along with other proponents of the strain theory including Evelyn (1941), McElroy et al (1944a) and Ferris et al (1943a), attributes such effects to the development of local negative pressures.

On the other hand, such mechanical actions would be ideally suited to coalescing the gas deposited from solution in the physical form described earlier. Such films or micro-bubbles in a cell would not be detectable by microscope but, with relative movement, may well assume the form described by Harvey as "large irregular masses which gradually change into small round bubbles".

Harvey gives no indication of the speeds with which he cut the connective tissue or moved his glass rod, but it would seem highly unlikely that he could develop any appreciable negative pressure by wracking back a microscope - particularly when even the 'tightest' tissues have Poisson ratios (σ) in the range 0.48-0.5 (McDonald, 1960). A fluid has $\sigma = 0.5$.

Most proponents of various forms of the conventional supersaturation approach to decompression sickness do not specify the means of formation of the embolism once their particular 'critical tension conditions' are exceeded. No reference could be found in connection with bends to the coalescence of anything other than haemorrahgic infarcts

(Goodman, 1961). The latter is hardly relevant to the gaseous case. This introduces the subject of the mechanical factors likely to influence the onset of symptoms and the many explanations for their effects.

4.42 Negative mechanical pressure vs. coalescence

There seems no dispute in the literature over the fact that stimulation of tissue greatly increases the probability of its displaying visible bubbles - particularly within cells. Harvey (1951a) attributes this to the augmentation of any external decompression by a superimposed mechanical strain arising from muscle contraction. This is postulated to produce vaporous cavitation, the cavities being subsequently filled with diffused gas.

Berg et al (1945), Harris et al (1945a), Henry (1945c and 1946), and Whitaker et al (1945) prefer to attribute the effects of stimulation to the rapid formation of CO_2. However, Gray has shown convincingly (section 1.44) that carbon dioxide has no significant influence upon the incidence of bends, while Harvey (1951a) has performed a pertinent experiment to dispel any remaining doubts. Harvey injected up to 1 c.c. of denucleated N, lactic acid into the aortas of 17 cats, after which eight showed bubbles in the vena cava upon decompression to 45,000 ft. Analysis of jugular blood gave no correlation between CO_2 tension and bubble production.

Blinks et al (1951) have found that violent muscular exercise is much more effective in producing bubbles in bullfrogs if applied during decompression rather than before. Harvey argues that the tension differential inducing cavitation is greater in the former case, while the parallel argument for coalescence is based upon the need for gas to be present.

The many cases in which Harvey tries to induce cavitation in animals by various mechanical means all seem to suffer from the disadvantage that he looks for bubbles in the vena cava. Any injury would tend to break membranes and enable extravascular gas to enter the blood. Such experiments include inflicting 200 blows with a mallet, or stretching the hindleg of a cat at a simulated altitude of 45,000 ft. - a slow forcible pull proving more effective than jerking. In his experiment in which he induces bubble formation in a cat's hindleg by crushing it in a vice prior to decompression, it is difficult to see how such an essentially compressive force can initiate phase separation. Repeating the experiment with a further set of 10 cats, postponement of crushing until after decompression, reduced the time of appearance of bubbles in the vena cava.

Harvey's results would seem better interpreted if coalescence were postulated as the rate-controlling mechanism for gas appearing in a detectable form.

Harvey's records show a very wide range of times to the appearance of the first bubble, ranging from 5 seconds to over 1000. Such a wide scatter of results is consistent with the random nature of coalescence. Using 10 anaesthetised decompressed cats for each set of observations, Harvey (1951b) found no appreciable difference in bubble occurrence whether applying 6 or 17 volt stimuli. This would indicate that the appearance of bubbles is not a function of the mechanical stress induced, although a difference has been noted if the experiment is performed after 32 minutes of pre-oxygenation.

In view of the previous conclusion that limited super-saturation is not the predominant mechanism in the worst possible case, it would seem reasonable to assume that the gas liberated in such equilibrated micro-regions form the pain-provoking embolism by coalescence or congregation.

4.43 Theory of coalescence

Ignoring gravitational considerations, any phase suspended in another will reach its lowest energy form when its total surface energy is a minimum. However, the interfacial area per unit mass increases the finer the dispersion. The lowest energy state for gas dispersed in tissue must occur when it has formed one bubble, the net energy change representing a thermodynamic driving force favouring coalescence.

The kinetics, however, are far less direct. The first requirement for two bubbles to merge into one is that they come in contact. This indicates that coalescence is greatly accelerated by motion, although the meeting of separate gas masses in tissue must be a somewhat random process governed by internal membrane geometry. Muscle contraction and elongation, would thus seem ideally suited to congregating any gas initially deposited as films within the locomotor system.

Simple experiments with two bubbles at a water-oil interface indicate that the number of collisions is the most significant parameter, there being a roughly equal chance of effecting coalescence upon each encounter. Such phenomena were more easily studied using mercury globules on a clean glass plate. Results were not recorded on account of the difficulty in defining a standard collision, but there was little doubt that the probability of two drops combining changed very little unless the surfaces had collected dirt.

Although Liebermann (1957) emphasizes the stability of bubbles lying in juxtaposition, the reduction of total interfacial energy may be effected by gas diffusion across the very thin liquid film which often separates them. Since it is most unlikely that two bubbles meeting in tissue would be of equal size, the smaller would have a higher internal gas pressure by virtue of surface tension. This would provide a driving force for diffusion such that the larger bubble would grow at the expense of the smaller. Moreover, the process would be accelerated as the size differential increased. Hence it is not a necessary condition that the intervening film should burst in order to combine the gas contained in two bubbles.

Whatever the mechanism, congregation of gas into an embolism within tissue is a process anticipated thermodynamically, but kinetically dependent upon two random factors. Hence coalescence would be expected to display a very wide scatter with respect to time, but to be accelerated by any local muscular activity.

This is in direct agreement with the very variable onset time of symptoms (section 1.25), and the marked reduction of those times when the subjects undertook exercise following decompression.

4.5 THE WORST POSSIBLE CASE

4.51 The postulated mechanism

The foregoing discussion indicates that initiation of gas phase separation is sufficiently random that there is a very appreciable chance of the worst possible conditions, i.e. maximum gas separation,

occurring in at least one micro-region of the critical tissue type. These zones would be so well seeded, with maximum diffusion distances for deposition so small, that phase equilibration is rapidly established at all points in the vicinity. The growth of am embolism to a size where its differential pressure is pain-provoking, is then effected by congregation, with possible coalescence, of the separated gas - a random process accelerated by the mechanical action of exercise.

While it might appear that the various facets of suspended transformation have been unduly laboured in coming to such a simple conclusion, dispensation with supersaturation in programming dives is a major departure from all fundamental theories of decompression sickness. The development of a quantitative hypothesis upon this basis thus requires a clear definition of the conditions for thermodynamic equilibrium.

4.52 Thermodynamic equilibrium

Two conditions must be satisfied for a bubble and the immediately adjacent liquid to be in thermodynamic equilibrium. These are:-

(i) the bubble must be mechanically stable, i.e. the total of all pressures acting upon the gas must equal the total of the partial pressures of all volatile constituents, and

(ii) there must be phase equilibration, i.e. the partial pressure of each constituent must equal the tension of the same substance in the tissue immediately adjacent to the bubble.

Hence the conditions for thermodynamic equilibrium at that point are given by:-

$$p + p_o + p_c + p_w = P + \delta + 2\gamma/y \qquad \text{(III)}$$

where p, p_o, p_c and p_w are the point tensions of inert gas, O_2, CO_2 and water vapour respectively. P is the absolute pressure external to the tissue whose elastic deformation (section 4.15) contributes δ to the net gas pressure. γ is the interfacial tension and y is the bubble radius.

4.53 Surface tension

Whatever form the gas may take upon initial separation from solution, it is the final congregated volume which determines the proximity to symptoms. For the limiting case, the radius of the bubble for the 'weakest' men is derived from dive analyses in section 8.65 as:-

$$y = 1.41 \text{ microns.}$$

The role of liquid-liquid phase interfaces in determining the frequency of gas nucleation has received much attention in section 4.27 with particular inference to the presence of fat in vivo. Lipids are known to be present as a bimolemlar film in most, if not all, membranes (summarised by Davson, 1964b), and hence quite widely dispersed in even the predominantly-aqueous tissues. After helping to initiate the gas phase, lipoidal material should continue to play a major role in modifying the gas-tissue interface, so minimising the total energy of the system. After reduction of the total interfacial area by coalescence of the gas, the lipid film should correspond to the 'condensed' condition, which Davson (1964b) describes in some detail. Taking the transition point in his curve for the condensed condition of a typical lipid as indicating the onset of compaction of the film, the corresponding surface tension may be read from his graph as:-

$$\gamma = 17.9 \text{ dynes cm}^{-2}.$$

Hence, using the above value of y, for marginal conditions:- $2\gamma/y = 190$ mm. Hg.

4.54 Conditions for phase separation

The finer the dispersion of gas, the smaller will be the value of y and the larger the excess of total tissue tension over absolute pressure needed for δ to exceed the critical value δ_1 (equations I and III). Thus 190 mm. Hg is the lowest feasible value of $2\gamma/y$ short of pain, and hence the value permitting the maximum extent of phase separation after coalescence.

Conforming to the concept of the worst case advocated in section 4.51, the set of parameters most likely to induce symptoms are thus:- $2\gamma/y = 190$ mm. Hg, and $\delta = \delta_1 = 10$ mm. Hg according to the value found experimentally for the weakest individuals by Inman and Saunders (section 4.15).

Equation III would thus predict the condition for phase equilibration following formation of a critical embolism as:-

$$p + p_o + p_c + p_w > P + 200 \text{ mm. Hg.} \qquad \text{(IV)}$$

From the above equation, it can be seen that determination of the quantity of gas in excess of equilibrium requires quantitative expressions for the tensions of all volatile substances with respect to internal and externally-imposed conditions. This introduces the dimension of time as a prime variable, posing the question of gas transport within the body and elucidation of the most realistic mathematical model for its estimation.

CHAPTER 5

TRANSPORT

CHAPTER 5 (Contd.)

TRANSPORT

5.1 GAS DISTRIBUTION

5.11 The system

In assessing the response of extravascular tissue tensions to changes in the inhaled atmosphere, it would seem essential to consider each major step in the transport system. These may be briefly listed as follows:-

1. Inhalation of the new atmosphere.
2. Dilution with exhaled gases in the alveoli.
3. Mass transfer with the blood by diffusion across the pulmonary membrane.
4. The distribution of the resulting 'arterial' blood to the capillaries, with its subsequent return to the lungs via the veins.
5. Mass transfer between capillary blood and interstitial fluid by diffusion and/or hydrodynamic pervasion of the endothelial membrane by pericapillary filtrate.
6. Mass transfer between cells and interstitial fluid by diffusion.

The volatile substances which can contribute to the formation of an embolism are water vapour, oxygen, carbon dioxide and any inhaled gas inert with respect to all chemical processes occurring within the body. In the alveoli the partial pressure of water vapour should be established at its equilibrium value for contact with plasma at body temperature.

While the three mass transfer operations are purely physical in the case of the inert gases, the capacity of blood for absorbing the metabolisable gases is considerably increased by the presence of red cells. The subsequent chemical equilibrations of the oxygen-haemoglobin-carbon dioxide system are well summarised by Roughton (1963).

Any delay in the uptake of inert gases afforded by the first three of the above steps may be ignored according to experimental results quoted by Ferris and Engel (1951). They show plots of arterial nitrogen tensions which reach the asymptote within 2-3 mins. of any change in alveolar pressure. Where this change is effected by compression or decompression, however, the delay should be even less.

The above reasoning would appear to justify the practice, popular in diving calculations, of ignoring any retarding influences of the respiratory processes in determining the uptake of volatile substances by tissue. This is the major implication made by equating arterial tensions to atmospheric partial pressures. However, while it would seem reasonable to omit a secular correction term, there would appear little justification for the common practice of ignoring the dilution of inspired by expired gases within the alveoli.

5.12 Alveolar Tensions

The very complex series of consecutive chemical reactions representing metabolism has one volatile reagent (oxygen) and one volatile product (carbon dioxide). The relative molecular ratio of CO_2 liberated to O_2 consumed is 1.0 for the combustion of carbohydrate, 0.80 for protein and 0.71 for fat, Davson (1964a) quoting a general value of 0.85 for the respiratory quotient for man.

For absolute external air pressures varying from 760 to 4640 mm. Hg , Hill and Greenwood (1905) record alveolar CO_2 tensions varying from 33.5 to 41.3 mm. Hg, and averaging 40 mm. Hg.

The reduction in alveolar O_2 tension would thus average 40/0.85 = 47 mm. Hg by virtue of metabolism.

For an atmosphere of mole fraction x of inert gas and (1 - x) of oxygen, saturation with water vapour would reduce the total air tension from P to $(P - p_w)$, i.e. the inhaled O_2 partial pressure from $(1 - x)P$ to $(1 - x)(P - p_w) - 47$ mm. Hg, and the inhaled N_2 partial pressure from xP to $x(P - p_w)$, where p_w is the saturation water vapour pressure at 37°C.

Arterial tensions are thus:-

$$P_x = (1 - x)(P - p_w) - 47 \text{ mm. Hg for } O_2,$$

$$P_A = x(P - p_w) \text{ mm. Hg for the inert gas,}$$

$$P_w = p_w \text{ mm. Hg for water vapour,}$$

$$P_c = 40 \text{ mm. Hg for } CO_2$$

$$\text{Total} = P - 7 \text{ mm. Hg.}$$

For air at ambient pressure, P = 760 mm. Hg , x = 0.8 and p_w = 47 mm. Hg , giving P_x = 93 mm. Hg - in agreement with the value of 94 mm. quoted by Albritton (1952) from experimental determinations.

The arterial inert gas tension (P_A) is thus given by

$$P_A = x(P - p_w) \qquad (V)$$

5.13 The rate-controlling process

Having concluded that none of the processes associated with respiration have any significant effect upon the time response of tissue

tension, the rate-controlling stages must be associated with the particular tissue itself. This raises the vital and most controversial issue of whether the uptake of inert gas by the critical tissue is limited by its blood perfusion rate, or diffusion, or both.

Most quantitative approaches to decompression sickness avoid the issue by assuming that the mean extravascular tension has a simple linear response to changes in atmospheric partial pressures, irrespective of the mechanisms involved. The severe limitations of such calculation methods have been discussed in section 1.6. Although well justified by decompression experience, the pioneer of the linear diffusion theory in diving (Hempleman - see section 1.65) has offered little defence of this proposed model in the light of a much wider physiological literature expressing conclusions overwhelmingly in favour of circulation as the rate-controlling process.

5.2 DIFFUSION vs. BLOOD PERFUSION

5.21 General

Before placing any quantitative interpretation upon data related to the exchange of inert substances within the body, it would seem imperative to establish whether diffusion or circulation is the predominating transport mechanism. What would be deduced as a blood perfusion rate from one standpoint could, in reality, be a function of the diffusion coefficients and micro-geometric dimensions of the 'phases' comprising the tissue. The literature would appear to contain many facts which are difficult

to reconcile with the popular belief that blood-tissue exchange is circulation-limited (Kety, 1951). This would suggest a re-assessment of this problem of fundamental interest and particular application to:-

(i) the uptake of anaesthetics,

(ii) the determination of regional blood flows, and

(iii) the nutrition of tissue, in addition to

(iv) the prediction of limiting conditions for the onset of marginal symptoms of decompression sickness.

The initial distribution of an inert substance in any organ must be effected by its bulk transport in solution by blood while uptake in the more remote regions, not hydrodynamically perfused, must occur by diffusion. Since these processes are in series, they must display interaction in the overall tissue response in which each must exert some finite influence. Neither process may be ignored as representative of insignificant capacity.

The relative contributions of 'stirred' and 'non-stirred' regions in limiting blood-tissue exchange must depend upon both their relative capacities and isolated response functions derived as the quantitative expressions most faithful to the histology of the particular tissue. Before discussing the mathematical models employed for such comparisons a mass balance for non-metabolisable substances is indicated, since this must be independent of any mechanisms or their relative prominence.

5.22 Mass balance

Consider the overall volume (V) of a particular tissue type to which the total arterial blood flow is $\dot{Q}_A$ and from which the fluid

drainage rate via the lymphatic system is $\dot{Q}_L$. A simple mass balance for water between blood and peri-capillary filtrate gives the total venous blood flow ($\dot{Q}_V$) from that volume as:-

$$\dot{Q}_A - \dot{Q}_V = \dot{Q}_L \qquad (15)$$

$\dot{Q}_A$, $\dot{Q}_V$ and $\dot{Q}_L$ have the dimensions of volume per unit time.

For inert solutes, where p_A, p_V and p_i are the arterial, venous and lymph tensions respectively, the net rate of influx of inert substances = $S_B(\dot{Q}_A p_A - \dot{Q}_V p_V) - S_i \dot{Q}_L p_i$ where S_B and S_i are the solubilities in blood and peri-capillary filtrate respectively - expressed in accordance with Henry's law as the concentration in equilibrium with unit partial pressure of the substance. If S_T is the corresponding value averaged over all zones of the tissue for which p_T is the mean tension,

$$\text{Net rate of uptake} = VS_T \frac{\partial(p_T)}{\partial t} = S_B(\dot{Q}_A p_A - \dot{Q}_V p_V) - S_i \dot{Q}_L p_i \qquad (16)$$

Substituting for $\dot{Q}_V$ (equation 15), the above expression becomes:-

$$\frac{\partial(p_T)}{\partial t} = s\left[B(p_A - p_V) - \dot{Q}_L(s'p_i - p_V)/V\right] \qquad (17)$$

where B is the blood perfusion rate ($\dot{Q}_A/V$), s is the blood:tissue partition coefficient (S_B/S_T) and s' is the peri-capillary filtrate: blood partition coefficient (S_i/S_B).

If lymph and venous concentrations are assumed to be equal then $s'p_i = p_V$ and equation 17 reduces to:-

$$\frac{\partial}{\partial t}(p_T) = sB(p_A - p_V) \qquad (18)$$

For a given input of arterial tension, the above equation contains one unknown too many to give a solution for p_T. It is this degree of indeterminancy which has encouraged many authors to approximate the system to the nearest limiting case in order to avoid any mathematical complexity.

The uptake or elimination of an inert substance must lie between the extreme cases of exchange being totally circulation-limited. or totally diffusion-limited.

5.23 Circulation limiting

The assumption that blood perfusion limits exchange presumes that there are no tension gradients, the substance in the blood leaving the tissue being in equilibrium with that in the tissue. This is expressed quantitatively by the approximation $p_T = p_V$ which then enables equation 18 to be solved.

For a step in arterial tension defined by $p_A = 0$ for $t \leq 0$ to $p_A = P_A$ for $t > 0$, integration gives:-

$$p_T = P_A \left(1 - \exp(-sBt) \right) \qquad (19)$$

If the approximation is justified, then the experimentally -determined exponential constants (e.g. λ values in fig. 17), would appear to provide a very simple means of determining local blood perfusion rates. Such an interpretation has been placed upon time constants by Kety (1951) and Jones (1951), and has since been widely used for determining blood perfusion rates by many including Hyman et al (1959) for skeletal muscle, Thorburn et al (1963) for kidney and Johansson et al (1964) for the myocardium.

5.24 Diffusion limiting

There are several alternatives in a diffusion-limited exchange, depending upon whether the resistance to mass transfer is taken as concentrated in the endothelial lining or not. If the former then the application of Fick's law to the capillary wall of thickness (z) and effective surface area (A) per unit volume of tissue gives:-

$$\text{Net rate of uptake} = D_m A(p_A - p_T)/z$$

where D_m is the diffusion coefficient of the capillary membrane.

Combination with equation 16 gives:-

$$\partial(p_T)/\partial t = k(p_A - p_T)$$

where $k = D_m A/zS_T V$.

Integrating the above differential equation for a step in arterial tension defined by $p_A = 0$ for $t \leq 0$ to $p_A = P_A$ for $t > 0$,

$$p_T = P_A \left(1 - \exp(-kt)\right) \qquad (20)$$

Thus another simple exponential response would be forecast - similar to equation 19.

However, any model must become circulation dependent if the blood perfusion is lowered until appreciably less solute is mechanically transported to the capillary walls than they are capable of transmitting.

5.25 Perfusion and endothelial membrane controlling

Since it has been assumed that extravascular tissue is effectively "fully-stirred" in both the preceding extreme cases, their combination to give a model incorporating both resistances would seem the next logical step. Morales and Smith (1944, 1945a, 1945b, 1948) have tried several such arrangements in modifying and developing the original ideas of von Schrotter (1906), Zuntz (1897), and Teorell (1937) to derive the overall uptake of an inert substance as a function of:-

(i) Arterial tension,
(ii) fat-water solubility ratio of the solute,
(iii) extravascular lipid content,
(iv) tissue blood volume,
(v) tissue volume,
(vi) rate of blood flow, and
(vii) tissue permeability in which all diffusional resistance is assumed to be confined to the capillary wall.

Although more comprehensive than most, their approach does not allow for any possible extravascular heterogeneity; the termination of their treatment at the endothelial membrane circumvents any need to specify any geometric form for the 3-dimensional structure of tissue. However, if the latter assumption is not made, then bulk diffusion must be considered as an alternative to membrane permeation as the rate-limiting process in the second extreme case (section 5.24).

5.26 Bulk diffusion

A geometric parameter must now be introduced such that the application (Appendix II) of Fick's law as:-

$\nabla^2 p = \frac{1}{D}\left(\frac{\partial p}{\partial t}\right)$, where p is the inert gas tension, enables the overall uptake (G) to be expressed in the form:-

$G = \text{Funct.}(r,t)$

r is a radial ordinate.

One model to which this expression is readily applied is that of Krogh (1918a). On the basis of microscopic observations, he illustrates the vascular bed as comprising cylindrical capillaries with parallel axes spaced on a regular triangular pitch. If extravascular tissue is still regarded as effectively homogeneous, the volume influenced by one capillary approximates quite closely to a very long annulus whose outer

surface is impermeable. This now becomes a case for exact mathematical analysis - Appendix II, whose results are summarised in fig. 4. This indicates that the response for a step in arterial tension is given by:-

$$G = G_{\infty}\left[1 - \frac{4}{(b^2-a^2)} \sum_{n=1}^{\infty} \frac{\exp(-\alpha_n^2 D t)}{\alpha_n^2\left[(J_o(a\alpha_n)/J_1(b\alpha_n))^2 - 1\right]}\right] \qquad \text{(VII)}$$

where $G = G_{\infty}$ for $t = \infty$, b is the radius of influence of one capillary of radius (a), α_n is the n^{th} root, real and positive, of the equation:-

$$J_o(a\alpha_n)\, Y_1(b\alpha_n) = Y_o(a\alpha_n)\, J_1(b\alpha_n) \qquad \text{(VIII)}$$

in which J and Y signify Bessel and Neumann functions respectively according to the nomenclature defined by Watson (1944).

Using equation VII, Kety (1951) has concluded that blood perfusion must be rate-limiting on the grounds that a tissue of average vascularity would attain 95% saturation by diffusion alone within 1 second of any change in capillary blood tension. Similar calculations are presented by Thews (1960 and 1963) for O_2, and by Forster (1964) for N_2O. The latter reaches the conclusion that diffusion can be neglected for all but the most avascular tissues on the basis that, to display a half-saturation time of even 54.7 seconds, the radius (b) of the tissue cylinder, would need to be 2194. Forster regards such a value as "unreasonably large".

5.27 The vital issue

While they may appear conclusive, the above calculations are all based upon values of diffusion coefficients determined by steady-state methods - particularly those of Krogh (1918a). The use of such values in transient equations is only permissible if extravascular tissue can be regarded as a medium of homogeneous diffusional resistance.

If a very simple analogy may be permitted to emphasize this vital point, tissue might be simulated by a rectangular block of copper into which has been cast lumps of asbestos. Heat transmitted between opposite parallel faces, maintained at different temperatures, would tend to take pathways within the boundaries of the copper. The apparent thermal conductivity determined by such a steady-state experiment should thus be of the same order of magnitude as that of copper, unless the asbestos content is excessive. However, such a value would be meaningless in calculating the overall thermal uptake of the same block totally immersed in a stirred bath of hot liquid. In the transient case the rate-limiting parameters are now the conductivity and geometric distribution of the asbestos since the latter represents the majority of the potential thermal capacity.

Thus the validity of the conclusions of Kety, Thews, Forster, Morales and Smith, in dismissing diffusion as rate contributing, depend entirely upon the presumption that extravascular tissue has homogeneous transmission properties. While any histological section indicates the heterogeneous morphology of tissue, the answer would appear to lie in the relative diffusion coefficients of the individual phases present.

5.3 DIFFUSION COEFFICIENTS

5.31 Steady-state values

The first doubts upon the validity of using diffusion coefficients determined by steady-state methods in transient equations are perhaps Krogh's remarks that it was necessary to wait some 20-30 minutes before steady transmission across tissue sections could be obtained. Using his diffusion coefficient of 4×10^{-4} cm.^{2} min.$^{-1}$ for N_2 in muscle, this would seem excessive for a uniform material in which his thickest section (290μ) should possess a transient response of half-saturation time of less

than 1 minute. It would indicate the presence of a much slower phase, contrary to the popular belief summarised by Forster's statement that "cell boundaries and tissue membranes appear to present little resistance to the diffusion of chemically inert gases".

It may be considered most significant that Krogh's 'steady-state' values of tissue diffusion coefficients range from 0.25 to 0.5 of those for the corresponding gases in water.

These factors are of the order to be anticipated for the fraction of cross-sectional area of tissue occupied by interstitial fluid whose volume fraction can range from 0.11 to 0.55 according to the sodium space values of Manery and Hastings (1939).

Hence Krogh's results are open to the interpretation that steady-state transmission across excised sections occurs largely by diffusion within the continuous extracellular phase. This implies geometric blocking of diffusion by cells in the manner illustrated earlier by use of a thermal analogy. However, such a conclusion is only justified if the diffusion coefficient of cellular material is several orders less than that in plasma and peri-capillary filtrate.

5.32 Transient diffusion coefficients

Such gross heterogeneity would certainly appear to be the case for polar substances at least. For the isolated fibres of a frog's sartorius muscle, Fenichel and Horowitz (1963) record values of diffusion coefficients ranging from 1.8×10^{-6} to 1.8×10^{-8} cm^2 $min.^{-1}$ for ten compounds - urea and various amides, amines and alcohols. This is several orders lower than the value of 8.2×10^{-4} cm^2 $min.^{-1}$ for urea in water (Perry, 1950). Dick (1959) has obtained coefficients in the range 9×10^{-7} - 3×10^{-9} cm^2 $min.^{-1}$ for diffusion of water in the protoplasm of various living cells, compared with 6×10^{-4} cm^2 min. for the self diffusion coefficient of water.

Values similar to those of Fenichel and Horowitz have been obtained by Harris and Burn (1949) for ^{24}Na in skeletal muscle fibres, although the use of charged particles leaves the results open to many alternative interpretations.

Considering molecules which are both chemically inert and non-polar, a value of 1.37×10^{-8} cm^2 $min.^{-1}$ for the diffusion coefficient of acetylene in the cytoplasm of skeletal muscle, has been derived from experimental data (section 5.48). This refers to exchange in the inner thigh muscle of a rabbit in which the initial uptake has been effected by both blood perfusion and exposure of an excised tissue section to an atmosphere of the inert gas.

A possible explanation for this value lying closer to the lower limit of the range of diffusion coefficients determined by Fenichel and Horowitz is the lower water content of rabbit muscle (77%)* compared with that of frog muscle (78.9 - 81.6%)*. If these values are any reflection of cellular compositions, the difference should have an appreciable effect upon the transmission properties as determined by hydrogen and other intermolecular bonding. The latter explanation is propounded by Fenichel and Horowitz to account for the enormous difference between values of the diffusion coefficient for the same gas in water and cellular material. This approach would seem well justified if cytoplasm, as a gel, is regarded as a phase intermediate between liquid and solid. Diffusion coefficients for the same substance frequently change by factors of the order of $10^5 - 10^8$ upon melting of the medium.

The foregoing explanation could account for the value of 0.129 $min.^{-1}$ (section 8.61) derived from the analysis of practical

*values from Altmann and Dittmer (1964).

conditions for the onset of marginal symptoms of decompression sickness. Taking the capillary radius (a) as 3.0 - 3.65 microns (section 8.63), the intracellular diffusion coefficient (D) would be $1.16 \times 10^{-8} - 1.72 \times 10^{-8}$ $cm^2\ min^{-1}$. On the other hand, a capillary diameter of 8.0μ (Burton, 1954) would give $D = 2.56 \times 10^{-8}$ $cm^2\ min^{-1}$. This lies within, yet towards the lower limit of the range of intracellular diffusion coefficients determined by Fenichel and Horowitz as $1.8 \times 10^{-6} - 1.8 \times 10^{-8}$ $cm^2\ min^{-1}$ for a variety of compounds in frog muscle fibres.

5.33 Conclusions

The feature of the results quoted in the preceding section would seem to be the unanimous deviation of values of diffusion coefficients determined by transient methods from the corresponding values estimated by steady-state methods. Moreover, they invariably deviate by a factor of $10^{-4} - 10^{-2}$ from those for the corresponding solutes in water.

This suggests that overall steady-state values retain little meaning when used in transient equations for tissue exchange, and that Kety, Thews and Forster were not justified in concluding that circulation alone is rate-limiting on the basis of such calculations.

A more realistic approach would require accounting for the individual transmission properties of each phase, their particular geometric distribution, and their overall interaction.

5.4 DERIVATION OF A GENERAL MODEL

5.41 General

In deriving a mathematical model, the foregoing argument emphasizes the need to differentiate between intracellular and extracellular regions. The latter effectively includes those regions which

are hydrodynamically perfused, and those in which the diffusion coefficient is appreciably greater than that of cytoplasm.

5.42 Compartmental models

With ions there is the additional barrier of the membrane itself, although this is sometimes afforded the properties of a 'physiological pump' for cations (Davson, 1964c). The membrane is taken as representing the total resistance to the uptake of sodium by cells in the compartmental models of Conn and Robertson (1955), Dobson and Warner (1957) and Persoff (1960). Persoff has demonstrated the superiority of such an approach over use of the linear overall bulk diffusion equations for interpreting ^{24}Na exchange data. This author accounts for the interaction between processes in series, although he does not terminate his analysis as expressions in the form conventionally used by system control analysts, e.g. Muller-Girard (1955) for the simplest mathematical manipulation. A comprehensive analysis of the response of 'catenated' compartments is presented by Robertson (1963).

5.43 Combined bulk diffusion

The perturbation terms (see Thaler and Brown, 1960) characteristic of such interactions are omitted by Perl et al (1965) in their analysis of data recorded by Rackow et al (1965) for the simultaneous elimination of nitrous oxide and cyclopropane from the whole body. They attempt to account for deviations of gas elimination data from a purely perfusion-limited approach by postulating linear overall bulk diffusion between the four principal tissue types into which they divide the human body.

However, they ignore the interaction between such inter-tissue diffusion and their initial uptake limited by blood perfusion. This would seem a gross approximation since the circulation close to any such postulated tissue interface must modify greatly the concentration contours implied by use of a bulk diffusion equation. Since many parameters are needed to describe the division of contact between the various tissue types the system is just determinant, i.e. the equal numbers of equations and unknowns provide no scope for proof of their model from their own data.

The case of diffusion into standard geometric forms, with simultaneous chemical reaction, has been well covered by Roughton (1952). However, one of the most realistic approaches, and least approximate mathematically, is probably that of Harris and Burn (1949). They take frog sartorius muscle to be a plane sheet of fluid of thickness (L) in which are immersed long parallel cylinders of radius (b) separated by extracellular channels of mean length L. Flux equations are then derived as partial differentials in time (t) and distance (z) in the net direction of diffusion ($0 \geq z \geq L$). Solution of these expressions gives mean values, averaged over z, for the intracellular solute concentration as $\bar{C}_c$ and corresponding extracellular concentration $\bar{C}_x$ as:-

$$\bar{C}_c = \frac{8C_c^o}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{(2n-1)^2} \left[\frac{\rho_2 \cdot \exp(\rho_1 t) - \rho_1 \cdot \exp(\rho_2 t)}{(\rho_2 - \rho_1)} \right]$$

$$\text{and } \bar{C}_x = 8C_x^o \sum_{n=1}^{\infty} \left[\frac{1}{(2n-1)^2 \pi^2} \left[\frac{\rho_2 \cdot \exp(\rho_1 t) - \rho_1 \exp(\rho_2 t)}{(\rho_2 - \rho_1)} \right] + \frac{D_x}{\eta^2 L^2} \left[\frac{\exp(\rho_1 t) - \exp(\rho_2 t)}{(\rho_2 - \rho_1)} \right] \right]$$

where, for n = 1, 2, 3 etc., ρ_1 and ρ_2 are the roots of:-

$$\rho^2 + \rho\left[\frac{2f}{b}\left(1 + \frac{V_c C_c^o}{V_x C_x^o}\right) + \frac{(2n-1)^2\pi^2 D_x}{\eta^2 L^2}\right] + \frac{2f(2n-1)^2\pi^2 D_x}{\eta^2 L^2} = 0$$

where C_c^o, C_x^o and V_c, V_x are intra and extracellular initial solute concentrations and volumes respectively. D_x is the extracellular diffusion coefficient and f is the surface permeability. The above expressions prove successful for interpreting the exchange of electrolytes, the approach resembling that of Conn and Robertson in so far as membrane penetration is taken as the total resistance to cell permeation. This is demonstrated by the absence of any intracellular diffusion coefficient in their quantitative expressions.

Using the above equations for comparison, Fenichel and Horowitz (1963), conclude that bulk diffusion, rather than surface permeation, is the operative mode of uptake by cells. If such a mechanism holds for the 10 polar compounds used by these authors, it should certainly hold for inert solutes whose molecules possess no dipole moment. The latter should experience no net force of attraction or repulsion for the fixed charges often attributed to membrane structures (see Davson, 1964c).

While bulk diffusion has been shown to be the relevant mode of uptake by skeletal muscle, it is quite probable that bulk diffusion is also the mode of uptake by the cells of many other tissue types. In addition to the complications of cell morphology, the effect of circulation cannot be ignored in deriving a model to represent the normal state of that tissue in the living animal.

5.44 General tissue model

The foregoing emphasis upon bulk diffusion in cells stresses the need for the closest adherence to the true internal geometry. Admittedly the complexity of any histological section indicates that no mathematical model can ever claim to give an exact simulation of the response characteristics of tissue exchange, but it would appear essential for any realistic approach to allow for:-

(i) significant contact between cells, and

(ii) boundaries of profile more random than those of the perfect geometric shapes assumed in previous analyses - Roughton (1952).

These observations have led the writer to postulate a general model incorporating circulation, which is applicable to most tissue types. The two prominent 'phases' are:-

(i) Cellular material of uniform diffusional resistance to inert non-polar solutes, the cells being irregularly distributed and of irregular profile.

(ii) Extracellular fluid comprising plasma and peri-capillary filtrate of diffusion coefficient comparable with that of water, and, in part at least, hydrodynamically perfused by solvent when the circulation is functioning.

Before deriving the overall uptake by such a system, with allowance for interaction between the component phases, it would seem essential to determine the isolated uptake responses of each.

RESPONSE PARAMETERS FOR DIFFUSION INTO PERFECT GEOMETRIC SHAPES

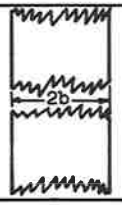
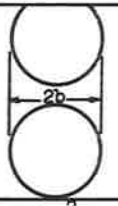
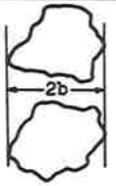
Geometric form	Perfect cases for analysis					Random biological cell
	Annulus (b/a=10)	Annulus (b/a=5)	Parallel slab	Solid cylinder	Solid sphere	
Side view End elevation						
Mass transfer area (A) Volume (V)	$2\pi a$ (per unit length) $\pi(b^2-a^2)$ (per unit length)		$2A$ $2bA$	$2\pi b$ πb^2	$4\pi b^2$ $4\pi b^3/3$	A V
(Ab/V)	0.202	0.411	1	2	3	(Ab/V)
General uptake equation	$G = G_\infty \cdot \left[1 - \sum_{n=1}^{\infty} R_n \cdot \exp(-a_n^2 Dt)\right]$					
R_n for n = 1, 2, 3	$\frac{4b^2}{(b^2-a^2)(ba_n)^2\left[(J_o(aa_n)/J_1(ba_n))^2-1\right]}$		$\frac{8}{\pi^2(2n-1)^2}$	$\frac{4}{(ba_n)^2}$	$\frac{6}{\pi^2 n^2}$	R_n
Root equation for (ba_n)	$J_o(aa_n)Y_1(ba_n)-J_1(ba_n)Y_o(aa_n)$		$\sin(n-1)\pi=0$	$J_o(ba_n)=0$	$\sin(n-1)\pi=0$	$(ba_n)=0$
First R_1 root (ba_1) (ba_2) $(a_2/a_1)^2$	0.958 1.103 4.95 20.1	0.931 0.412 5.72 16.4	0.810 1.571 4.72 9.00	0.692 2.405 5.52 5.27	0.608 3.140 6.28 4.00	R_1 (ba_1) (ba_2) -
Reference to derivation of R_n and (ba_n)	Crank (1956)		Carslaw and Jaeger (1959)			-

Fig. 3

5.45 Response of an isolated irregular cell

The above quantitative interpretation of tissue as a 2-phase system requires some parameter indicative of the relative linear dimensions in which cytoplasm is distributed. Each cell must have a volume (V), a surface area (A) available for exchange with interstitial fluid and a linear dimension - say an effective mean diameter (2b). (Ab/V) is thus a dimensionless group characteristic of the particular cell, and defined in terms of practical parameters. Although not unique to a particular cell, the group provides a simple ordinate for the comparison of shapes too irregular for any feasible description of their boundaries in terms of Cartesian co-ordinates.

Moreover, this comparison can be extended to a sphere, cylinder, flat plate, annulus or any of the other perfect geometric cases in which bulk diffusion can be analysed exactly - see fig. 3. (Ab/V) varies widely from a value of 3 for a sphere to 0 for a cylindrical cavity in an infinite medium, and thus provides a useful abcissa for determining the response constants for the biological case by interpolation.

This interpolation is rendered feasible by the universal form of the time constants ($\alpha_n^2 D$ in fig. 4) necessary to describe the transmission response of any perfect geometric shape. Application of the various sets of boundary conditions to solutions of the general equation for diffusion in a homogeneous medium, $\nabla^2 p = (\partial p/\partial t)/D$, enables the uptake of an inert solute to be described exactly (Appendix II) for all perfect geometric cases in the form:-

$$G = G_{\infty} \left[1 - \sum_{n=1}^{\infty} R_n \exp\left(-\alpha_n^2 Dt\right) \right] \qquad (21)$$

where p is the tension of inert gas, D is its diffusion coefficient in cytoplasm, G is the uptake by the particular shape for a step in the surrounding fluid tension and $G = G_{\infty}$ for $t = \infty$, R_n is the n^{th} coefficient and α_n is the n^{th} root of the ancillary equation particular to each set of boundary conditions. They are calculated for 5 perfect geometric shapes in Appendix II. The first root term, $R_1 . \exp(-k_1 . Dt)$, where $k_n = \alpha_n^2 D$, usually predominates (fig. 3).

Interpolation for the essential constants R_1, α_1, R_2, α_2, etc. of the irregular biological cell is rendered feasible by the smoothness of the curves obtained by plotting these terms against (Ab/V) for the perfect geometric cases.

This is illustrated by plots of $(\alpha_1^2 / \alpha_2^2)$ and $(b\alpha_1)$ in fig. 4. It is thus possible to obtain values for the constants enabling the response of an isolated cell to be expressed by equation 21.

5.46 Response of the isolated extracellular phase

Derivation of the uptake response of isolated extracellular material is a very different matter when the circulation is functioning. Landis and Pappenheimer (1963) discuss evidence for the pervasion of cell walls by solvent suggesting some hydrodynamic perfusion of the interstitial spaces. The increased lymph flow with exercise, demonstrated by White (1933), suggests that the turnover of pericapillary fluid reflects the circulation rate. Thus it would seem reasonable to assume that the extracellular regions behave as though they are a 'fully-stirred' zone. Even

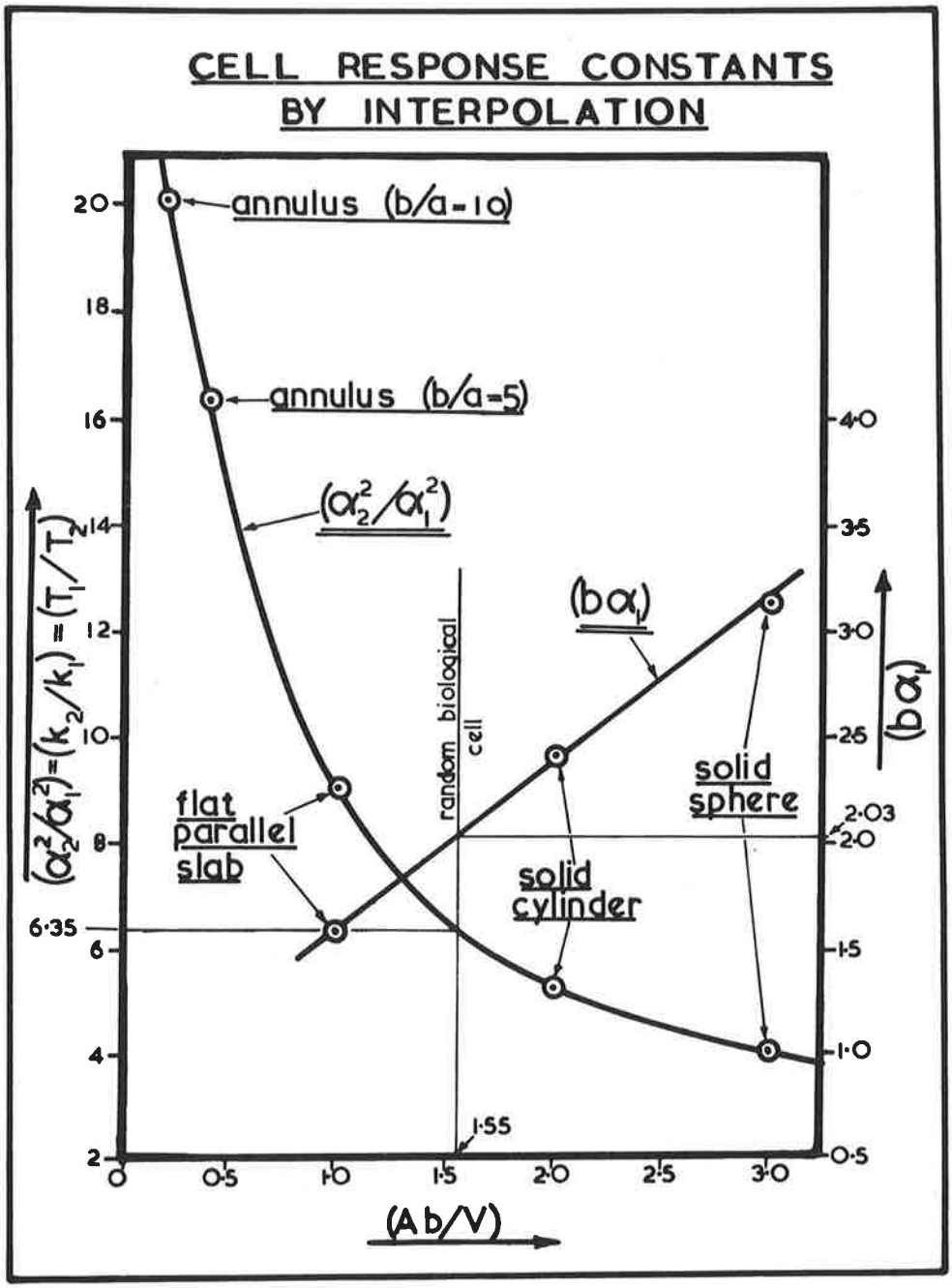

CELL RESPONSE CONSTANTS
BY INTERPOLATION
annulus (b/a=10)
annulus (b/a=5)
(α_2^2/α_1^2)
$(b\alpha_1)$
random biological cell
flat parallel slab
solid sphere
solid cylinder
$(\alpha_2^2/\alpha_1^2)=(k_2/k_1)=(T_1/T_2)$
$(b\alpha_1)$
(Ab/V)
20
18
16
14
12
10
8
6·35
6
4
2
4·0
3·5
3·0
2·5
2·03
2·0
1·5
1·0
0·5
0
0·5
1·0
1·5
2·0
2·5
3·0
1·55

Fig. 4

if there is no solvent motion in the interstitial spaces, the vascularity of most tissues is such that the extracellular regions most remote from an open capillary would attain 95% saturation by diffusion within 1 second of a change in capillary tension. This estimation is similar to the Kety, Thews and Forster type of calculation justifying perfusion as the rate-limiting process within a dilute aqueous medium. The essential difference lies in the fact that the latter authors have envisaged the equivalent 'fully-stirred tank' as the whole tissue whereas, in this approach, its boundaries terminate at the cell walls.

Thus it may be claimed that there are no significant extracellular concentration gradients, a conclusion which implies that both venous blood and lymph drainage leave in equilibrium with extracellular fluid (of tension p_i), i.e. $p_i = p_V = p_L$ (22)

Applying a mass balance for the solute in the extracellular zone:-

$$\text{Net influx} = \dot{Q}_A \cdot S_B \cdot p_A - \dot{Q}_V \cdot S_B \cdot p_V - \dot{Q}_L \cdot S_i \cdot p_i = V_i \cdot S_i \frac{\partial}{\partial t}(p_i)$$

where V_i is the volume of extracellular fluid.

Little error is introduced by equating $\dot{Q}_L \cdot S_i \cdot p_i$ to $\dot{Q}_L \cdot S_B \cdot p_i$ since $S_i \simeq S_B$ for many inert solutes and $\dot{Q}_L \ll \dot{Q}_A$.

Substituting for p_A and p_V (equation 22) and $\dot{Q}_V$ and $\dot{Q}_L$ (equation 15), the above equation reduces to:-

$$(p_A - p_i) = k_i(\partial p_i/\partial t) \qquad (23)$$

where $k_i = s\dot{Q}_A/V_i = sB/\beta_i = 0.693/T_i$ (24)

in which β is the volume fraction of extracellular fluid and T_i is the corresponding half-saturation time for the linear process.

For the isolated process, integration of equation (23) for a step in arterial tension defined by $p_A = 0$ for $t < 0$ to $p_A = P_A$ for $t \geq 0$, gives:- $p_i = P_A(1-\exp(-Bst/\beta_i))$, i.e. a simple exponential resembling equation (19).

If the circulation has stopped, then capillary locations are no longer relevant, and solute must reach the cell walls by diffusion through interstitial fluid from the nearest source of solute. For tissue thicknesses of 100μ or more, extracellular diffusion times can no longer be ignored and k_i must be replaced by k_i' - which is now a function of macro-dimensions. If these dimensions are many times greater than the mean diameters of cells, then the extracellular material may be regarded as a uniform mass of serum of cross-sectional area reduced in proportion to that occupied by extracellular fluid. This would not change the isolated response of that zone if the tissue were cut into the overall form of a flat parallel-faced slab.

Thus for a section of thickness (L), placed upon an impermeable surface and exposed at the other face, fig. 3 gives the time constant for isolated extracellular response as:-

$$k_i' = \frac{\pi^2 D_\omega}{4L^2} = \frac{0.693}{T_i'} \qquad (25)$$

where T_i' is the corresponding half-saturation time, and D_ω is the diffusion

coefficient of water. Little error should be introduced into the response analysis by using only the first root term of the linear bulk diffusion equation since:-

(i) the first term represents 81% of the total response (fig. 3).

(ii) the second root responds 9 times faster so that this and higher roots would display little deviation from the imposed pressure fluctuation at the exposed face.

Extracellular response can thus be expressed in linear form for both the perfused and non-perfused cases.

5.47 Interaction

So far, expressions describing the isolated uptake response of each of the two principal phases have been derived. However, since the extra- and intracellular regions lie in series, account must be taken of their mutual interaction. The resulting perturbation terms are too large to be ignored when deriving the overall tissue response, and represent the source of mathematical complexity. The latter can be reduced to reasonable proportions, however, if the system described can be reduced to a linear equivalent, which is ideally suited for analysis by Laplace transforms (Thaler and Brown, 1960).

While such linearity holds for the extracellular phase, whether circulation is operative or not (equations 23 and 25), the cells present a case far less inducive to analysis. However, the multi-exponential form of their response (equation 21) suggests that each component term,

$R_n.\exp(-\alpha_n^2 Dt)$ in fig. 3. may be regarded as an individual portion of the extracellular material displaying linear response with respect to the interstitial fluid.

The histological model advanced here may thus be transformed to the compartmental equivalent illustrated in fig. 5.

The root terms of the bulk diffusion response (equation 21) are represented as chambers in parallel to each other, yet in series to the interstitial fluid. Over the practical range of response times the third and higher roots are so 'fast' that the capacity they represent may be considered equilibrated with interstitial fluid.

The muscle fibre, recorded by Fenichel and Horowitz (1963) displaying the slowest uptake response, corresponds to a half-saturation time ($t_{\frac{1}{2}}$) of 12.4 minutes. The second root would thus have $t_{\frac{1}{2}}$ = 1.4 minutes (parallel slab) and, for the third, $t_{\frac{1}{2}}$ = 0.5 minutes. Considering the correspondingly reduced capacities (values of R_n) of higher roots, the linear equivalent (fig. 5) should introduce little error in applying the model proposed in this thesis.

However, any model is worthless until proven experimentally.

Since adequate experimental data could not be found in the literature, the experimental program described in section 6.3 was undertaken. Data have been recorded for the uptake of inert non-polar gases by a single tissue type, skeletal muscle of the rabbit, for the two cases of:-

1. Extracellular uptake effected by perfusion,
2. Extracellular uptake effected by exposing an excised tissue section to the gas.

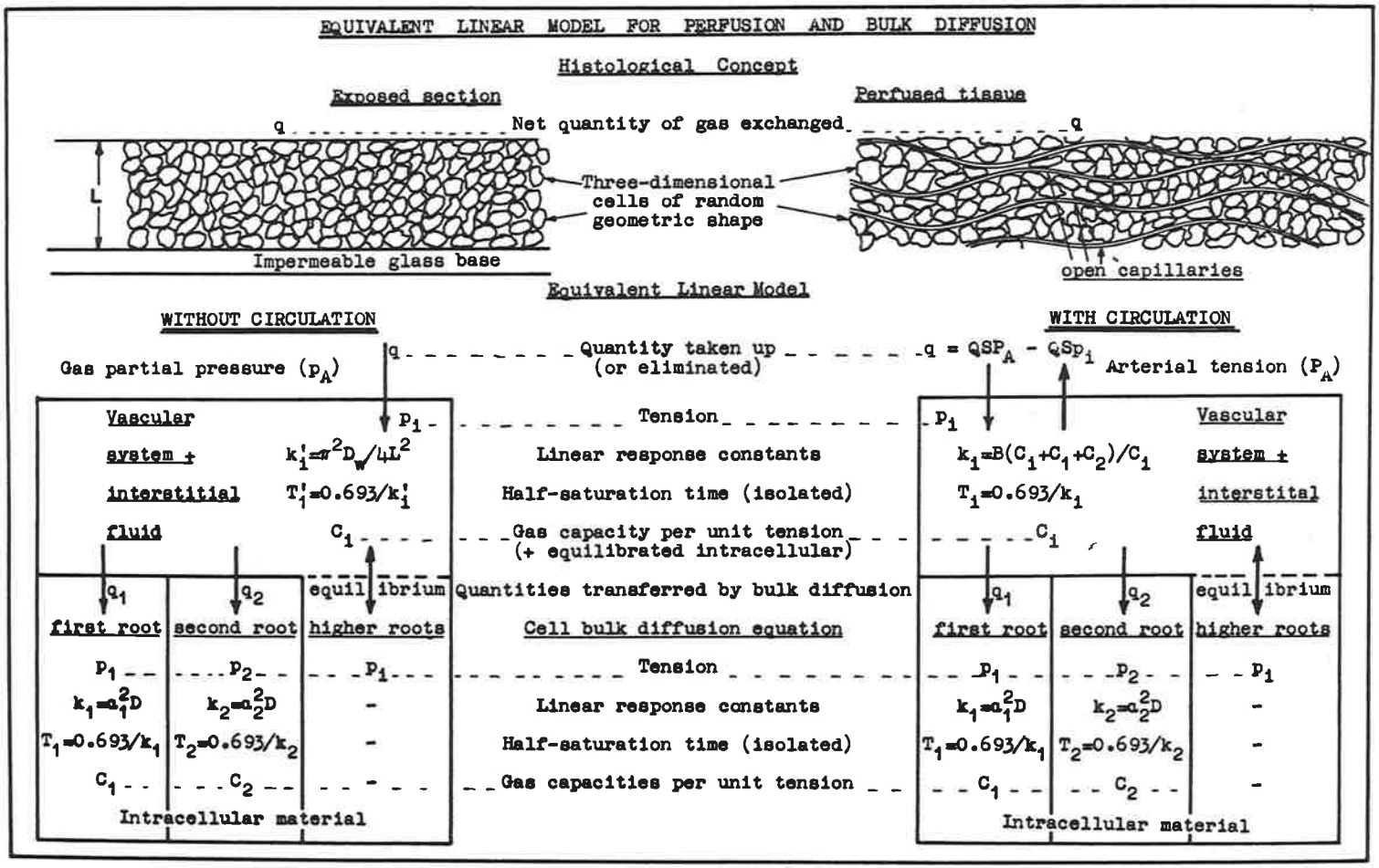

EQUIVALENT LINEAR MODEL FOR PERFUSION AND BULK DIFFUSION
Histological Concept
Exposed section
Perfused tissue
q
Net quantity of gas exchanged
q
L
Three-dimensional cells of random geometric shape
Impermeable glass base
open capillaries
Equivalent Linear Model
WITHOUT CIRCULATION
WITH CIRCULATION
Gas partial pressure (p_A)
q
Quantity taken up (or eliminated)
$q = QSP_A - QSp_i$
Arterial tension (P_A)
Vascular system + interstitial fluid
p_1
Tension
$k_1'=\pi^2 D_w/4L^2$
Linear response constants
$T_1'=0.693/k_1'$
Half-saturation time (isolated)
C_i
Gas capacity per unit tension (+ equilibrated intracellular)
q_1
q_2
equilibrium
Quantities transferred by bulk diffusion
first root
second root
higher roots
Cell bulk diffusion equation
p_1
p_2
p_i
Tension
$k_1=a_1^2 D$
$k_2=a_2^2 D$
Linear response constants
$T_1=0.693/k_1$
$T_2=0.693/k_2$
Half-saturation time (isolated)
C_1
C_2
Gas capacities per unit tension
Intracellular material
$k_1=B(C_1+C_1+C_2)/C_1$
$T_i=0.693/k_1$
Vascular system + interstital fluid
Intracellular material

Fig.5

It was felt that the justification for any postulations would be greatly enhanced if the same model could be used to correlate both sets of data, i.e. where exchange occurred both with and without circulation. Both cases are therefore considered in the following quantitative interpretation of the model.

5.48 Quantitative interpretation of the model

The great advantage of the hypothetical model advanced in fig. 5 is the fact that each inter-compartmental mass transfer process can be expressed quantitatively by a single linear equation. This provides three expressions in addition to three for the transient mass balances - one for each compartment. Such a system is thus ideally suited to analysis by use of Laplace transforms, the mathematics being presented in Appendix IV using the symbols indicated in fig. 5.

Eliminating the transient variables q_1, q_2, P_1, I_2 and p_i from the six equations, q can be readily derived for a step in arterial or external tension, defined by $p_A = 0$ for $t \leq 0$ to $p_A = P_A$ for $t > 0$, as:-

$$q = A_1.\exp(-0.693t/\theta_1)+A_2.\exp(-0.693t/\theta_2)+A_3.\exp(-0.693/\theta_3)$$

with circulation, (26)

OR, $$q = A'_1.\exp(-0.693t/\theta'_1)+A'_2.\exp(-0.693t/\theta'_2)+A'_3.\exp(-0.693/\theta_3)$$

without circulation. (27)

which represent exact solutions if:-

with circulation

$$\theta_1\theta_2\theta_3 = T_1T_2T_i \quad (28)$$

$$\theta_1\theta_2+\theta_2\theta_3+\theta_3\theta_1 = T_1T_2+T_iT_1(1+\beta_2)+T_iT_2(1+\beta_1) \quad (29)$$

$$\theta_1+\theta_2+\theta_3 = T_1+T_2+T_i(1+\beta_1+\beta_2) \quad (30)$$

without circulation

$$\begin{cases} \theta'_1\theta'_2\theta'_3 = T_1T_2T'_i & (31) \\ \theta'_1\theta'_2+\theta'_2\theta'_3+\theta'_3\theta'_1 = T_1T_2+T'_iT_1(1+\beta_2)+T'_iT_2(1+\beta_1) & (32) \\ \theta'_1+\theta'_2+\theta'_3 = T_1+T_2+T'_i(1+\beta_1+\beta_2) & (33) \end{cases}$$

Equations 26-33 are derived in Appendix IV.

If the geometric concept (fig. 5) of the histology of tissue is correct, and remains essentially the same immediately after death of the animal as it was for circulation under anaesthetic, then T_1, T_2, β_1 and β_2 should be the same in both cases for the same gas. Moreover, if these constants are known, then each run with circulation (i.e. each set of θ' values) enables T'_i to be determined according to equation 28, 29 or 30. This provides three separate estimations of the blood perfusion rate (B) as determined from each value of T'_i according to equation 24.

Rather than derive T_1, T_2, β_1 and β_2 from the runs with perfusion, it is simpler to derive them from data recorded for the excised tissue, since a knowledge of T_i from equation 24 effectively reduces a cubic to a quadratic solution. An analysis of such experimental data (fig. 19) is given in table 7.

The following features of table 7 would indicate that the model (fig. 5) is realistic for the interpretation of data from excised tissue:-

1. The close agreement of values of T_1T_2 in line 7, since both T_1 and T_2 should be constant - 2 degrees of determinancy (ξ).

ANALYSIS OF ACETYLENE UPTAKE WITHOUT CIRCULATION (fig. 19)

	Quantity and derivation	Eqn.	Run III	Run IV	Run V	Mean	ξ
1.	L (mm.)	-	2.96	1.91	1.05	-	
2.	experimental results (fig. 19) θ'_1 (min.)	-	52	40.6	30.3	-	
3.	(section 6.34) θ'_2 (min.)	-	22	8.8	5.6	-	
4.	θ'_3 (min.)	-	3.1	3.8	2.8	-	
5.	$T'_i = 0.693 \times 4L^2/\pi^2 D_\omega$ (min.)*	25	26.3	11.0	3.31	-	
6.	$\theta'_1\theta'_2\theta'_3$ (min.^{3})	-	3548	1361	474	-	
7.	$T_1T_2 = \theta'_1\theta'_2\theta'_3/T'_i$ (min.^{2})	31	133.9	124.1	143.8	133.9	2
8.	$\theta'_1\theta'_2+\theta'_2\theta'_3+\theta'_3\theta'_1 = \Sigma\theta'_1\theta'_2$ (min.^{2})	-	1387	544	270	-	
9.	$(T_1+T_2+\beta_1T_2+\beta_2T_1) = (\Sigma\theta'_1\theta'_2-T_1T_2)/T'_i$	32	46.8	38.3	38.8	41.3	2
10.	$(\theta'_1+\theta'_2+\theta'_3) = \Sigma\theta'_1$ (min.)	-	77.1	53.2	38.7	-	
11.	$(\Sigma\theta'_1-T'_i) = T'_i(\beta_1+\beta_2)+(T_1+T_2)$	33	50.8	42.2	35.6	-	1
	Plotting $(\Sigma\theta'_1-T'_i)$ vs. T'_i { gradient = $(\beta_1+\beta_2)$ = 0.69; intercept = (T_1+T_2) = 33.7						

TABLE 7

*$D_\omega = 9.36 \times 10^{-4}$ cm^2 min^{-1} (Perry, 1950).

θ'_1, θ'_2 and θ'_3 are half-saturation times obtained from the experimentally-determined response curve for each run upon excised sections of 'white' inner thigh muscle of the rabbit.

2. The close agreement of values of $(T_1+T_2+T_1\beta_2+T_2\beta_1)$ in line 9, since T_1, T_2, β_1 and β_2 should all be constant - 2 degrees of determinancy (ξ).

3. The linear plot of $\Sigma\theta'$ vs. T'_i since both β_1 and β_2 should be constant in the gradient term $(\beta_1+\beta_2)$, and both T_1 and T_2 should be constant in the intercept term (T_1+T_2) - 1 degree of determinancy (ξ).

Taking mean values:- $T_1T_2 = 133.9 \text{ min.}^2$,

$$T_1+T_2+\beta_1T_2+\beta_2T_1 = 41.3 \text{ min.}$$

$$\beta_1+\beta_2 = 0.69$$

$$T_1+T_2 = 33.7 \text{ min.},$$

these equations give the following values for acetylene in skeletal rabbit muscle:-

$$\left.\begin{aligned} T_1 &= 29.1 \text{ min.} \\ T_2 &= 4.6 \text{ min.} \\ \beta_1 &= 0.51 \\ \beta_2 &= 0.18 \end{aligned}\right\} \; C_2H_2$$

For a tissue with negligible fat content, β_1 and β_2 will remain the same for any gas. T_1 and T_2, representing a pure diffusion process in all cases, should be inversely proportional to the diffusion coefficient for the particular gas. Applying the Graham's law correction factor of $\sqrt{85/26} = 1.81$, the following values should hold for ^{85}Kr:-

$$\left.\begin{aligned} T_1 &= 52.6 \text{ min.} \\ T_2 &= 9.3 \text{ min.} \\ \beta_1 &= 0.51 \\ \beta_2 &= 0.18 \end{aligned}\right\} \; ^{85}Kr.$$

Justification for applying Graham's law is enhanced by the nature of the gases used, which are not only inert but also non-polar. Molecules of these particular diffusing solutes should thus experience very little hindrance by hydrogen or other intermolecular bonding present in the cytoplasm (Fenichel and Horowitz, 1963).

The above values for krypton, derived from excised tissue, enable three separate determinations of perfusion rate to be made for each degree of circulation - if the same geometric model still holds.

ANALYSIS OF ^{85}Kr ELIMINATION WITH CIRCULATION (fig. 17).

Quantity and derivation	Eqn.	Run I	Run II
experimental results (fig. 17) (section 6.33) θ (mins.)	-	86	197
θ_1 (mins.)	-	20.4	27.3
θ_3^2 (mins.)	-	6.7	6.5
$\theta_1\theta_2\theta_3$ (min.^{3})	-	11730	38210
$\theta_1\theta_2+\theta_2\theta_3+\theta_3\theta_1 = \Sigma\theta_1\theta_2$ (min.^{2})	-	2465	7443
$\theta_1+\theta_2+\theta_3 = \Sigma\theta_1$ (min.)	-	113.1	248.8
$T_i = \theta_1\theta_2\theta_3/T_1T_2$ (min.)	28	26.8	87.5
$T_i = (\Sigma\theta_1\theta_2 - T_1T_2)/(T_1+T_2+\beta_1T_2+\beta_2T_1)$ (min.)	29	27.2	90.6
$T_i = (\Sigma\theta_1 - T_1 - T_2)/(1+\beta_1+\beta_2)$ (min.)	30	30.9	110
Mean T_i	-	28.3	96.0
Standard deviation of T_i values	-	6.5%	10.4%
Blood perfusion rate (B) from mean T_i $B = 69.3/(1+\beta_1+\beta_2)T_i$ (ml./100 ml. min.)	24*	1.63	0.48
Opportunities to prove/disprove model (ξ)		2	2

TABLE 8

*s ≈ 1 for an aqueous type and $\beta_i = \frac{C_i}{C_i+C_1+C_2} = \frac{1}{1+C_1/C_i+C_2/C_i} = \frac{1}{1+\beta_1+\beta_2} = 0.66$

θ_1, θ_2 and θ_3 are half-saturation times obtained from the experimentally-determined response curve for each run using the inner thigh muscle of a rabbit.

The agreement between the three determinations of perfusion rate for each degree of anaesthesia was rather better than anticipated. It indicates that the geometric model outlined in Fig. 21 is realistic. The higher standard deviation in Run II (table 8) may be attributed to the poorer control of the degree of anaesthesia.

While tables 7 and 8 would provide sufficient data for making a comparison between diffusion and circulation as the rate-limiting process in this particular tissue, it is interesting to note that the T_1 and T_2 values common to both perfused and non-perfused systems give $T_1/T_2 = 6.35$. According to the plots (fig. 4) of basic response parameters summarised in fig. 3 for the perfect geometric forms, $\alpha_2^2/\alpha_1^2 = 6.35$ corresponds to $Ab/V = 1.55$, i.e. an effective reduction of $(2 - 1.55)/2$ in the area of a perfect cylinder available for mass transfer from interstitial fluid. This would suggest contact between neighbouring muscle fibres, in the undisturbed state, to the extent of approximately 22% of their surface area. This contact is visualised in the form presented by Wiedemann (1963) whose illustration is reproduced in fig. 6.

The same value of $Ab/V = 1.55$ corresponds to $b\alpha_1 = 2.03$ (fig. 4). But, from fig. 5, $T_1 = 0.693/D\alpha_1^2$ minutes i.e. for acetylene:-

$$D/b^2 = 0.579 \text{ min.}^{-1}.$$

It is difficult to know what value to take for the effective mean diameter (2b) of a cell of random geometric form. However, if 2b is taken as equal to the intercapillary distance for vasodilated gastrocnemius 'white' rabbit muscle, then Kety's (1951) capillary count for this tissue gives $b = 15.4\mu$, and thus:-

$$D = 1.37 \times 10^{-8} \text{ cm}^2 \text{ min}^{-1} \text{ for acetylene.}$$

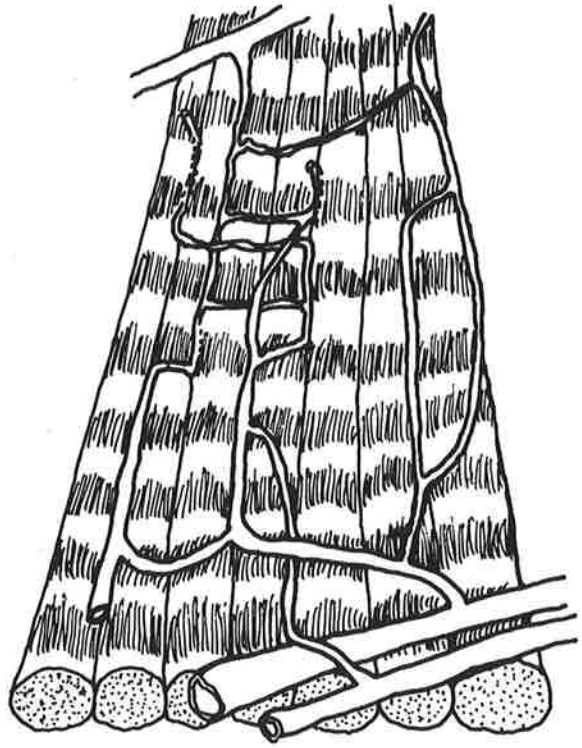
The significance of this value is discussed in section 8.65.

5.49 Implications

The foregoing analysis is rendered feasible by the time constants, λ_1, λ_2, λ_1', λ_2' etc. recorded in figs. 17 and 19, being so clearly

MUSCLE FIBRES

ILLUSTRATING MUSCLE BANDS & CAPILLARY VESSELS



RE-DRAWN FROM WIEDEMANN (1963)

Fig. 6

defined. This occurs by virtue of the large number of points (80-120) obtainable for each scintillation counter or dilatometer run.

The realism of the proposed model, applied to 'white' skeletal rabbit muscle, may be assessed from a comparison of similar fundamental quantities derived by separate means in tables 7 and 8. With three equations (28, 29, 30 or 31, 32, 33) for each of five runs and only six basic unknowns (T_1, T_2, β_1, β_2 and the two perfusion rates) the system is over-determinant, their being nine opportunities to prove, or disprove, the model. These are indicated in the columns headed ξ. Mathematically, the evidence could have been presented more convincingly if the same quantity, say T_1 or T_2, had been determined ten times.

The quantitative incorporation of the concept of a 3-dimensional cell of random profile seems a reasonable offer in mitigation for the gross geometric irregularities observed in most histological sections.

While the method affords no means of estimating the true volume fraction of the interstitial fluid and vascular system, devoid of rapidly equilibrating cellular material, the estimated 22% contact between muscle fibres seems to be of a reasonable order. The same may be said of the blood perfusion rates of 1.63 and 0.48 ml/100 ml. min determined for light and deep anaesthesia (table 8).

While a value of 15.4μ for the effective radius of a cell may seem open to question, the model would appear sufficiently well proven to claim that the diffusion coefficient of intracellular material is within an order of values determined by other transient methods. Thus inert

non-polar compounds would appear to have values of D in rabbit muscle fibres roughly 10^4 times smaller than those for the same gases in water. However, it is not essential to determine diffusion coefficients to demonstrate this gross heterogeneity between intra- and extracellular material.

Whether the concept of an irregular cell is justified or not, it would appear most significant that two out of three of the fundamental time constants extracted by the foregoing analyses are the same for each run. This is particularly relevant to the diffusion vs. perfusion controversy since, after a Graham's law adjustment, they are also the same whether the circulation is operative or not. This serves to support the belief that they refer to a purely diffusional process. Corresponding to half-saturation times of T_1 = 52.6 minutes and T_2 = 8.3 minutes for krypton, they represent delays comparable to that imposed by circulation for which T_i = 28.3 minutes for light anaesthesia. Representing processes in series, these values indicate that neither would predominate to the extent that the other could be ignored. However, diffusion would be at least 90% limiting at high perfusion rates such as the values of 30-40 ml/100 ml minute associated with exercise. This is in direct agreement with the radiosodium clearance curve of Renkin(1958) for dog skeletal muscle.

While the foregoing comparison refers to the 'white' skeletal muscle of the rabbit, it seems quite probable that a similar shift of emphasis from circulation towards diffusion as rate-limiting might well apply to other tissues. While autoradiographs, such as employed by

Thorburn et al, (1963) may be used to identify experimental elimination constants with the particular tissue types comprising an organ, they would most likely represent only the slowest terms ($n=1$ in fig. 3), for their particular regions.

While relevant to decompression sickness, the foregoing analyses make the more serious implication that there is little justification in the popular determination of regional blood flow rates as the experimental time constants obtained by direct response analysis (i.e. λ_1, λ_2, and λ_3 in fig. 17). To allow for diffusion, a far more rigorous mathematical treatment is indicated, based upon a realistic model for which one suggestion is presented in this section.

Before adapting the model to the tissue type critical in diving, a check must be made of its ability to explain the chief examples of many facets of blood-tissue exchange.

5.5 MODEL RELEVANT TO DECOMPRESSION SICKNESS

5.51 General

The foregoing discussion and derivations infer that diffusion would make a far larger contribution towards limiting inert gas uptake than is generally accepted in the literature, (e.g. Forster, 1964). However, this revised contribution has only been shown to exceed all others in limiting blood:tissue exchange in the case of skeletal muscle, although it could apply elsewhere.

5.52 The worst case

The selection of a mathematical model for predicting marginal symptoms of decompression sickness suffers from the extreme disadvantage of not knowing with certainty which is the critical tissue type. However, there is very good reason to believe that the site of pain is closely connected to the locomotor system (section 3.23). This proximity of the critical tissue type to skeletal muscle thus indicates that the foregoing discussion of processes contributing to exchange limitations, and the model of the irregular cell, could be relevant to this case - particularly if tendon or supporting tissue is regarded as a mechanical extension of muscle fibres.

If the concept of irregular cellular boundaries is accepted, then the worst cases for desaturation must occur in the few random instances where two or more cellls would completely envelop a capillary. While these may represent no more than several occurrences in several million possible sites, these would be the locations which would retain the largest quantities of separated gas if nucleated during decompression.

Such sites would represent the particular case of the general model expounded in section 5.4, in which the extracellular region is reduced to the intravascular content.

If diffusion coefficients in cytoplasm are really smaller than those for water by the factor of about 10^{-4} derived earlier, then such restriction in exchange is further enhanced if the alternative source of extracellular solute nearest to the isolated capillary is another capillary.

THE WORST POSSIBLE CASE

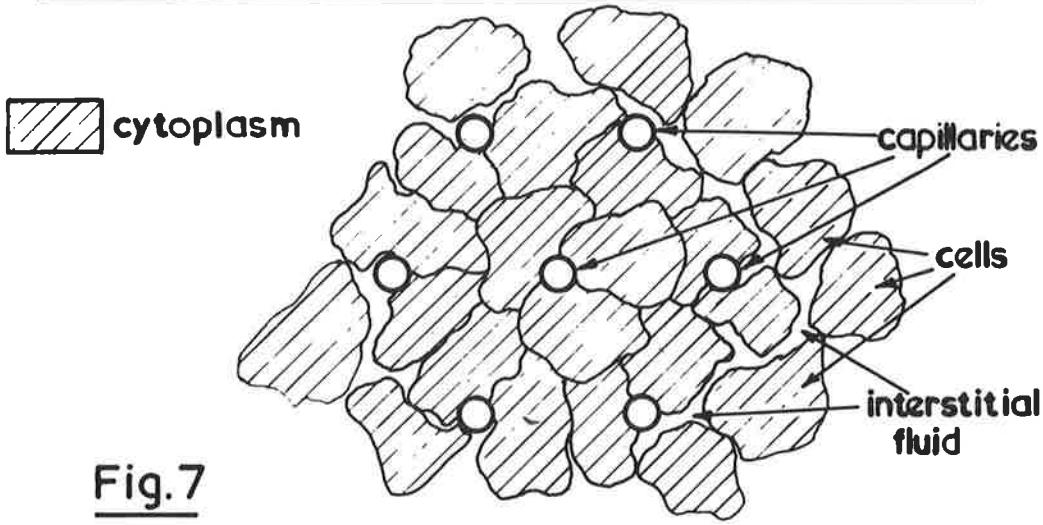


Fig.7

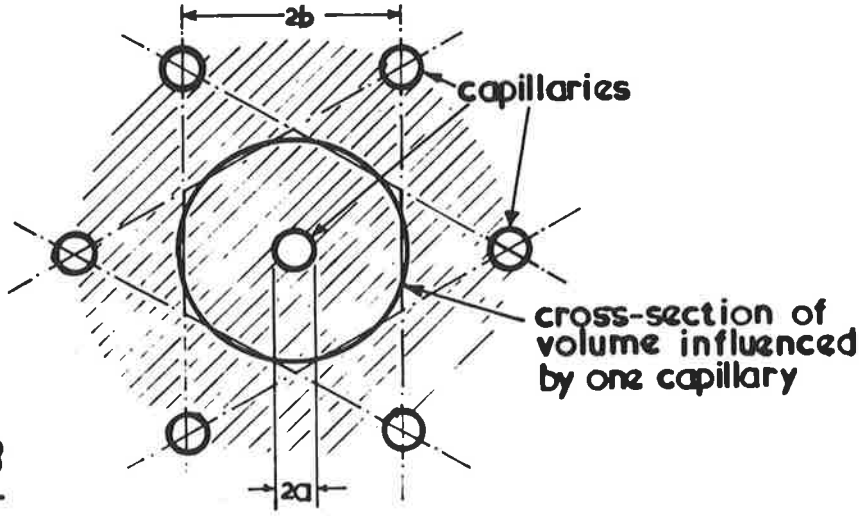


Fig.8

The worst possible case is therefore that in which the irregular distribution of cells has led to a capillary being separated from its nearest neighbours by cytoplasm and the appropriate membranes only. Such a possible occurrence is illustrated in fig. 7.

5.53 Model for decompression sickness

The few sites representing the worst possible location for phase separation may be expressed quantitatively as the particular case of the general model (section 5.4) in which:

1. The extracellular volume (V_i), in equation 24, is reduced to the value for the intravascular content for which Haldane and Priestley (1935b) quote a general value of 4%. Thus $\beta_i = 1/(1+\beta_1+\beta_2)$ is reduced from 0.66 (section 5.48) to approximately 0.04. Hence the half-saturation time (T_i) of the extracellular zone should be reduced to 1-2 mins. under a similar state of anaesthesia, but should be even more rapid under normal conditions. Hence little error is introduced by equating capillary to arterial blood tension of the inert gas, i.e. from equation V.

$$p = x(P - p_w) \text{ , for } r \leq a. \qquad \text{(IX)}$$

2. Any error introduced by the above approximation is further reduced by the increase in half-saturation times (T_1, T_2) corresponding to the roots of the equation for bulk diffusion into the extracellular zone. The area per unit length available for mass transfer with the cell is reduced to $2\pi a$, thus increasing $T_1 = 0.693/\alpha_1^2 D$ (fig. 3) for C_2H_2 from 29.1 mins. up to a value in the region of 64 mins. This figure is reached on the basis that $a\alpha_1 = 0.285$ for $b/a = 5$ (fig. 4) and $D = 1.37 \times 10^{-8}$ cm^2 min^{-1} (section 5.48).

Hence little error should be introduced by ignoring the effect of circulation, having a half-saturation time of 1-2 mins., in series with intracellular material having a half-time in the region of 64 mins. The worst possible case may thus be regarded as one in which the capillary tension of inert gas may be taken as equal to the alveolar value (equation IX), intercapillary uptake occurring by radial diffusion into the intervening cytoplasm. This is illustrated in the mathematical model shown in fig. 8 which retains the Krogh concept of capillaries of radius (a), spaced on a regular triangular pitch of distance 2b between centres.

5.54 Radial diffusion

The application of Fick's law to a mass balance for the inert gas at any point within an isotropic medium may be expressed quantitatively (Carslaw and Jaeger, 1959) as:

$$\nabla^2 p = \frac{1}{D}\left(\frac{\partial p}{\partial t}\right)$$

It is shown in Appendix II that simple radial coordinates may be used, when the above equation reduces to:

$$\frac{1}{r} \cdot \frac{\partial}{\partial r}\left[r \left(\frac{\partial p}{\partial r}\right)\right] = \frac{1}{D}\frac{\partial p}{\partial t} \qquad (X)$$

where r is a radial co-ordinate.

From fig. 8, it can be seen that little error should be introduced if the hexagonal form of the cross-section of the volume of influence of one capillary is approximated to a circle of radius b. The cytoplasm influenced by that capillary may thus be described as a hollow cylinder of infinite length and radial dimensions $a \leq r \leq b$.

For a step in capillary tension defined by: $(\Delta p)_a = 0$ for $t \leq 0$ to $(\Delta p)_a = x(\Delta P)$ for $t > 0$, at $r \leq a$, the tension at radius (r) has been derived from equation 209 in Appendix II as:-

$$(\Delta p)_r = x(\Delta P)\left[1 - \pi \sum_{n=1}^{\infty} \frac{(J_o(r\alpha_n)Y_o(a\alpha_n) - Y_o(r\alpha_n)J_o(a\alpha_n))\exp(-\alpha_n^2 Dt)}{\left[(J_o(a\alpha_n)/J_1(b\alpha_n))^2 - 1\right]}\right]$$

$$= x(\Delta P)\Phi(r,t) \qquad \text{(XI)}$$

where $\pm\alpha_n$ are the roots, all real and simple, of equation VIII.

The total gas (G), expressed as a volume (reduced to standard pressure and body temperature), entering unit length of extravascular tissue by virtue of the step in absolute pressure (ΔP), may be obtained by applying Fick's law to the capillary wall, i.e.

$$\frac{dG}{dt} = -2\pi aDS \left(\frac{\partial p}{\partial r}\right)_{r=a}$$

where the net solubility of the inert gas in cellular material (S) is expressed as a volume of gas (reduced to standard pressure and body temperature) per unit volume and per unit partial pressure.

From the application of the above expression to equation XI, it can be seen from equation 212 in Appendix II that the gas uptake per unit volume of extravascular tissue (g) may be derived as:-

$$g = G/\pi(b^2 - a^2) = x(\Delta P)\, S\psi(t) \qquad \text{(XII)}$$

where $$\psi(t) = 1 - \frac{4}{((b/a)^2 - 1)} \sum_{n=1}^{\infty} \frac{\exp(-\alpha_n^2 Dt)}{(a\alpha_n)^2\left[(J_o(a\alpha_n)/J_1(b\alpha_n))^2 - 1\right]} \qquad \text{(XIII)}$$

since $$\frac{4}{((b/a)^2-1)} \sum_{n=1}^{\infty} \frac{1}{(a\alpha_n)^2 \left[(J_0(a\alpha_n)/J_1(b\alpha_n))^2 - 1 \right]} = 1$$

Thus equation XI enables the tension of inert gas to be determined at any point and time (t) following a step in absolute pressure (ΔP). The total uptake of inert gas per unit volume of extravascular tissue is given by equation XII.

5.55 Approximations

In justification for neglecting the effect of circulation, in the worst possible case only, it has been shown that the half-time of the first root may be of the order of 4 times greater than that for the general model of the irregular cell (section 5.53). However, all roots of the same Fourier series would be increased by similar factors, greatly increasing the error introduced by the original assumption that the capacity represented by the third and higher root terms may be considered equilibrated with extracellular fluid. Hence, in the worst possible case, $\Psi(t)$ in equation XII cannot be taken as simply the sum of two exponential terms, the analysis of decompression data requiring the full use of equation XIII.

However, for dives of short duration, the number of terms which become significant relative to the first ($n = 1$) in equation XIII may be quite large. Fortunately, for small values of t there are a number of good approximations.

Until molecules diffusing from one capillary meet those from another, the boundary condition at $r = b$ has no effect. The cytoplasm may then be regarded as an infinite medium with a hollow cylindrical cavity of radius (a), from which equation 213 (Appendix II) gives:-

$$\Psi(t) \simeq \frac{8}{\pi^2((b/a)^2-1)} \int_0^t \int_0^\infty \frac{\exp(-Du^2t)\partial u.\partial t}{u\left[(J_o(au))^2+(Y_o(au))^2\right]} \qquad \text{(XIV)}$$

Appendix II contains further approximations for $\Psi(t)$ until, for the smallest values of t, equation 216 gives:-

$$\Psi(t) \simeq 4\sqrt{Dt/a^2}/\pi((b/a)^2-1) \qquad \text{(XV)}$$

Thus equation XV indicates that, for small values of t,

$$g \propto G \propto \sqrt{t}.$$

The significance of this derivation is discussed in section 8.33.

5.56 Dimensions

g is a volume ratio and hence dimensionless. Thus for equation XII to be dimensionally homogeneous, $\Psi(t)$ must be dimensionless, and so must $(a\alpha_n)$ in equation XIII, (au) in equation XIV and (Dt/a^2) in all equations including XV.

The only independent variable (t) for total uptake can always be incorporated into the group (Dt/a^2) and other dimensionless groups, e.g. α_n^2Dt in equation XIII may be expressed as $(a\alpha_n)^2(Dt/a^2)$. Thus the time response of the system for a step in arterial tension is well characterized by plotting $\Psi(t)$ versus (Dt/a^2). Once the plot of these two dimensionless quantities has been established for the relevant (b/a) ratio (fig. 43), variations in D, S, (ΔP), x, or even a (for small values of t), require arithmetic adjustments only. The apparent mathematical complexity of equations XIII and XIV should thus not detract from the use of this approach

in decompression analysis. It should, in fact, be no more difficult by this method than by the conventional exponential approach once the relationship between $\Psi(t)$ and (Dt/a^2) has been expressed graphically.

5.57 Inert gas elimination without phase separation

Provided phase separation has not occurred, the exchange of inert gas in tissues should be a perfectly reversible process, i.e. equations XIII, XIV or XV could be used to describe $\Psi(t)$ in equation XII whether values of ΔP are positive or negative. In such circumstances, the net gas eliminated (G') and the net gas per unit volume of extravascular tissue(g') are related to (t) according to equation XII as:-

$$g' = G'/\pi(b^2-a^2) = x(\Delta P)S\Psi(t) \qquad (34)$$

Where phase separation has not occurred, the net gas content after a number of absolute pressure changes may be calculated by employing the principle of superposition. This is in accordance with the general approach employed by advocates of supersaturation theories of decompression sickness (section 1.6).

For a dive of duration (θ) at maximum absolute pressure (P_b), followed by conventional staging consisting of time τ_1 spent at pressure P_1, τ_2 at P_2, τ_m at P_m etc. in returning to the initial pressure P_o, the net gas uptake by the tissue is given by:-

$$g-g' = xS\left[(P_b-P_o)\Psi(t)-(P_h-P_1)\Psi(t-\theta)-\sum_{m=1}^{m}(P_m-P_{m+1})\Psi(t-\theta-\sum_{m=1}^{m}\tau_m)\right] \qquad (35)$$

since the jump from pressure P_m to P_{m+1} is delayed by time $\theta+\tau_1+\tau_2\ldots\tau_m$ from the initial submersion.

The start of decompression is the particular instant when $t = \theta$, such that the quantity of gas taken up by the tissue per unit volume is given by equation XII as:-

$$g = \alpha\beta(P_b - P_o)\ \psi\ (\theta) \qquad \text{(XVI)}$$

since $\Delta P = P_b - P_o$

However, whenever the separation of gas from solution occurs, the blood:tissue exchange process is no longer reversible and hence the above approach cannot be extended to estimate desaturation by decompression in nucleated zones. Thus equation 35 cannot be used for estimating g' in the worst possible case, unless it can be proven that no point has exceeded the condition for thermodynamic equilibrium, Since, the proximity to possible phase separation is determined by the total tension of all volatile solutes, predictions of inert gas desaturation WITH DECOMPRESSION would seem best postponed until the concentrations of the metabolisable gases have been estimated.

5.6 THE INHERENT UNSATURATION

5.61 Equilibrium

In order to estimate the quantity of gas available for coalescence into an extravascular embolism, it is essential to know the concentration distribution of each volatile substance at the moment of phase separation. In the worst possible case, where phase equilibration is rapidly established (section 4.5), the excess of total tension over absolute hydrostat

pressure is then representative of the gas separating from solution at that point. This is shown for a single stage in decompression for the arbitrary radial distribution illustrated in fig. 2.

According to equation IV phase separation can occur at any point where $(p + p_o + p_c + p_w) > P + 200$ mm. Hg.

While equation XI enables p to be determined for the model postulated, the metabolisable gases cannot be assumed to respond in the same transient manner as the inert substances. Moreover, the necessity of living tissue to maintain continuous chemical reaction suggests a tendency for the distributions of the gases, essential to metabolism, to deviate towards steady-state conditions.

5.62 Water Vapour

The tension of water (p_w) in cytoplasm is defined as the partial pressure of water vapour in equilibrium with cytoplasm. This must deviate from the vapour pressure of water, which is 47 mm. Hg. (Perry, 1950) at body temperature (37°C), by an amount equal to the depression of the vapour pressure by the solutes present.

However, cellular material shows no excessive deviation (Davson, 1964) in osmotic pressure from that of normal physiological saline whose concentration lies in the region of 120-140 mM.NaCl. Applying Raoult's Law to this dilute solution, the depression in the vapour pressure would be $47 \times 2 \times 0.13/18 = 0.70$ mm. Hg, assuming NaCl to be completely ionised.

Since osmotic pressure and depression of the vapour pressure are both colligative properties pertinent to dilute solutions, the same deviation should apply to the isotonic cellular material. Thus there should be negligible error, relative to practical absolute pressures, in taking:- $p_w = 46$ mm. Hg. (XVII)

5.63 Metabolism

One volatile substance (oxygen) is consumed by metabolism and another (carbon dioxide) is produced in comparable molecular numbers. Taking the general value for the respiratory quotient quoted in section 5.12, the blood:tissue molar exchange rates for CO_2 and O_2 should thus be in the ratio 0.85:1 for steady-state conditions.

Moreover, their resistances to transfer between the capillary and the site of chemical reaction should not differ greatly since both gases must take the same route, although in reverse directions. This differential would be determined by the relative partition coefficients (equation 24) if blood:tissue exchange were perfusion-limited, or by Graham's Law if diffusion were rate-controlling. Taking the latter as pertinent to the worst possible case (section 5.52) the resistance to carbon dioxide venting should not exceed that for oxygen assimilation by a factor of more than $\sqrt{48/32}$, i.e. a ratio of 1.22:1.

Taking:- (transfer rate) = (driving force)/(resistance), the molar concentration differentials between serum and the region of metabolic activity should lie in the approximate ratio of $0.85 \times 1.22:1$, or 1.04:1 for $CO_2:O_2$.

To remain consistent with the general model expounded for inert gases in section 5.44, in which the extracellular region is regarded as a 'fully-stirred' zone devoid of any appreciable tension gradients capillary serum concentrations of O_2 and CO_2 must be taken as equal to the corresponding values in venous blood. Thus the foregoing conclusion can be expressed quantitatively in the form:- (Driving force for CO_2) = $C_{co_2} - C'_{co_2}$ $\approx$ (driving force for O_2) = $C'_{o_2} - C_{o_2}$, where C_{o_2} and C_{co_2} are the concentrations of O_2 and CO_2 at a point in the cell and C'_{o_2} and C'_{co_2} are the corresponding values for plasma in the venous blood. This is illustrated in fig. 9 and may be re-expressed as:-

$$C_{co_2} + C_{o_2} \approx C'_{o_2} + C'_{co_2} \qquad (36)$$

If $(C'_{o_2} + C'_{co_2})$ were regarded as constant the above equation would imply that the molecular concentration rise of carbon dioxide in cells, induced by metabolism, roughly equals the simultaneous fall in the molecular concentration of oxygen.

However, it is total tension, and not total concentration, which is the relevant parameter in determining the proximity of a system to gas phase separation, i.e. $(p_o + p_c)$ is required in equation IV.

5.64 Oxygen and carbon dioxide tensions

Defining point tensions of O_2 and CO_2 in cells as p_o and p_c respectively, and p'_o and p'_c as the corresponding values in venous blood, equation 36 becomes:-

$$(p_o - p'_o)S_{o_2} \approx (p'_c - p_c)S_{co_2}$$

where S_{o_2} and S_{co_2} are the solubilities of O_2 and CO_2 in aqueous fluid.

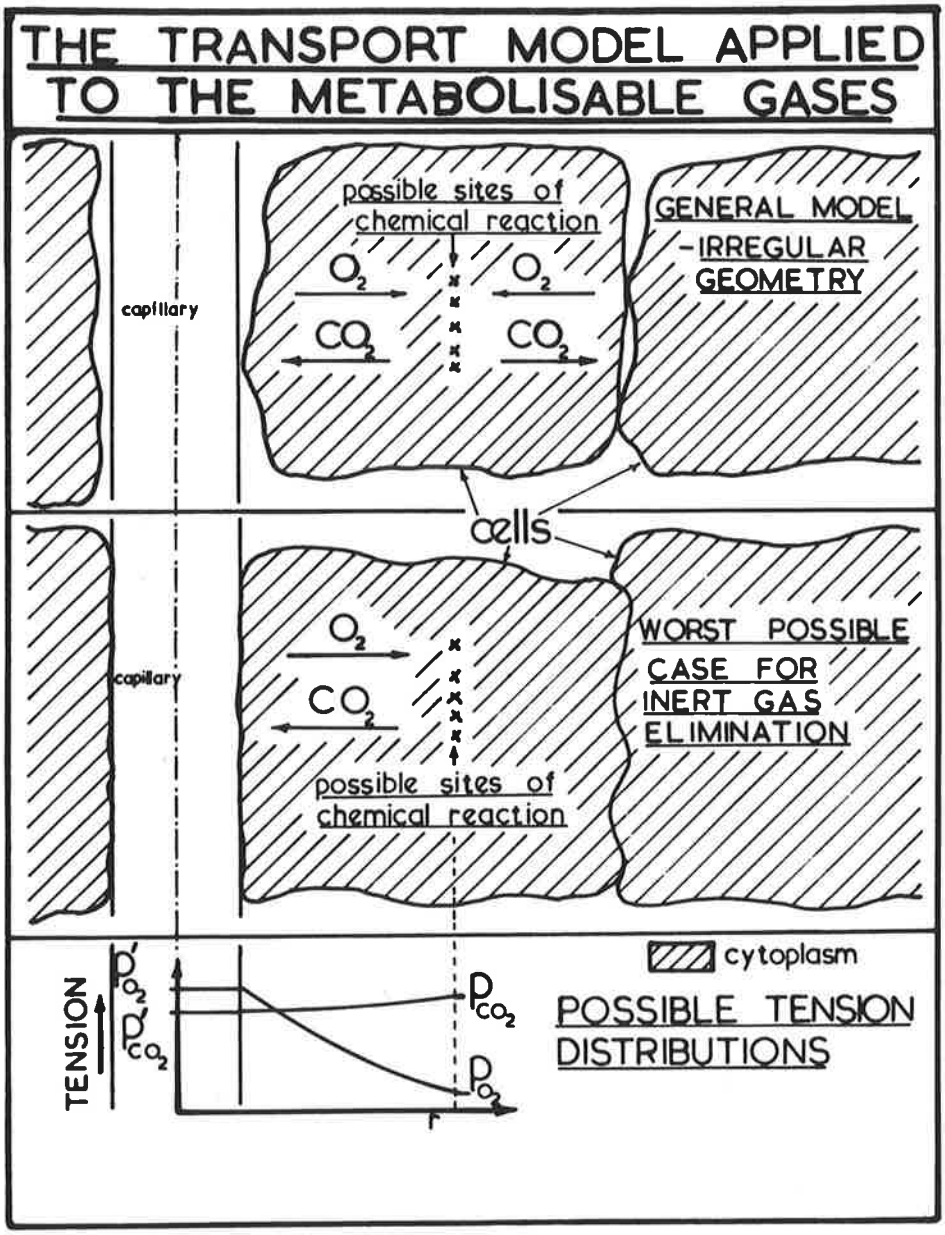

THE TRANSPORT MODEL APPLIED TO THE METABOLISABLE GASES
capillary
possible sites of chemical reaction
O_2
O_2
CO_2
CO_2
GENERAL MODEL - IRREGULAR GEOMETRY
cells
capillary
O_2
CO_2
possible sites of chemical reaction
WORST POSSIBLE CASE FOR INERT GAS ELIMINATION
cytoplasm
TENSION
P'_{O_2}
P_{CO_2}
P_{CO_2}
P_{O_2}
r
POSSIBLE TENSION DISTRIBUTIONS

Fig.9

However, the solubility of carbon dioxide in water is much greater than that of oxygen - as illustrated by the Henry's constants quoted by Perry (1950) of 2.09×10^3 atmos. for CO_2 and 5.07×10^4 atmos. for O_2, giving $S_{CO_2}/S_{O_2} \simeq 24$.

This holds in both plasma and cytoplasm since metabolism represents a steady-state condition.

Thus, $(p'_o - p_o) \approx 24(p_c - p'_c)$

giving:- $$(p_o + p_c) \approx (p'_o + p'_c) - 23(p_c - p'_c) \qquad (37)$$

Now CO_2 is generated within the cell and hence $p_c > p'_c$, leaving $(p_o + p_c) < p'_o + p'_c$.

> Hence, relative to capillary blood, there is an inherent unsaturation induced by metabolism by virtue of the continuous conversion of a volatile substance into another of much higher solubility.

Moreover, this tension differential should increase with the metabolic rate (M) which is proportional to the rate of generation of CO_2, hence to the rate of transmission of CO_2, and thus to the gradient $(p_c - p'_c)$ in fig. 9. Thus equation 37 may be re-expressed as:-

$$(p_o + p_c) \simeq (p'_o + p'_c) - 23K'M \qquad (38)$$

where K' is a proportionality constant.

$(p_o + p_c)$ can thus vary between $(p'_o + p'_c)$ if metabolism has stopped ($M = 0$), to the other extreme where chemical reaction offers no resistance to conversion. In this case every oxygen molecule reaching the necessary site in the cell is immediately consumed, so reducing the local oxygen tension to zero.

If $p_c = 0$, equation 38 gives $(p_c - p'_c) = p'_c/24$ when $(p_o + p_c) = p'_c/24 + p'_c$.

Hence $(p_o + p_c)$ can lie anywhere between $(p'_o + p'_c)$ and $(p'_c + p'_c/24)$ depending upon the metabolic rate, i.e.

$$(p'_o + p'_c) > (p_o + p_c) > p'_c + p'_c/24 \qquad (39)$$

Moreover, $(p_o + p_c)$ will also vary between these limits according to location along the concentration gradients. Whether resorting to the very complex mathematics used by Blum (1960) for estimating concentration profiles around capillaries under steady-state conditions, or keeping to the model of the less regular geometry advocated in this thesis, there should be a marked decrease in total tension in going from the cell membrane to the site of reaction. This is consistent with the experimental measurements of Davies and Bronk (1957) who have demonstrated a rapid decrement in O_2 tension around capillaries.

Without knowing the identity of the critical tissue type, and hence its metabolic rate, no expression for $(p_o + p_c)$ more specific than equation 39 can be derived. Thus the estimation of $(p_o + p_c)$ is largely a matter of determining the total venous tension $(p'_o + p'_c)$ as the maximum, or worst possible case for phase separation.

5.65 Venous tension of carbon dioxide

The arterio-venous difference for CO_2 is determined by the quantity of that gas entering unit volume of blood, i.e. it is a function of the metabolic rate, the blood flow and the physico-chemical characteristic of the blood perfusing that tissue. If the circulation and metabolic rates

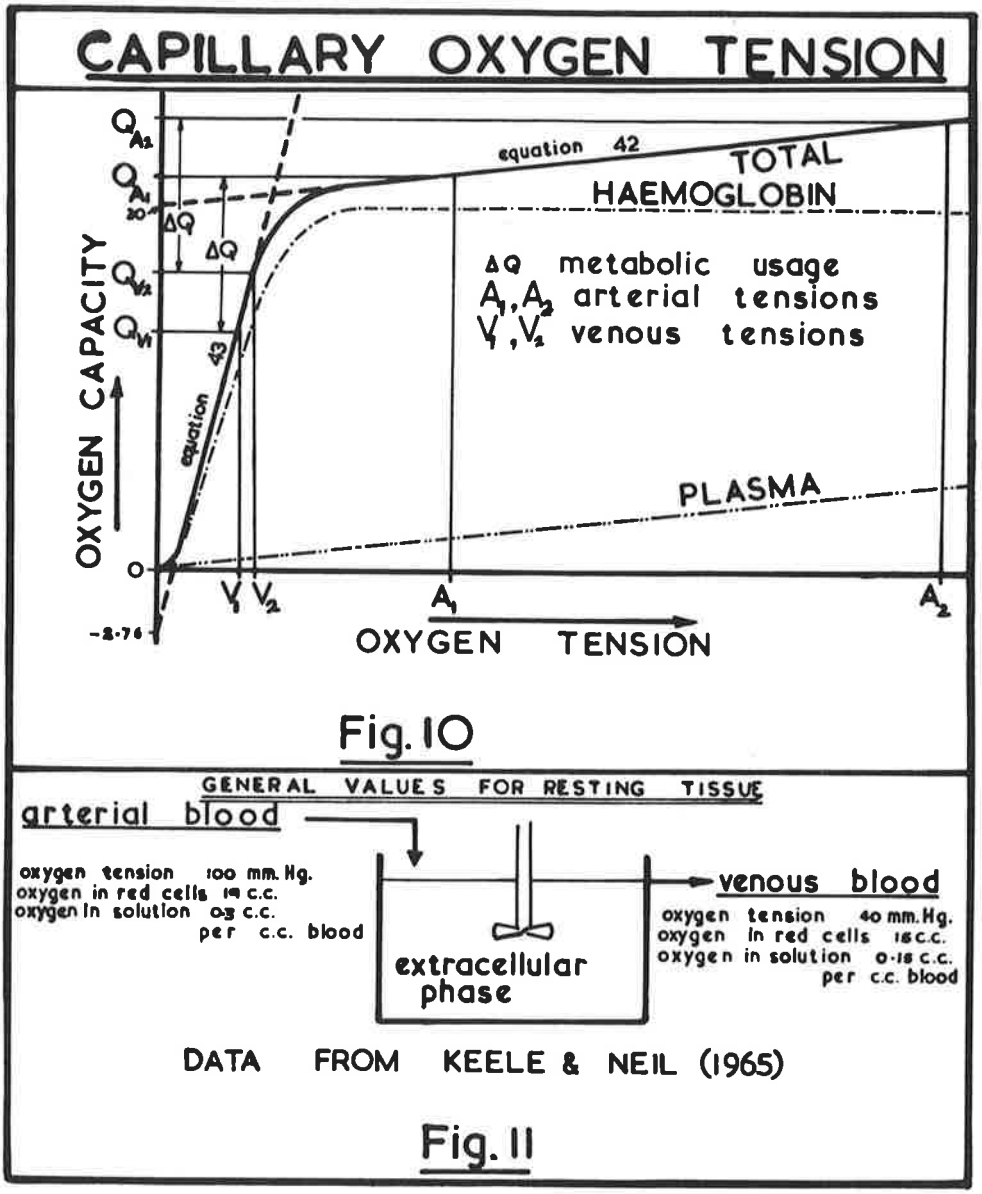

CAPILLARY OXYGEN TENSION
OXYGEN CAPACITY
OXYGEN TENSION
equation 42
TOTAL HAEMOGLOBIN
ΔQ metabolic usage
A1, A2 arterial tensions
V1, V2 venous tensions
PLASMA
equation 43
ΔQ
ΔQ
20
0
-2·76
V1
V2
A1
A2
GENERAL VALUES FOR RESTING TISSUE
arterial blood
oxygen tension 100 mm. Hg.
oxygen in red cells 19 c.c.
oxygen in solution 0·3 c.c.
per c.c. blood
extracellular phase
venous blood
oxygen tension 40 mm. Hg.
oxygen in red cells 15 c.c.
oxygen in solution 0·15 c.c.
per c.c. blood
DATA FROM KEELE & NEIL (1965)

Fig. 10

Fig. 11

are constant, the A-V difference for carbon dioxide should be constant also. Moreover, the rise should be roughly independent of the arterial tension of oxygen since the only source of CO_2 is its generation in the tissue.

Thus little error should be introduced, relative to normal diving pressures, by assuming that the venous tension of CO_2 is the same for the same exercise level at all depths, i.e. equal to its surface value which is quoted as 46 mm. Hg. by Keele and Neil (1965).

Thus $p'_c = 46$ mm. Hg. (40)

Although not identified, the critical tissue type should conform to the above equation since it would seem fair to state that the total cardiac output is distributed, and controlled, such that each tissue is perfused in accordance with its metabolic demands. Moreover, such circulation is regulated (Johnstone, 1966) to accommodate any change in those demands, the opposing effects of metabolism and local blood flow tending to reduce any error in equation 40.

5.66 Venous tension of oxygen

The cells of a tissue must consume a certain quantity of O_2 to function normally. If this demand for oxygen by the critical tissue is taken as the average for the whole circulation, for the same reasons as expressed for CO_2, then the consumption per unit volume of perfusing blood (figs 10 and 11) is given by:-

$$Q_A - Q_V = 4.15 \text{ ml. } O_2/\text{ml. blood} \quad (41)$$

Q_A and Q_V are the quantities of O_2 contained in unit volume of arterial and venous blood of the same haematocrit value (saturated Hb containing 20 ml. O_2/ml. blood).

For a given exercise level, the metabolic demand should remain independent of depth, and hence equation 41 should hold irrespective of the absolute hydrostatic pressure. The derivation of a quantitative expression for venous oxygen tension therefore reverts to the problem of relating the capacities of arterial and venous blood to their respective tensions.

The affinity of oxygen for blood is fully covered by the classical work of Roughton (1963) who displays its uptake as a number of successive reversible chemical reactions. The capacity versus tension curve is then expressed quantitatively in terms of the equilibrium constants, and other parameters, of those stages.

However, the accuracy gained by use of Roughton's equations in this case would hardly justify the associated mathematical complexity. Moreover, such a comprehensive description of the whole curve (fig. 10) by one equation is not necessary in diving since:-

1. The arterial tension of oxygen is always in excess of 100 mm. Hg, such that no more than a 5% error is introduced by assuming the haemoglobin to be 100% saturated. Keele and Neil (1965) quote 95% for 100 mm. Hg partial pressure.

$$\text{Thus } Q_A \approx 20 + S_p \cdot P'_O \text{ ml. } O_2\text{/ml. blood} \qquad (42)$$

where S_p is the solubility of oxygen in serum and P'_O is the arterial oxygen tension.

2. The venous tension of oxygen should not exceed 60 mm. Hg, since the risk of convulsions (section 1.45) rule out any diving in which the arterial tension exceeds about 1,500 mm. Hg. 60 mm. Hg. is within the steep linear region of the curve shown in fig. 10 of oxygen uptake for a CO_2 tension of 40 mm. Hg.

The venous tension may be expressed as a linear function of the oxygen capacity by extending the linear region of the experimental sigmoid curve for the $Hb - HbO_2$ system. While any error in extrapolation will be discussed later, the data of Keele and Neil (fig. 11) would indicate that the steep linear region can be expressed by:-

$$Q_V \simeq 0.46(p'_o - 6) + S_p.p'_o \text{ ml. } O_2/\text{ml. blood}$$

Taking their value of $S_p = 0.003$ ml. O_2/ml. blood mm. Hg. tension,

$$Q_V \simeq 0.463\ p'_o - 2.76 \qquad (43)$$

while equation 42 becomes $Q_A \simeq 20 + 0.003\ P'_o$

Making the above substitutions for Q_V and Q_A in equation 41,

$$p'_o \simeq 40.3 + 0.006\ P'_o \text{ mm. Hg.} \qquad (44)$$

An indication of the smallness of the error involved in reducing the blood dissociation curve to two linear stages, may be obtained by considering the case of ground level. For Keele and Neil's (1965) arterial tension of $P'_o = 100$ mm. Hg., equation 44 gives $p'_o = 40.9$ which is very close to their experimental venous value of 40 mm. Hg.

In section 5.12, P'_o was derived in terms of the absolute hydrostatic pressure as:-

$$P'_o \simeq (1 - x)(P - p_w) \text{ mm. Hg.}$$

Eliminating P'_o from the two preceding equations:-

$$p'_o \simeq 40 + 0.006(1 - x)(P - 46) \text{ mm. Hg.} \qquad (45)$$

taking $p_w = 46$ mm. Hg. (equation XVII).

5.67 Total intracellular tension

Combining equations 40 and 45,

$$(p'_o + p'_c) = 86 + 0.006(1 - x)(P - 46) \text{ mm. Hg.} \qquad (46)$$

Substitution of this expression and equation XVII in equation 39 now gives the total of CO_2 and O_2 tensions in the cell as:-

$$86 + 0.006(1-x)(P-46) > (p_o+p_c) > 2.5 \times 10^{-4}(1-x)(P-46) + 46 \text{ mm. Hg.}$$

While the above expression refers to steady-state conditions, the only terms which can vary under transient conditions are those which are functions of P, i.e. $0.006(1 - x)(P - 46)$. However, $0.006(1 - x)(P - 46)$ is almost negligible with respect to 132. For air at atmospheric pressure, $P = 760$ mm. Hg, and $x = 0.8$, giving $0.006(1 - x)P = 0.9$ mm. Hg which is certainly negligible with respect to total tension. Hence a negligible error is introduced by reducing the above expression to:-

$$86 > (p_o + p_c) > 46 \text{ mm. Hg.}$$

Incorporating water vapour according to equation XVII,

$$132 > (p_o + p_c + p_w) > 92 \text{ mm. Hg.} \qquad (XVIII)$$

Thus the total tension of gases $(p + p_o + p_c + p_w)$ at a point in the cytoplasm, radial distance (r) from the axis of the nearest capillary, is given by:-

$$132 + p > (p + p_o + p_c + p_w) > p + 92 \text{ mm. Hg.}$$

But p is the sum of the equilibrium value for the initial state ($P = P_o$) and the transient components for subsequent changes in P. In section 5.12 the initial level is given by $p = x(P_o - p_w)$, while the transient changes can be determined by equation XI, giving a total inert gas tension:-

$$p = x(P_o - 46) + \Sigma\, x(\Delta P)\, \Phi\,(r,t)$$

Thus, for a single rapid compression from $P = P_o$ to a 'bottom pressure' ($P = P_b$) at time $t = 0$, $\Delta P = P_b - P_o$ giving the total transient point tension at radius (r) as:-

$$(p+p_o+p_c+p_w) = (p_o+p_c+p_w) + x\left((P_o-46) + (P_b-P_o)\, \Phi\,(r,t) \right) \text{ mm. Hg.} \qquad \text{(XIX)}$$

where $\Phi(r,t)$ is given by equation XI.

For the particular case of inert gas equilibration ($t = \infty$), $\Phi(r,t) = 1$, when equations XVIII and XIX give:-

$$92+x(P-46) < (p+p_o+p_c+p_w) < 132 + x(P-46), \text{ for all values of r.} \qquad (47)$$

Hence $(p+p_o+p_c+p_w) < P$ if $P > (132-46x)/(1-x)$

For air ($x = 0.8$), the absolute pressure should exceed the total tension of all volatiles for $P > 476$ mm. Hg.

> Thus, even when the inert gas has come to equilibrium, there should be an 'inherent unsaturation' for any absolute pressure in excess of a particular value (a threshold of 476 mm. Hg in the case of air).

Summarising the foregoing mathematical derivations, this 'inherent unsaturation' arises from two sources:-

1. Metabolism, by which a gaseous substance (O_2) is converted into another of much higher solubility (CO_2) in comparable molecular numbers.

2. The equilibrium characteristics of the reaction

$$Hb + O_2 \rightleftharpoons HbO_2$$

enhanced by the metabolic demand for oxygen being well in excess of that conveyed in physical solution by the plasma in arterial blood. Thus capillary O_2 tensions should fall very rapidly to below 100 mm. Hg , whatever the alveolar O_2 tension, in order to permit supply of the bulk of the required oxygen by chemical dissociation of oxy-haemoglobin. This should hold for all 'convulsion-free' cases where the venous tension lies within the sigmoid region of the oxygen 'capacity versus tension' curve for blood. This is illustrated in fig. 10 where equal metabolic usage (Δq) would reduce widely differing arterial oxygen tensions (A_1 and A_2) to very similar venous tensions (V_1 and V_2).

Defining the inherent unsaturation (Δp) as:-

$$(\Delta p) = P - (p+p_o+p_c+p_w),$$

equation 47 would predict:-

$$(1-x)\,P - 92 + 46x \geq (\Delta p) \geq (1-x)\,P - 132 + 46x \text{ mm. Hg.} \qquad (48)$$

For practical dives $(92 - 46x)$ or $(132 - 46x)$ are very small by comparison with $(1 - x)P$.

Before discussing the important implications of an inherent unsaturation, increasing linearly with external pressure, it is imperative to ascertain that such a mathematically-derived concept is reconcilable with practical observations.

5.68 Practical evidence for unsaturation at ground level

The feature of this 'inherent unsaturation' , is that it persists after sufficient time has elapsed to enable the inert gas to equilibrate with tissue and for the metabolisable gases to re-attain steady-state conditions. Originally, it was overlooked by many workers who estimated

nitrogen tensions as the difference between total absolute pressure and the sum of the other gases which can be readily estimated by chemical means, as described by Peters and Van Slyke (1932). However, this differential is now well recognized (Rahn, 1961), the following list giving typical values for mixed venous blood quoted by Piiper (1963a).

CO_2	46 mm. Hg.	Subject breathing air at 760 mm. Hg.
O_2	41 mm. Hg.	
H_2O	47 mm. Hg.	
N_2	574 mm. Hg.	
Total	708 mm. Hg.	

The net unsaturation is thus 52 mm. Hg. Aksnes and Rahn (1957) obtain a value of 54 mm. Hg for the mixed venous blood of dogs.

Lategola (1964) has demonstrated the development of a negative pressure of 41-48 mm. Hg , with respect to atmosphere, within rigid capsules implanted in dogs. More detail of his method is contained in section 6.42.

However, Lategola makes the surprising statement that his silicone rubber membrane does not pass water vapour. This would seem most unlikely from the writer's survey of manufacturer's specifications. Moreover, it would invalidate his claim to have measured the total tension differential with respect to the atmosphere, the implication being that he has merely measured the vapour pressure of water at body temperature - 46 mm. Hg compared with his readings of 41-48 mm. Hg.

The inherent unsaturation would seem to be well demonstrated by the extent of decompression which the body can tolerate before any indications of phase separation can be detected. These include:-

1. X-ray data such as described by Ryder et al (1945) who found the first indications of any change with aerial decompression occurring at an equivalent altitude in the region of 12,000 feet. This corresponds to a threshold pressure (section 5.67) of 483 mm. Hg.

2. A manometer connected to the spinal cord of two men showed a sudden increase in the volume of spinal fluid at simulated altitudes of 10,500 feet (512 mm. Hg) in one case and 12,000 feet in the other. These values, recorded by Walsh (1941) and Boothby et al (1940), seem indicative of the onset of gas phase separation. Similar pressures have been recorded by Armstrong (1939) for goats.

3. The above pressure range also represents the minimum altitude at which bends have been recorded (Allan, 1945), Eggleton et al (1945) quoting 12,000 feet (483 mm. Hg) as the value "below which ill effects of any kind are rare".

The above list indicates that the gas phase is established for pressures of 483-512 mm. Hg , which is consistent with the threshold of 476 mm. Hg derived theoretically in section 5.67.

5.69 Evidence of unsaturation for pressures above atmospheric

Having rejected the conventional concept of limited supersaturation (section 4.34), it is essential to find an alternative driving force for desaturation following decompression. Since this could be provided by the 'inherent unsaturation' , it is essential to ascertain whether such a tension differential would increase with depth - as forecast by the basic physical chemistry, and expressed quantitatively by equation 48.

While there seems little doubt that an inherent unsaturation of at least 43 mm. Hg exists at ground level, no mention could be found in the literature to its direct measurement or prediction at higher pressures.

The best indirect evidence is provided by Lambertsen et al (1953) in their studies of the effect of hyperbaric oxygen upon brain. For a rise in arterial O_2 tension from 26 to 2100 mm. Hg, the venous O_2 tension increased from 17.8 to only 75 mm. Hg.

For $x = 0$(100% O_2) and $P'_o = 2100$, equation 44 gives $p'_o = 57$ mm. Hg.

This difference of 18 mm. Hg is negligible with respect to the total effective oxygen contribution of $(P'_o - p'_o) = 2025$ mm. Hg towards the inherent unsaturation. This amounts to less than 1% of the minimum unsaturatior of 1968 mm. Hg predicted by putting $x = 1$ and $P = 2100$ in equation 48.

While no other evidence could be found as convincing as the above, it is interesting to note that the foregoing equations can be used tc predict the O_2 tensions of renal pelvic urine, so collected to minimise the effect of any chemical reaction with oxygen. For dogs exposed to increased barometric pressures the correlation is given in table 9 for the data of Rennie et al (1958).

URINE OXYGEN TENSION IN DOGS

Oxygen tensions in mm. Hg.			Error as % of unsaturation
Inspired O_2	Urine O_2	p'_o equation 345	
150	35 ± 1.5	40	saturated
760	39 ± 1.7	44.6	0.6%
1140	57	47.1	0.9%
1520	77, 76	49.1	1.7%
2280	86	60.0	1.1%

TABLE 9

Many workers have searched for bubbles by dissecting decompressed animals. With cessession of the circulation upon death, it would seem

reasonable to suppose that the tissue would consume every available molecule of oxygen, such that the upper limit for Δp in equation 48 would apply. This gives the inherent unsaturation in cells as:-

$$\Delta p = (1 - x)P - 92 + 46x \text{ mm. Hg}$$

The unsaturation in living cells in an animal living in air ($x = 0.8$) at 3 p.s.i. gauge (915 mm. Hg) would thus be 128 mm., such that phase separation should be initiated by rapid decompression upon reaching 915-128 = 787 mm. Hg. It is thus regarded as most significant that 3 p.s.i. gauge is the minimum pressure from which Harris et al (1945b) were able to detect bubbles upon decompressing rats to atmospheric pressure (section 4.32). The 27 mm. Hg difference may be attributed to lack of inert gas equilibration following the 3 hours or so for which he held his animals at the higher pressure, or to the excess pressure drop necessary to produce sufficient gas to be visible.

More direct evidence supporting the concept of an "inherent unsaturation", increasing linearly with absolute pressure and mole fraction of oxygen, is provided by the experimental investigation described in section 6.4. The results are consistent with equation 48.

5.7 TRANSPORT FOLLOWING DECOMPRESSION

5.71 The total driving force

The pressure of the gas separating from solution in tissues can only exceed that of the surrounding atmosphere by the small terms accounting for surface tension and tissue elasticity. The latter should not exceed a total of 200 mm. Hg (equation IV). Apart from these minor adjustments, the total tension of all components of the separated gas must therefore equal the absolute hydrostatic pressure.

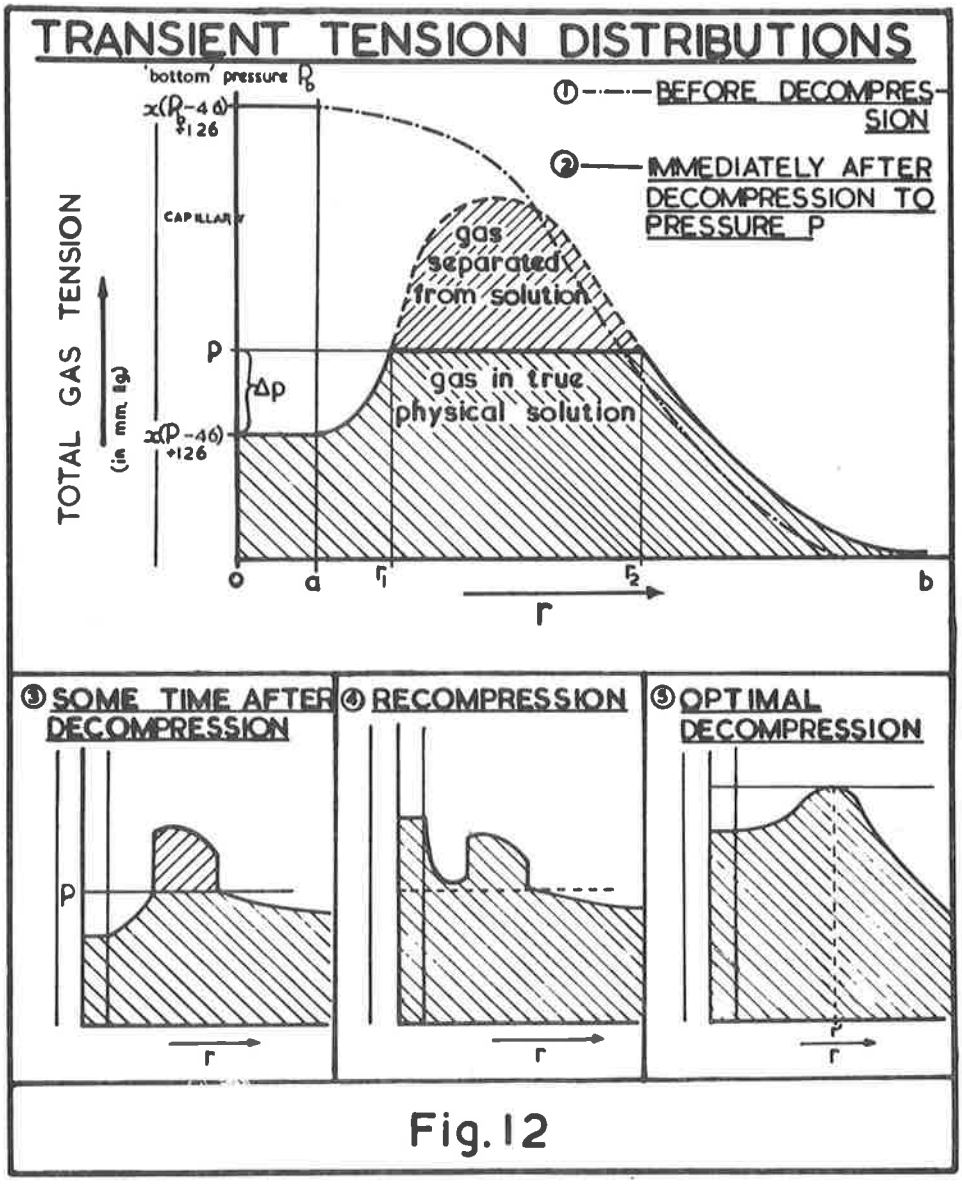

TRANSIENT TENSION DISTRIBUTIONS
'bottom' pressure P_b
$x(P_b - 46) + 126$
CAPILLARY
TOTAL GAS TENSION
(in mm. Hg)
$x(P - 46) + 126$
P
Δp
① BEFORE DECOMPRESSION
② IMMEDIATELY AFTER DECOMPRESSION TO PRESSURE P
gas separated from solution
gas in true physical solution
0
a
r_1
r_2
b
r
③ SOME TIME AFTER DECOMPRESSION
④ RECOMPRESSION
⑤ OPTIMAL DECOMPRESSION

Fig. 12

However, soon after decompression to an ambient pressure P, the blood will reach another steady-state condition as determined by the new depth (equation 48).

> A few cycles of the blood should then be sufficient to re-establish the inherent unsaturation with respect to the new absolute pressure and, therefore, with respect to the separated gas. Hence there should be a total tension differential between capillary blood and the separated gas, or any embolism into which it may be congregated. The immediately adjacent aqueous layers remaining in equilibrium with the separated gas, the above differential would constitute a driving force for the transport of gas to the capillary. This would cause any film or bubble to redissolve gradually.

The system, as visualized for the worst possible case, is illustrated by the radial transient mass balance illustrated in fig. 12 (graph 2). In this diagram, the driving force for tissue desaturation following decompression is that designated Δp since separated gas cannot contribute to a point tension but merely serves as a reservoir maintaining that tension at the value for phase equilibration until it is exhausted.

The inherent unsaturation would thus have the effect of "nibbling" at the separated gas as illustrated in fig. 12 (graph 3). For decompressions from dives of short duration this should occur at both inner and outer boundaries of the annular zone of nucleation, since regions more remote from the capillary could still be relatively unsaturated.

However, before the movement of separated gas to the capillaries can be placed upon a quantitative basis, it would seem imperative to ascertain the redistribution of individual tensions by virtue of the phase changes.

5.72 The metabolisable gases

Since the boundaries of any cavity in tissue, are aqueous fluids, the partial pressure of contained water vapour in the gas phase should rapidly re-equilibrate to the saturation value at body temperature following any change, i.e. $p_w = 46$ (equation XVII).

Oxygen is somewhat similar in so far as any excess over the normal tension would be rapidly consumed by local metabolism. This rapid re-adjustment should be greatly facilitated by the finely dispersed state in which gas should be deposited by decompression, resulting in very short diffusion paths to the nearest site of its assimilation by chemical reaction.

Carbon dioxide, however, must be vented to the capillary, but its solubility in aqueous tissue is some 47 times that of nitrogen (Perry, 1950). Hence any CO_2 in the separated gas, in excess of the normal tension in the cytoplasm, will be rapidly dissipated relative to N_2. This is justified by the fact that equal drops in nitrogen or carbon dioxide partial pressures in any bubble would require the loss of equal numbers of molecules. However, equal tension gradients would represent a 47:1 CO_2:N_2 ratio for the concentration gradients, and concentration gradient is the parameter determining diffusion rates. The diffusion coefficients are of similar order.

Hence the above arguments indicate that H_2O, O_2 and CO_2 tensions in any separated gas will revert to their normal values in the surrounding fluid far more rapidly than any inert substance, and may thus be expressed by equation XVIII, i.e.:-

$$132 > (p_o + p_c + p_w) > 92 \text{ mm. Hg.}$$

Since the foregoing deduction is theoretical, it would seem desirable to obtain some practical justification before continuing this approach. The best experimental data for this purpose is probably the analysis of subcutaneous gas, where surface tension effects may be ignored since the gas pockets are relatively large, i.e. $y \gg 1.42$ microns in equation III.

5.73 Subcutaneous gas analyses

The very rapid equilibration of carbon dioxide relative to nitrogen has been demonstrated by Campbell (1924), whose analyses of samples of 500-1000 c.c. subcutaneous injections of air showed that the CO_2 tension reaches a steady 50 mm. Hg within minutes. The N_2 was not completely absorbed for 20 days.

The oxygen tension fell from 150 to 50 mm. Hg in 10 hours, reaching a steady value of 20-30 mm. Hg after $1\frac{1}{2}$-3 days, indicating an absorption rate approximately 10 times faster than that of N_2. This factor should be greatly increased for the finer dispersion afforded by gas separating from solution by decompression, where a relatively larger zone of tissue could receive its oxygen for metabolism from the gas phase reservoirs.

While Campbell has used rabbits at atmospheric pressure, his results are largely confirmed by Coryllos and Birnbaum (1932) using dogs. Moreover, the steady tensions of carbon dioxide and oxygen are in close agreement with values of 50 mm. (CO_2) and 20 mm. Hg (O_2) recorded by Van Liew (1962) when analysing injected gas equilibrated with rat liver.

Taking water vapour as the saturation value (46 mm. Hg) the above experimental results give:-

$$P_o \leftrightarrow P_c + P_w = 116 \text{ to } 126 \text{ mm. Hg.}$$

This experimental range lies well within the limits predicted theoretically by equation XVIII, and so enables those limits to be narrowed. The worst possible case, corresponding to the maximum phase separation, thus occurs when:-

$$P_o \leftrightarrow P_c + P_w = 126 \text{ mm. Hg.} \qquad \text{(XX)}$$

While surface tension may be ignored for large masses of gas, elastic deformation may not. Allowing 10 mm. Hg for this effect (see section 4.15), the tension of N_2 in the separated gas must therefore equal $(P + 10 - 126)$, giving a value of 644 mm. Hg for P = 1 atmosphere. On a dry gas basis this would imply a nitrogen fraction of 644/(760 - 46), or 90.1% N_2. This is in good agreement with the experimental value of 90% quoted by Rahn (1961).

The metabolic rate should increase with exercise such that $(p_o + p_c + p_w)$ should approach the lower limit given by equation XVIII. Taking $(p_o + p_c + p_w)$ = 92 mm. Hg , the nitrogen fraction for exercise should amount to (760 + 10 - 92)/(760 - 46), or 95.1% on a 'dry gas' basis.

Blinks et al (1951) quote a value of 95% N_2 for the analysis of bubbles taken from guinea pigs exercising at atmospheric pressure. Similar experimental values are quoted for rats by Harris et al (1945c).

5.74 Driving force for the inert gas

The preceding correlations, which support the validity of equation XVIII, refer to systems in which large amounts of gas have been injected. The curvature of the gas-fluid interface is thus so small that the pressure differential attributable to surface tension is negligible. The same argument should apply to initial gas separating from solution by decompression provided it is deposited as films following the more gradual contours of lipid-aquous boundaries (see section 4.4). Moreover, prior to coalescence, or congregation of this gas, no appreciable mechanical stress should be created by elastic deformation of the tissue. This is contrary to the foregoing case.

When both 'mechanical' terms in the pressure balance expressed by equation III are neglected, the total tension of all gases in the bubble must equal the hydrostatic. Substituting for O_2, CO_2 and H_2O partial pressures according to equation XVIII, one obtains the tension of inert gas in the separated gas $(p)_{gas}$ as:-

$$P - 92 > (p)_{gas} > P - 132 \text{ mm. Hg.}$$

However, the tension of inert gas in the capillary $(p)_{r \leq a}$ is given by equation V as:-

$$(p)_{r \leq a} = P_A = x(P - 46) \text{ mm. Hg.}$$

Since $x < 1$, it can be seen from the above expressions that $(p)_{gas} > (p)_{r \leq a}$ and, moreover,

$$(1 - x)P - 92 - 46x > ((p)_{gas} - (p)_{r \leq a}) > (1 - x)P - 132 + 46x$$

Hence it can be seen from equation 48 that:-

$$(p)_{gas} - (p)_{r \leq a} = \Delta p.$$

i.e. the driving force for venting separated inert gas via the capillary is identical to the inherent unsaturation. Such a differential would be increased with increase of the 'mechanical' terms in equation III as coalescence proceeded. The most conservative estimate for staging is thus:-

$$(p)_{gas} - (p)_{r \leq a} = (\Delta p) = (1 - x)P - 132 + 46x \text{ mm. Hg.} \qquad \text{(XXI)}$$

> The above expressions imply that within a few cycles of the blood following a decompression which caused, or has increased gas phase separation, the driving force for venting this gas to the atmosphere is equal to the "inherent unsaturation".

Moreover, equation XXI indicates that this tension differential is of sufficient magnitude to account for an appreciable loss of gas during staging (Δp = 224 mm. Hg for x = 0.8 and P = 2 atmospheres).

> Hence it would seem reasonable to claim this blood-bubble tension differential as the true driving force for venting gas from tissue following phase separation, thus obviating the need to retain the conventional concept of limited supersaturation which is at variance with so many aspects of diving (section 1.6).

If this departure from conventional reasoning is correct, then it is particularly significant that Δp should increase with P.

5.75 The feature of the thermodynamic approach

In the foregoing sections it has been shown how an inherent unsaturation, arising from the differential solubility of the metabolisable gases in both blood and tissue, may become the main source of the driving force for inert gas removal following phase separation. While the conventional 'supersaturation' approaches assume the greatest bubble-blood tension differential for the lowest absolute pressure (equation 4), the reverse is predicted by equation XXI. This comparison

is illustrated in fig. 12 (graph 2) by Δp for the latter case as opposed to the tension differential between capillary and peak extravascular tensions for the conventional approaches, i.e. only gas in true physical solution can contribute to the driving force.

> The approach developed in this thesis would thus give reason to dispute the accepted Naval practice of giving a diver a large and rapid initial "pull" towards the surface in the belief that they are obtaining the maximum excess of tissue over blood tension. However, equation XVIII would recommend a larger driving force, in the worst possible case, if the diver were kept much deeper - particularly during the initial stagings.

This fundamental deviation from conventional reasoning represents the major contribution of this thesis, the ultimate test of its validity resting upon its ability to predict conditions for marginal symptoms. Its practical implications are more serious in casting doubts upon the proximity of the published decompression tables to the true optimal decompressions which the body can tolerate.

While the foregoing analysis predicts the driving force for losing gas following a phase change, the quantity of gas so eliminated must be expressed quantitatively before testing the validity of this reasoning upon diving data.

5.76 Gas distribution following phase separation

Considering the model relevant to the worst possible case (fig. 8) the radial distribution of total gas tensions, following a dive of period θ spent at a'bottom pressure' of P_b, is given by equations XIX and XX as:-

$$(\underline{p} + \underline{p}_o + \underline{p}_c + \underline{p}_w) = 126 + x\left(\underline{P}_o - 46 + (\underline{P}_b - \underline{P}_o)\Phi(\underline{r},\theta)\right) \text{ mm. Hg.}$$

If the diver is suddenly raised to a lower absolute pressure (P), then the radial zones which become supersaturated and/or nucleated by virtue of this decompression are determined by the expression for phase equilibration (equation IV). The inner and outer radii (r_1 and r_2 respectively) of this annular region are then given by:-

$$126 + x\left(P_o - 46 + (P_b - P_o)\Phi(r,\theta)\right) = P + 200$$

r being the only variable; the two real roots to the above expression must determine r_1 and r_2.

This is roughly checked by taking the case of an 'effectively infinite' time ($\theta = \infty$), spent at depth when equation XI for $\Phi(r,\theta)$ gives $r_1 = a$ and $r_2 = b$ as real solutions if:-

$$x(P_b - 46) \geq P + 74 \text{ mm. Hg},$$

i.e. the nucleated/supersaturated zone is the complete extravascular region which one would anticipate for uniformly distributed inert gas.

The distribution of tension excess available for phase separation (ξ) is then defined by:-

$$\xi = x\left(P_o - 46 - (P_b - P_o)\Phi(r,\theta)\right) - P - 74 \text{ mm. Hg.} \qquad \text{(XXII)}$$

Since it has been shown that bubble and tissue tensions of the metabolisable gases resume their former values within a very short time of any change, the tension excess represents the quantity of inert gas coming out of solution. Thus the partial molar volume of inert gas (reduced to body temperature) capable of coming out of solution in an annular segment of unit length, and thickness dr, is $2\pi r\beta\xi dr$. However,

the inert gas partial pressure is $(P+\delta+2\gamma/r-p_o-p_c-p_w)$ or $(P+74)$ mm. Hg, compared with a total pressure of $(P+200)$ mm. Hg. Thus the total volume of gas, reduced to the above conditions, separating in that segment =

$$\frac{2\pi rS(P+200)\xi}{P+74}\,dr.$$

Maintaining the same temperature, but applying Boyle's law to convert from standard pressure (P_o) to the ambient absolute pressure of the gas $(P + 200)$ mm. Hg , the corresponding volume (dv) is given by:-

$$dv = \frac{P_o}{(P+200)} \cdot \frac{2\pi rS(P+200)\xi dr}{(P+74)}$$

Hence the total volume of gas coming out of solution for thermodynamic equilibrium, i.e. that separating within the annulus $r = r_1$ to $r = r_2$ is given by:-

$$\int_o^v dv = \int_{r_1}^{r_2} \frac{P_o 2\pi rS\xi dr}{(P+74)}$$

Substituting for ξ according to equation XXII,

$$v = \frac{2\pi SP_o}{(P+74)} \int_{r_1}^{r_2} r\left[x(P_o-46-(P_b-P_o)\Phi(r,\theta))-P-74\right] dr \qquad \text{(XXIII)}$$

This expression gives the total volume of all gases liberated within a very short time of decompression for thermodynamic equilibrium throughout the zone.

5.77 Gas elimination following phase separation

However, upon waiting at the new pressure P, the separated gas will be gradually "eaten away" under the influence of the re-established bubble-blood driving force defined by $(p)_{gas} - (p)_{r \leq a}$ for which the most conservative estimate is given by (Δp) in equation XXI.

Thus r_1 will slowly increase as the gas is redissolved at its site of separation. Unless $r_2 = b$ immediately after decompression, r_2 should decrease very slowly as the region $b \geq r \geq r_2$ approaches saturation. These movements of r_1 and r_2 are illustrated in fig. 12 (graph 3).

Mathematically the phase change introduces two transition points in the total tension versus radius curve, the resulting discontinuous function rendering analysis very difficult if not impossible. There would thus appear to be two courses of action open to obtain a solution:-

1. To build an analogue to simulate the exact system or to resort to numerical methods. The former approach has been adopted since much of the crucial data is very irregular - particularly where a diver has been towed over the uneven bottom of the sea bed and decompressed suspended from a drifting boat in tidal channels. It is felt that the history of such dives is more easily fed mechanically to an analogue than programmed for a computer.

2. To make large approximations. Although these could in no way compete with the previous suggestion, the unsaturation developed in this thesis is so directly opposed to the conventional approaches that any approximate method should be sufficient to give a preliminary indication, justifying the building of an analogue based upon those principles.

5.78 An approximate method

Since the separated gas acts as a reservoir at constant tension, and the capillary tensions are constant, the loss of the inert

volatile component to the blood should conform more closely to steady-state than the transient conditions expressed by equation 35.

If it is assumed that gas is deposited at the same effective mean radius ($\bar{r}$) for each decompression, then the rate of loss of inert gas (reduced to S.T.P.) is given as:-

$$\frac{dG'}{dt} = 2\pi SD(\Delta p)/\log(\bar{r}/a)$$

i.e. $$g' = \frac{G'}{\pi(b^2-a^2)} = \frac{2(\Delta p)SDt}{(b^2-a^2)\log(\bar{r}/a)}$$

In the worst possible case (Δp) will assume its smallest value. This will occur for elimination prior to coalescence, when the minimum value of Δp is given by equation XXI.

Thus for m stagings following phase separation, consisting of time τ_1 spent at pressure P_1 etc. (as per the case without nucleation - section 5.58), the total inert gas eliminated per unit volume of tissue is given by:-

$$g' \approx \frac{2SD\Sigma(\Delta p)_m \tau_m}{(b^2-a^2)\log(\bar{r}/a)} = \frac{2SD\Sigma\tau_m((1-x)P_m-132+46x))}{(b^2-a^2)\log(\bar{r}/a)} \qquad \text{(XXIV)}$$

substituting for (Δp) according to equation XXI.

Equation XXIV is the appropriate expression for g' when phase separation has occurred, while equation 35 applies when it has not. Since these expressions summarise the derivation of the thermodynamic from conventional approaches, it would seem opportune to compare their interpretations of elimination data before proceeding to the final quantitative step of this theoretical synthesis.

5.79 Oxygen 'wash-out' with decompression

The 'wash-out' of nitrogen from the whole body has been recorded by Willmon and Behnke (1941) for various exposures and decompression stages. Their results are quoted in table 10.

The salient points of agreement with the proposed hypothesis are:-

1. The random nature of values for the same decompression where equilibrium conditions are exceeded according to equation III, i.e. random nucleation in runs vii-x.

INERT GAS 'WASH-OUT' WITH DECOMPRESSION

(Data from Willmon and Behnke, 1941)

No.	Exposure		Depth of stop (feet)	No. of tests	c.c. N_2 eliminated		Total
	Time (mins.)	Depth (feet)			at stop (3-30 mins.)	at surface (33-90 mins.)	
(i)	75	100	20	1	1478	834	2312
(ii)	75	100	50	2	1533	957	2590
(iii)	75	100	100	2	1415	739	2154
(iv)	30	100	44	1	1343	548	1891
(v)	30	100	50	1	1312	565	1877
(vi)	30	100	66	1	1341	522	1863
(vii)	30	100	0	1	626	401	1027
(viii)	30	100	0	11	1191	499	1690
(ix)	30	100	0	1	892	856	1748
(x)	30	100	0	1	1147	511	1658

TABLE 10

N.B. 3 mins. is taken to reach the stop, and a further 3 mins. from stop to surface.

2. Almost constant elimination rates where such equilibrium conditions were not exceeded, i.e. runs iv-vi.

3. Elimination rates for 'wash-out' without phase separation should be greater than those in which it has occurred, since g' predicted by equation 35 exceeds g' estimated by equation XXIV, i.e. values for runs iv-vi exceed those for runs vii-x, and the rate in run (i) exceeds that in run (ii).

The only apparent anomaly is run (iii) in which the rate of elimination of N_2 is slower than runs (i) and (ii). However, 30 mins. at a partial oxygen pressure of 4 atmospheres is well into the danger zone for convulsions (section 1.45).

Thus the overall approach would seem consistent with the data in table 10 and the decreased rate of 'wash-out' of N_2 recorded at altitude by Jones et al (1942).

5.8 PREDICTION OF MARGINAL SYMPTOMS

5.81 Total gas separating from solution

While the volume of gas separating from solution is given exactly by equation XXIII, it becomes very difficult to perform the necessary integration without resort to graphical methods. Such difficulties are greatly enhanced when it is necessary to analyse any procedure other than the simple decompression to which equation XXIII refers.

While the pneumatic analogue (section 6.6) can largely accommodate such complexities, a rapid analytical method is also desirable. This is attainable by a mass balance if it is assumed that the tissue region remote from the nucleated zone ($b \geq r \geq r_2$) reaches saturation within the period for marginal symptoms to become manifest. This is reasonable since such regions would tend to gain gas from the start of the dive, and should have acquired a total tension of gases in excess of (P_o + 200) mm. Hg when the (dive + staging + onset) times expire. Moreover,

such equilibration would automatically enable the mass balance to account for the "nibbling" effect at the outside of the separated gas - as shown by a decrease of r_2 in fig. 12 (graph 3).

The problem is therefore one of estimating the loss of separated gas from the other boundary of the nucleated zone ($r = r_1$).

5.82 Allowances for metabolisable gases

In section 5.7 the partial pressures were calculated for each constituent of the gas initially separating from solution. However, for the onset of pain, the mechanical effects of surface tension and elastic deformation cannot be ignored. Thus, according to the full expression for mechanical equilibrium in the bubble (equation IV), $(p)_{bubble} = P + 200 - (p_o + p_c + p_w)$ mm. Hg. Substituting for $p_o + p_c + p_w$ according to equation XX,

$$(p)_{bubble} = P + 74 \text{ mm. Hg.} \qquad \text{(XXV)}$$

But the total tension of all gases must equal the absolute pressure of all gases (P + 200 mm. Hg). Hence, applying Avagadro's law:-

$$\text{(Total volume of gas)} = \frac{(P + 200)}{(P + 74)} \text{ (partial molar volume of inert gas)} \qquad \text{(XXVI)}$$

5.83 Mass balance with phase separation

A simple mass balance for the inert gas, expressed as a volume reduced to standard pressure (P_o) and body temperature, may be effected for unit volume of the critical tissue type as follows:-

Quantity of inert gas entering tissue at depth = g (section 5.54)

Quantity of inert gas leaving tissue during decompression = g'

(section 5.78)

Quantity of inert gas in tissue before compression = $x(P_o-46)S$ taking the alveolar value of inert gas tension (section 5.12) for $P = P_o$ and $p_w = 46$ mm. Hg.

Thus the total quantity of inert gas present in all phases in extravascular tissue, conforming to the worst possible case (section 5.53), is $g - g' + x(P_o - 46)S$, expressed as volume units in accordance with the definition of S.

But the inert gas tension in the separated gas is given as $(P + 74)$ mm. Hg in equation XXV. Since this is in thermodynamic equilibrium with the inert gas in solution, in the worst possible case the quantity of inert gas remaining in true physical solution = $(P + 74)S$. Hence the maximum quantity of inert gas which can separate from solution

$$= g - g' + x(P_o - 46)S - (P + 74)S.$$

Applying equation XXVI to account for the contribution to the total volume of separated gas made by CO_2, O_2 and H_2O, the total quantity of separated gas =

$$\frac{(P + 200)}{(P + 74)} \left(g - g' + x(P_o - 46)S - (P + 74)S \right)$$

But such quantities refer to the volume reduced to standard pressure (P_o) corresponding to the definition of solubilities adopted in this text. Hence the net volume of gas separating per unit tissue volume (v/V) under an absolute gas pressure of $(P + 200)$ mm. Hg, can be obtained by applying Boyle's law as:-

$$\frac{v}{V} = \frac{P_o}{(P+200)} \cdot \frac{(P+200)}{(P+74)} \left(g - g' + x(P_o-46)s - (P+74)s \right)$$

5.84 Condition for marginal symptoms

Application of the above equation for v/V to equation II completes the derivation of the final comprehensive expression defining limiting conditions for the possible occurrence of symptoms. Thus, at any time after reaching an absolute hydrostatic pressure (P), by any decompression format from a dive of duration (θ) at pressure P_b, marginal symptoms can occur if:-

$$\frac{P_o}{(P+74)} \left(g - g' + x(P_o-46)s - (P+74)s \right) > \delta'/K \qquad \text{(XXVII)}$$

Defining a crucial parameter for proximity to symptoms (F) by:-

$$F = v/V = \delta/K \qquad \text{(XXVIII)}$$

this will have a critical value (F_c) for the possible occurrence of symptoms given by

$$F_c = \delta'/K \qquad \text{(XXIX)}$$

F_c should be a constant for a particular individual of a given modulus (K value). Morever the use of such a constant, determined experimentally, obviates most objections to the inferred assumption that all gas separating in one zone is coalesced to form the extravascular embolism responsible for symptoms. The use of a critical parameter F_c presumes that the volume of any bubble eventually formed is proportional to the total volume of gas separating from solution at the final pressure.

The quantitative expressions of this whole approach can now be summarised, and each theoretical variable reduced to fundamental parameters.

5.85 Summary of quantitative derivations

Page 177 Equation XXX should read

$$F/P_o = \frac{(g - g' + x(P_o - 46)S - (P+74)S)}{(P+74)} > F_c/P_o$$

in which, $g = xS(P_b - P_o)\psi(\theta)$ (XVI)

where $\psi(t) = 1 - \frac{4}{((b/a)^2-1)} \sum_{n=1}^{\infty} \frac{\exp(-\alpha_n^2 Dt)}{(a\alpha_n)^2 \left[(J_o(a\alpha_n)/J_1(b\alpha_n))^2 - 1 \right]}$ (XIII)

α_n being the n^{th} root, real and positive, of the equation

$$J_o(a\alpha_n)Y_1(a\alpha_n) = Y_o(a\alpha_n)J_1(b\alpha_n) \quad \text{(VIII)}$$

All solubilities are expressed as a gas/liquid volume ratio per mm. Hg partial pressure.

In equation XXX, g' can be similarly reduced to fundamental quantities for stages τ_m at pressures P_m at which phase separation has occurred,

$$g' \approx \frac{2\pi D \Sigma \tau_m ((1-x)P_m - 132 + 46x)}{(b^2 - a^2)\log(\bar{r}/a)} \quad \text{(XXIV)}$$

5.9 DECOMPRESSION OPTIMISATION

5.91 Object

The ultimate test of the thermodynamic hypothesis, whose quantitative synthesis from fundamental parameters is summarised in the foregoing section, lies in its ability to correlate practical data. If it proves successful, then the practical value of such a theory should lie in facilitating:-

1. The redistribution of the total decompression time now recommended to allow a greater margin of safety.

or 2. The revision of the whole decompression format to permit divers to surface in the minimum time with the same margin of safety.

Since the occurrence or non-occurrence of symptoms is the simplest test of any decompression, the second approach will be followed here. However, any optimisation must be based upon some criterion considered most pertinent to the parameter to be conserved - in this case decompression time.

5.92 Criterion for optimisation

Equation XXVII expresses the belief that it is only a volume of gas present in the critical tissue type in excess of a certain minimum value which can give rise to symptoms. For a given dive, the fastest overall decompression should thus be obtained if:-

1. Gas is permitted to separate from solution such that, in the worst possible case, its final volume is just below pain-provoking proportions. For the practical case of a diver returning to the surface ($P = P_o$), equation XXX gives the condition for safety as:-

$$\frac{g - g' - S(P_o(1-x) + 74 - 46x)}{(P_o + 74)} < F_c/P_o \qquad \text{(XXXI)}$$

2. The gas initially present in excess of the total tissue quantity, from which this minimum volume could separate at pressure P_o, is vented under the maximum driving force for desaturation. The latter is

greatest for the maximum hydrostatic pressure when phase separation has occurred (Δp in equation XXI). However, the reverse trend applies if the pressure is increased beyond the thermodynamic equilibrium condition (equation IV) such that phase separation cannot occur.

Thus the fastest elimination of the excess gas should be effected by continuously adjusting the pressure such that the critical tissue type is maintained just on the brink of a phase change. By this means the total excess gas should be removed most rapidly over the highest pressure range for which this condition is followed.

These criteria are sufficient to enable an optimal decompression format to be defined quantitatively.

5.93 Optimal decompression format

According to the foregoing reasoning, the thermodynamic approach would predict the shortest decompression time for a diver to return safely to the surface by adhering to the following sequence:-

1. A very rapid 'pull' from a bottom depth (H_b) to an "equilibrium" depth (H_e) beyond which any further rapid rise to the surface could cause phase separation.

2. A continuous decompression from depth (H_e), maintaining the system just on the brink of phase separation at the radial distance (r') where total tensions are a maximum. Such a condition is illustrated in fig. 12 (graph 5), this slow rise continuing until a "surfacing" depth (H_s) is reached.

3. Rapid decompression to the surface (absolute pressure P_o) from H_s, values of the latter being selected such that phase separation occurs to the extent that the volume of gas liberated at P_o is just insufficient to provoke symptoms.

The problem now becomes one of expressing quantitatively H_ϵ, H_s and the depth (H) versus t relationship for $H_\epsilon > H > H_s$.

5.94 Quantitative expression

Upon completion of the duration (θ) of a dive at a depth H_b, or absolute pressure of $(H_b + 33)$ feet of salt water, the maximum total tension at any point cannot exceed that of the region immediately adjacent to the capillary. However, this value will equal the maximum attainable with time (fig. 12, graph 1) which is the absolute hydrostatic pressure less the "inherent unsaturation". Thus it should be theoretically possible to effect an instantaneous decompression equal to the "inherent unsaturation" without causing any phase separation for which equation XXI gives:-

$$H_b - H_\epsilon = \Delta p = \left((1 - x)(H_b + 760) - 132 + 46x\right) \text{ mm. Hg.}$$

Reverting to pressure and tension units of feet of salt water gauge (s.w.g.), where 33 feet (s.w.g.) $\equiv$ 760 mm. Hg, the above expression gives H_ϵ as:-

$$H_\epsilon = xH_b - 27.3 + 31.0x \text{ feet (s.w.g.)} \qquad (49)$$

The depth for direct surfacing (H_s) is determined by residual gas available for separation, i.e. writing equation XXXI as:-

$$\frac{(g - g') - S(36.1 - 31.0x)}{36.1} = F/P_o \qquad (50)$$

where $(g - g')$ is now given, for the total decompression time (T), by equation 35 since no phase change has occurred, i.e.:-

$$(g - g') = \chi S \left[H_b \Psi(\theta + \tau) - (H_b - H_\epsilon)\, \Psi(\tau) - \int_{H_\epsilon}^{H_s} \Psi(t - \theta - \tau)\, dH \right] \qquad (51)$$

The relationship between H and t is dependent upon continuous location ($r = r'$) of the peak total tension which should coincide with that of maximum inert gas tension p', i.e.

$$p = p' \text{ for } r = r' \text{ where } \frac{\partial p}{\partial r} = 0 \text{ and } \frac{\partial^2 p}{\partial r^2} < 0 \qquad (52)$$

While no analytical solution could be found to equations 50-52, approximations do not seem warranted at this stage in view of the ease with which optimisations can be determined using a thermal analogue (section 6.5).

5.95 Experimental justification

From a semi-quantitative survey of the foregoing expressions, the thermodynamic approach would predict an optimal decompression from a 200 foot dive comprising:-

1. Rapid decompression to 157.5 feet compared with a maximum of 83.5 feet suggested by conventional theory.

2. Continuous decompression from 157.5 feet to a depth of 20-35 feet, depending upon the individual.

3. Direct surfacing from 20-35 feet compared with the conventional final 10 foot staging (U.S. Navy, 1964).

> While these represent drastic changes from conventional procedures, the thermodynamic approach would appear to be in for closer agreement with the purely empirical methods devised by native pearl divers (Appendix I).

These men invariably surface directly from the depths of 25-40 feet. The fact that such dives are regularly performed in the sea is the strongest evidence in favour of the thermodynamic approach. However, an exact quantitative correlation might be better postponed pending consideration of some experiments designed to test the more fundamental aspects of the hypothesis.

CHAPTER 6

EXPERIMENTAL

6.6 The Pneumatic Analogue

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EXPERIMENTAL

6.1 PERSPECTIVE

The literature contains a wealth of practical data of the most varied nature upon which to prove or disprove any hypothesis for decompression sickness. One of the major tasks of this thesis has been the collection and organisation of this mass of information which is so conflicting in many of its published interpretations. It is therefore felt that the practical approach is better directed towards devising conclusive experiments to test the salient features of the hypothesis. The vital questions would seem to be:-

1. Is cavitation at liquid-liquid interfaces as random as recorded for the other cases of suppressed transformation?

2. Is a single tissue as heterogenous in its transport properties as its histological appearance might indicate?

3. Does the diffusion coefficient of inert non-polar gases in cytoplasm differ from the values for the corresponding substances in water by the same large factor recorded for ions and polar compounds?

4. Does the inherent unsaturation increase linearly with both absolute hydrostatic pressure and mole fraction of inhaled oxygen as the physico-chemical analysis would predict?

The other phase of the work in which experimentation would seem desirable is the building of analogues for:-

1. Predicting optimal decompressions with the object of testing any predictions upon animals which are similar to man in their susceptibilit to decompression sickness.

2. Analysing the wealth of diving data with minimal mathematical approximation.

The latter is probably the more important for a hypothesis whose potential value lies in the quantitative nature of its expression.

6.2 CAVITATION AT LIQUID-LIQUID INTERFACES

6.21 Preliminary investigation and precautions

Preliminary decompression of water, in contact with either olive oil or liquid paraffin, indicated that when cavitation occurred it did so at the liquid-liquid interface. However, it was almost impossible to be certain that no micro-bubbles were present before decompression.

To help overcome this difficulty the procedure was adopted of feeding the denser liquid in through a tube to the bottom of the vessel containing the lighter liquid, whose upward displacement created a fresh phase interface. This precaution was intended to give direct liquid-liquid contact. Attempts to verify that all gas occlusions had been eliminated took the following forms:-

1. Pairs of liquids were taken of almost equal refractive indices such that any micro-bubble present before decompression stood out clearly when the interface was strongly illuminated and viewed from an angle oblique to the direction of light transmission.

THE DECOMPRESSION CELLS

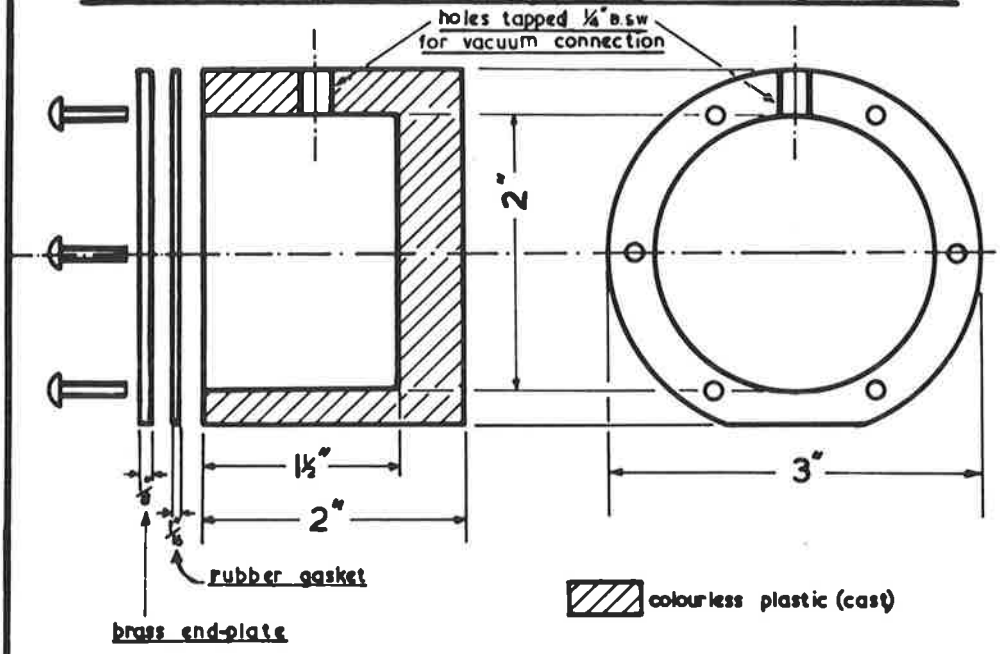


Fig.13

FLOW DIAGRAM
(OF THE PRESSURE CONTROL SYSTEM)

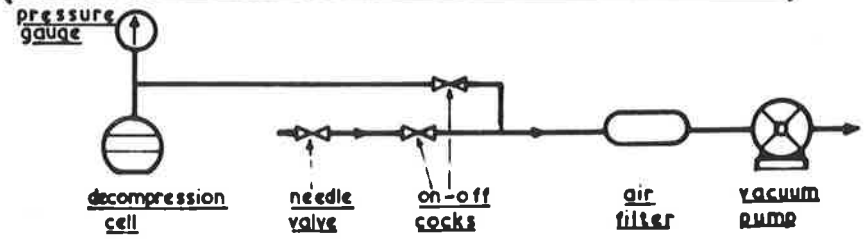


Fig. 14

2. The extinction angle of the interface was measured and verified as that for direct contact between the liquid phases, and not that for total internal refraction at an intervening gas layer.

The first method is particularly applicable to detecting micro-bubbles while the second is directed at films of gas, Adam (1930) stating that the reflective powers of a liquid surface are changed by even a monomolecular layer of gas.

6.22 Apparatus

The foregoing optical requirements effectively determine the dimensions of the cell for the liquids as having:-

1. At least one flat face for straight illumination by light transmitted parallel to the interface.

2. A circular section such that liquid-container and container-air boundaries exist which are perpendicular to the path of light transmitted from the centre of the container. The walls would then have no influence upon the extinction angle measured at that point.

A cylindrical form is thus suited to both requirements provided the cell is filled such that the liquid-liquid interface coincides with the geometric axis. A machine drawing of the final design is given in fig. 13. Other features of the cell are the use of only one gasket and its construction from a hard colourless copolymer (Hills, 1965).

The equipment for pressure control and measurement is very simple - as shown in fig. 14. Various degrees of decompression are maintained by balancing the continual bleed into a 2-litre buffer chamber against its exhaust to a vacuum pump.

6.23 Gel-oil interfaces

Many substances were tested in an attempt to find a suitable system for investigating cavitation at the gel-oil interface. The only boundary sufficiently smooth to give a recognisable mirror image of simple objects was obtained by running a 20% solution of calf-skin gelatine at 50-60°C into liquid paraffin. Upon cooling to room temperature the required gel-oil interface was formed. Using a telescopic eyepiece mounted in a frame to ensure its alignment with the cell axis, an extinction angle of 43° to the normal was recorded for the interface. This corresponded closely to values measured for the individual phases by an Abbé refractometer of $\mu_{oa} = 1.4465$ and $\mu_{ga} = 1.3377$ at 25°C, since $\text{cosec}^{-1}\ (1.4465/1.3377) = 43.7°$. μ_{oa} and μ_{ga} are the refractive indices of paraffin oil to air and 20% gelatine solution to air respectively. Every time this method of filling was used the same result was obtained indicating a direct gel-oil interface.

When the reverse procedure was used, i.e. pouring the oil on to the gelatine solution, an extinction angle of 67° was recorded. This corresponds to an angle of $\text{cosec}^{-1}\ \mu_{oa} = \text{cosec}^{-1}\ 1.4465 = 67.1°$ implying an air film at the gel-oil interface.

Placing the eyepiece at 55° to the normal, ten decompressions to minus 20 inches Hg failed to give any change of intensity detectable by eye. However, repeating the experiment in an open dish, but adding the oil last and distorting the interface by alternate compressions in perpendicular directions, a careful microscopic examination of an area

of 100 cm.^{2} revealed 10 bubbles. These were observed without decompression indicating that they were formed by coalescence of the initial film. Diameters were of the order of 4-8 microns.

The liquid paraffin used was Shell "Ondina Oil 33" which is very clear and of density 0.8 gm. cm.$^{-3}$. According to the extinction angles this oil phase was found to give a direct interface with any aqueous liquid if the latter, as the denser, was added last.

6.24 Suitable systems

No two pure immiscible liquids could be found of refractive indices sufficiently close to ensure the detection of any bubbles formed at their interface. However, the refractive index of liquid paraffin could be matched quite simply by blending two hydrophylic substances.

A suitable mixture proved to be 90% glycerol + 10% water which gave a refractive index of 1.4469 compared with 1.4465 for the paraffin oil used previously. Acetic acid 30% w/w in water was also satisfactory, the interface with paraffin oil disappearing at room temperature.

All liquids were kept in open containers to ensure their saturation with air.

6.25 The standard test

In any statistical approach it is essential to adopt the same procedure to minimise the effect of variables other than those under investigation. The following standard test was adopted:-

The containers were cleaned and dried with towelling and then polished with soft paper tissue. Although crude, this procedure appeared adequate since at no stage during any test was bubble formation observed at the walls of the cell; nor were any formed in the bulk of either liquid or at the rubber gasket which had been previously soaked in the paraffin oil.

The cell was filled as prescribed earlier with the denser liquid displacing the lighter from the bottom upwards.

A standard exposure time of 4 minutes was adopted since preliminary runs showed that most bubbles formed very soon after decompression and very seldom after 2 minutes. The number of bubbles forming was recorded, and the liquid samples discarded after each run.

6.26 Liquid-liquid decompression

The frequency of bubble occurrence was measured with variation of:-

1. Decompression i.e., applied vacuum.
2. Degree of liquid-liquid dispersion.
3. Gas concentration.
4. Temperature.

For every combination of these variables 20 runs were performed, this being the number regarded as significant by Strasberg (1956). Dispersion of the liquids was obtained by shaking the cell when required, while saturation with acetylene was employed to increase concentration without varying tension.

580 runs were performed, the results of which are recorded in table 11.

CAVITATION AT THE LIQUID-LIQUID INTERFACE

System		Number of bubbles formed within the first 4 minutes of decompression																													
		Glycerol*						Dispersed glycerol*						glycerol*						acetic acid*							acetic acid**					
Decompression		5	10	15	20+	20	28	5	10	15	20	25	28	20 inches of mercury (ΔP)																	
Temperature (°C)		25	25	25	25	25	25	25	25	25	25	25	25	20	25+	30	35	40	45	20	25	30	35	40	45	50	20	25	30	35	40	45	50
	1	-	-	-	-	3	-	-	-	-	7	-	11	9	-	4	7	-	16	7	6	12	5	2	-	2	7	4	25	9	21	14	16
	2	-	-	3	6	-	11	-	-	-	9	7	-	-	6	-	12	15	8	1	-	2	10	5	10	4	13	11	19	7	13	21	8
	3	-	-	-	-	8	17	-	-	-	-	12	15	-	-	-	3	-	1	14	4	5	8	-	4	22	4	22	4	3	7	7	21
	4	-	-	-	2	13	5	-	-	-	-	7	13	11	2	14	8	2	-	-	11	-	2	6	6	8	7	17	14	23	24	10	7
	5	-	-	7	-	2	20	-	-	3	5	-	-	-	-	-	-	-	6	4	2	6	6	8	14	11	21	5	12	19	16	31	27
Run	6	-	-	4	-	8	14	-	7	-	-	15	5	6	-	8	16	16	-	2	5	1	-	11	1	6	3	11	2	7	10	4	11
	7	-	-	-	8	-	8	-	-	5	2	19	14	-	8	10	4	8	10	2	13	6	7	7	3	1	6	9	23	11	25	16	8
Number	8	-	4	-	-	8	15	-	-	-	-	-	8	-	-	3	-	5	9	7	6	11	3	5	21	7	17	14	7	4	5	12	17
	9	-	-	-	4	16	11	-	7	-	-	10	-	8	4	-	5	9	3	3	-	4	8	-	-	9	-	21	14	12	11	8	16
for	10	-	-	-	17	-	-	-	-	-	-	5	10	-	17	12	9	-	-	-	6	1	11	3	8	10	5	14	11	7	17	14	6
	11	-	-	-	-	7	10	-	-	-	4	15	18	-	-	-	-	-	22	5	7	9	7	5	11	5	15	6	8	20	8	18	24
each	12	-	-	13	11	-	12	-	-	7	-	4	7	-	11	-	8	-	1	5	5	5	4	9	1	4	4	10	5	11	11	14	29
	13	1	-	-	-	6	-	-	-	1	14	-	24	13	-	-	10	7	3	2	-	-	4	5	2	18	7	14	14	16	15	11	8
series	14	-	3	-	-	-	21	-	-	-	-	13	-	-	-	16	-	11	12	9	4	4	3	4	-	7	17	3	7	8	4	7	10
	15	-	-	-	7	13	-	-	-	-	5	-	6	-	7	-	-	-	-	1	4	5	14	10	2	6	16	-	2	8	9	16	7
	16	-	-	1	6	4	5	-	-	-	-	5	12	9	6	8	5	4	2	6	5	5	2	2	7	2	8	11	21	12	19	11	21
	17	-	7	-	-	7	4	-	2	-	-	-	7	-	-	11	3	-	5	1	-	6	4	6	13	7	9	4	19	4	12	8	10
	18	-	-	2	1	-	10	-	-	4	5	3	12	7	1	-	-	10	9	-	8	8	3	9	-	2	12	9	9	10	7	24	8
	19	-	-	-	-	7	-	-	-	-	-	7	11	-	-	-	3	3	-	5	4	2	9	7	8	2	5	7	4	14	16	14	20
	20	-	-	-	12	2	18	-	-	-	11	24	2	-	12	1	-	7	5	2	7	9	4	6	11	8	8	3	13	9	12	11	15
Total number of bubbles (N)		1	14	30	74	104	181	0	16	20	62	146	175	63	74	87	93	97	115	76	97	100	114	110	122	141	184	195	233	214	262	269	289
Fraction of nucleated runs (p)		0.5	.15	.30	.50	.70	.75	0	.15	.25	.45	.70	.80	.35	.50	.50	.65	.60	.75	.85	.80	.90	.95	.90	.85	1.0	.95	.95	1.0	1.0	1.0	1.0	1.0

TABLE 11

*Both phases saturated with air. **Both phases saturated with acetylene. +The same results.
N.B. The oil phase is liquid paraffin in every run. Shell "Ondina Oil 33".

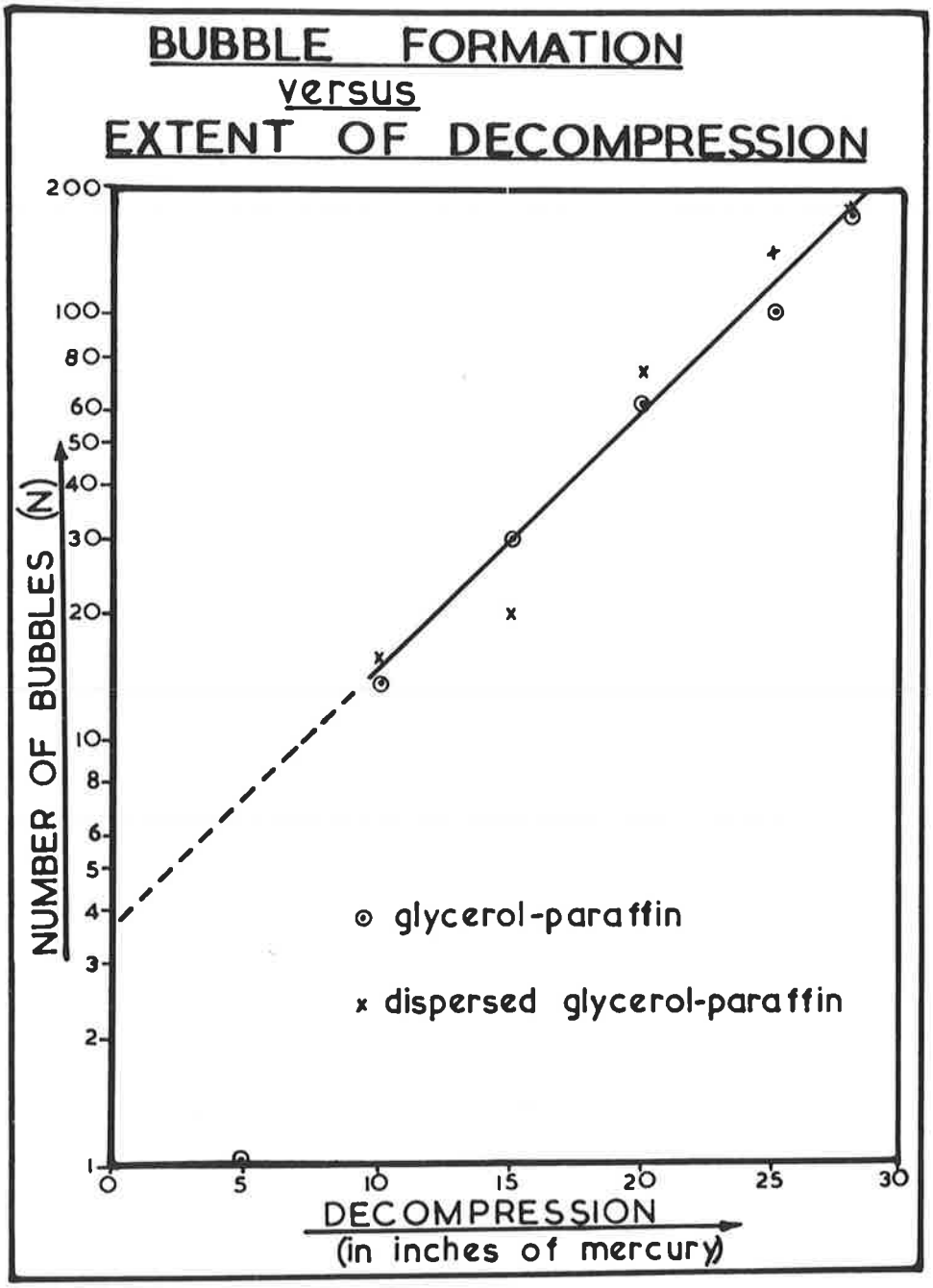

BUBBLE FORMATION
versus
EXTENT OF DECOMPRESSION
NUMBER OF BUBBLES (N)
200
100
80
60
50
40
30
20
10
8
6
5
4
3
2
1
0
5
10
15
20
25
30
DECOMPRESSION
(in inches of mercury)
⊙ glycerol-paraffin
x dispersed glycerol-paraffin

Fig. 15

Semi-log plots of the number of bubbles formed are given for (i) Decompression as the variable (fig. 15).

(ii) Temperature variation (fig. 16).

In the latter case the ordinates are selected to give simple Arrhenius plots, there being some doubt about the justification for drawing straight-line relationships. While more points, or more runs per point, might have reduced this uncertainty, it must be remembered that each acetic acid line represents 140 runs.

6.27 Analysis of results

The following points would seem to emerge from figs. 15 and 16:-

1. There would appear to be very little increase in the probability of forming a bubble by more intimate dispersion of the two liquid phases.

2. The plot of log (N) versus decompression (ΔP) would appear remarkably linear over the range indicated.

3. The foregoing plot would indicate quite appreciable chances of bubble formation for decompressions exceeding 5 ins. (127 mm.) Hg. If any metastable limit exists it must be very small by comparison with the nucleation thresholds conventionally postulated in diving (see section 1.6), whether taken upon a constant differential or a pressure ratio basis.

4. For the same decompression and temperature, there would seem to be a greater probability of phase separation using a more soluble gas.

5. While the doubts about drawing straight lines through the points of the Arrhenius plots (fig. 16) would not justify any quantitative analysis, it would seem fair to say that the gradient of the glycerol/paraffin oil system just exceeds that for acetic acid/paraffin oil.

Hence from the simple Maxwell-Boltzmann approach, $N = W_1 \exp(-E/R\Theta)$, we have:-

$E_g > E_a$, where E_g and E_a are the activation energies of cavitation at the glycerol/paraffin oil and acetic acid/paraffin oil interfaces respectively.

Employing the drop weight method described by Davies and Rideal (1963), and applying the correction factor of Harkins and Brown (1919), the following interfacial tensions were measured at 35°C:-

Glycerol/air,	$\gamma_a = 61.6$ dyne/cm	$E_g \propto \gamma_a + \gamma_o - \gamma_{oa} =$
paraffin oil/air,	$\gamma_o = 29.8$ dyne/cm	55.7 dyne/cm
glycerol/paraffin oil,	$\gamma_{oa} = 35.7$ dyne/cm	(equation 13)

Acetic acid/air	$\gamma_a = 42.2$ dyne/cm	$E_a \propto \gamma_a + \gamma_o - \gamma_{oa} =$
paraffin oil/air	$\gamma_o = 29.8$ dyne/cm	56.9 dyne/cm
acetic acid/paraffin oil	$\gamma_{oa} = 15.1$ dyne/cm	

i.e. $E_g > E_a$.

which agrees with the previous deduction from the Arrhenius plots. While this does not prove equation 13, the result is compatible with the thermodynamic argument expressed in section 4.28.

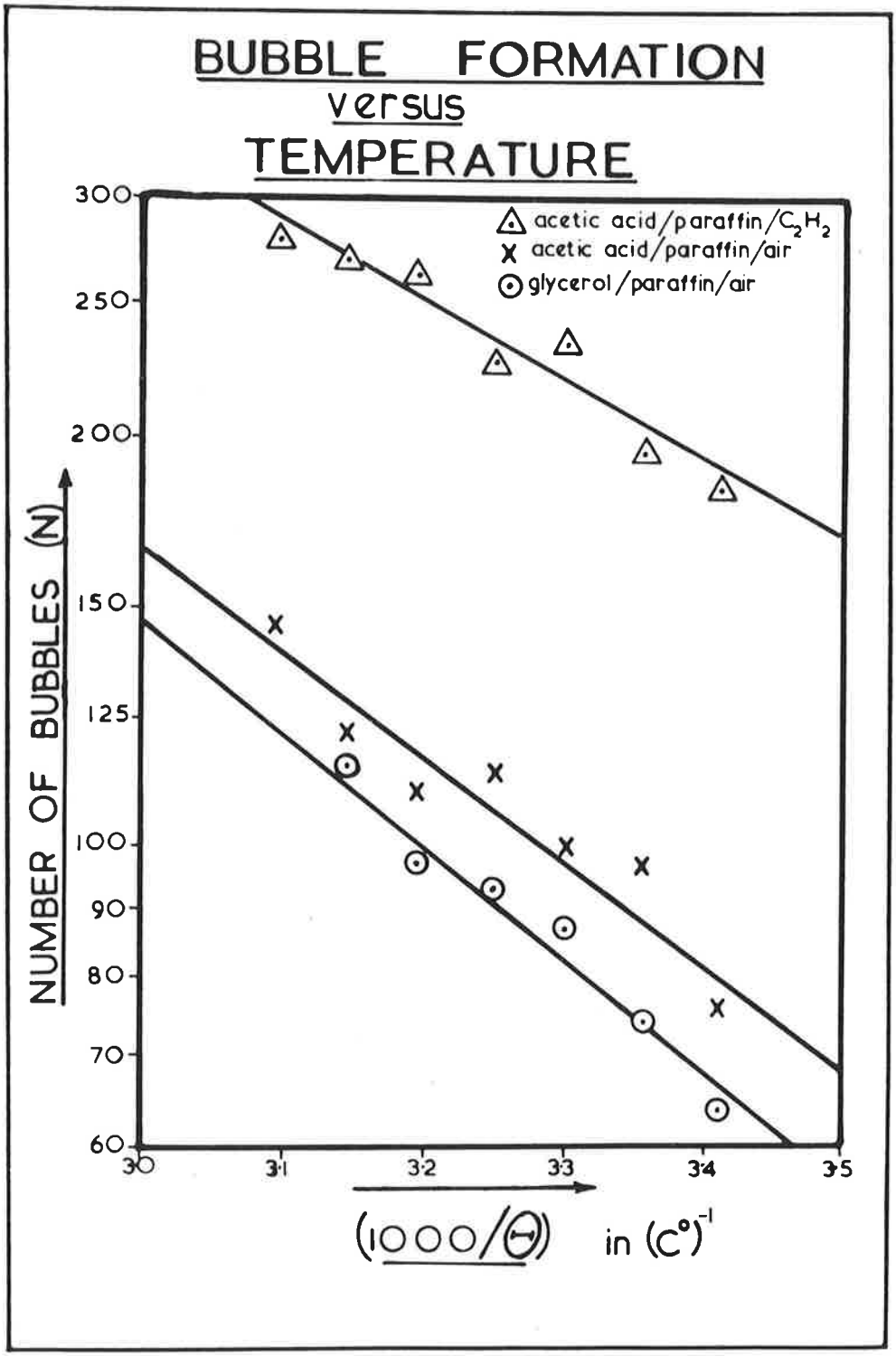

BUBBLE FORMATION
versus
TEMPERATURE
acetic acid/paraffin/C2H2
acetic acid/paraffin/air
glycerol/paraffin/air
NUMBER OF BUBBLES (N)
300
250
200
150
125
100
90
80
70
60
3·0
3·1
3·2
3·3
3·4
3·5
(1000/Θ) in (C°)-1

Fig. 16

While a more quantitative physical analysis has proved most interesting, it is hardly relevant to the problem of decompression sickness. The simple conclusion drawn from these results is that cavitation at a liquid-liquid interface is a random process and, if relevant to the critical tissue type, it would seem unwise to rule out the possibility of bubble formation for any degree of supersaturation.

6.3 TRANSPORT

6.31 Object

The vital and controversial issue of whether diffusion or circulation is the rate-limiting process in blood:tissue exchange may be reduced to the more specific questions of:-

1. Does tissue respond as though uniform in the transient case?

2. Do exponential time constants derived by the conventional analysis of experimental data (figs. 17 and 19) represent:-

   (a) blood perfusion rates,

   (b) a function of diffusion coefficients and tissue micro-geometric dimensions, or

   (c) a combination of the above in which each makes a significant contribution?

In attempting to verify the more comprehensive model derived in section 4.2 for an appraisal of these questions, practical results are required from experiments designed to offer the most critical assessment.

632 Design of experiments

Appendix III outlines the arguments by which the advocates of blood perfusion, as the rate-controlling process, attempt to explain most of their deviations fromthe simple linear model (section 5.1) in terms of parallel arterio-venous pathways. However, any complex postulations related to the preferential channelling of blood through different sets of vessels, under different conditions, must be inoperative when the circulation has ceased. Thus, if fundamental parameters derived from excised tissue are in agreement with those for the same tissue perfused with blood, then there is good reason to believe that:-

1. There has been no appreciable micro-geometric change upon death of the animal, and

2. If the same mathematical model can interpret both sets of data, it would seem to be realistic.

This would suggest two sets of experiments upon one particular tissue type:-

(a) when the inert tracer is administered to the tissue in the living animals by intra-arterial infusion.

(b) when a section of the same tissue excised from the freshly-killed animal is exposed to the inert gas.

Skeletal muscle is the tissue type selected by Fenichel and Horowitz (1963), largely on the grounds of uniformity, for their classical differentiation between bulk diffusion and surface permeation as the operative mode of uptake of inert solutes by muscle fibres. However, a muscle with more mechanical 'cohesion' than the

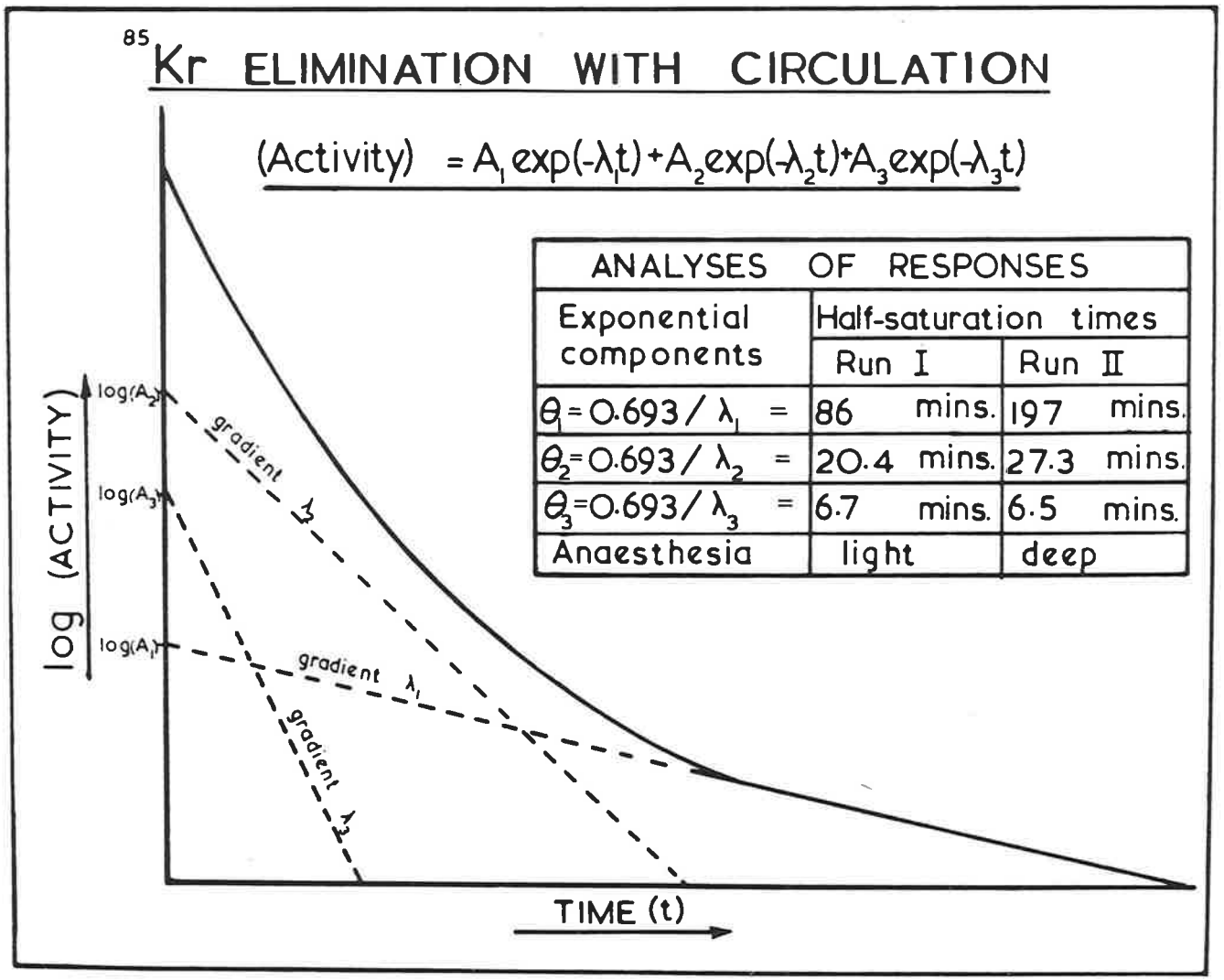

85Kr ELIMINATION WITH CIRCULATION
(Activity) = A1 exp(-λ1t) + A2exp(-λ2t) + A3exp(-λ3t)
ANALYSES OF RESPONSES
Exponential components
Half-saturation times
Run I
Run II
θ1 = 0.693 / λ1 = 86 mins. 197 mins.
θ2 = 0.693 / λ2 = 20.4 mins. 27.3 mins.
θ3 = 0.693 / λ3 = 6.7 mins. 6.5 mins.
Anaesthesia light deep
log (ACTIVITY)
log(A2)
log(A3)
log(A1)
gradient λ2
gradient λ1
gradient λ3
TIME (t)

Fig.17

frog's sartorius would seem better suited for cutting into thick unfixed sections. In view of these considerations, and the greater relevance to decompression sickness of any constants derived from a warm-blooded animal, the inner thigh muscle of a rabbit was selected. This tissue is readily accessible for monitoring radioactivity in the living animal, and is of sufficient size to provide the thick sections required for the other case - i.e. uptake without circulation.

Selected gases must be not only inert but also non-polar in order to minimise retardation by charged groups fixed to membranes or associated with any active transport mechanism. ^{85}Kr is thus ideal, a good experimental method for monitoring in the living animal being described by Thorburn et al (1963), whose apparatus was used. However, its availability did not permit the use of the same gas for the excised sections.

Only dilatometric means were available to follow the uptake of gas by excised tissue sections. An inert non-polar gas with a high solubility was thus selected to provide the maximum sensitivity, acetylene proving suitable since its solubility in water is 1.46 ml. at S.T.P./ml. H_2O atm. - Perry (1950). It is inert to body tissues and presents a molecule with no dipole moment.

6.33 Method for perfused tissue

The apparatus for monitoring radioactivity, and maintaining uniform infusion rates, was exactly as described by Thorburn et al (1963) in their study of the nutrient blood flow to kidney. The

necessary surgery was performed by Dr. G.D. Thorburn and the experiments completed during a short visit by the writer to the Department of Physiology at the University of New South Wales.

A fine polyvinyl chloride catheter was introduced into the aorta of a 3 Kgm. rabbit anaesthetised by the injection of nembutal into a prominent vein in the ear. This permitted the continuous intra-arterial infusion of ^{85}Kr, at an arbitrary concentration in saline, the rate being maintained constant. The β and γ emissions were recorded for every minute by a scintillation counter whose $\frac{1}{2}$" diameter probe was rested in full but gentle contact with the exposed left inner thigh muscle. The probe and whole region of incision were covered by a pad of cotton wool to prevent undue heat loss from the exposed tissue.

The abrupt termination of the infusion after 10 mins. represented a step in arterial krypton tension, since the quantity re-circulated past the lungs has been reported to be very small (Chidsey et al, 1959). After applying corrections for background radioactivity and the paralysis time of the counter, the subsequent exchange response of the muscle could be analysed into three well-defined exponential terms. Enumerated according to their order of extraction, the respective time constants (λ_1, λ_2 and λ_3) are shown in fig. 17. θ_1, θ_2 and θ_3 are the respective half-saturation times, i.e. $\theta_1 = 0.693/\lambda_1$ etc.

Since counting was continued for 3 hours following cessation of the infusion, the worst error is probably that of maintaining the constant blood flow required by the mathematical analysis described in

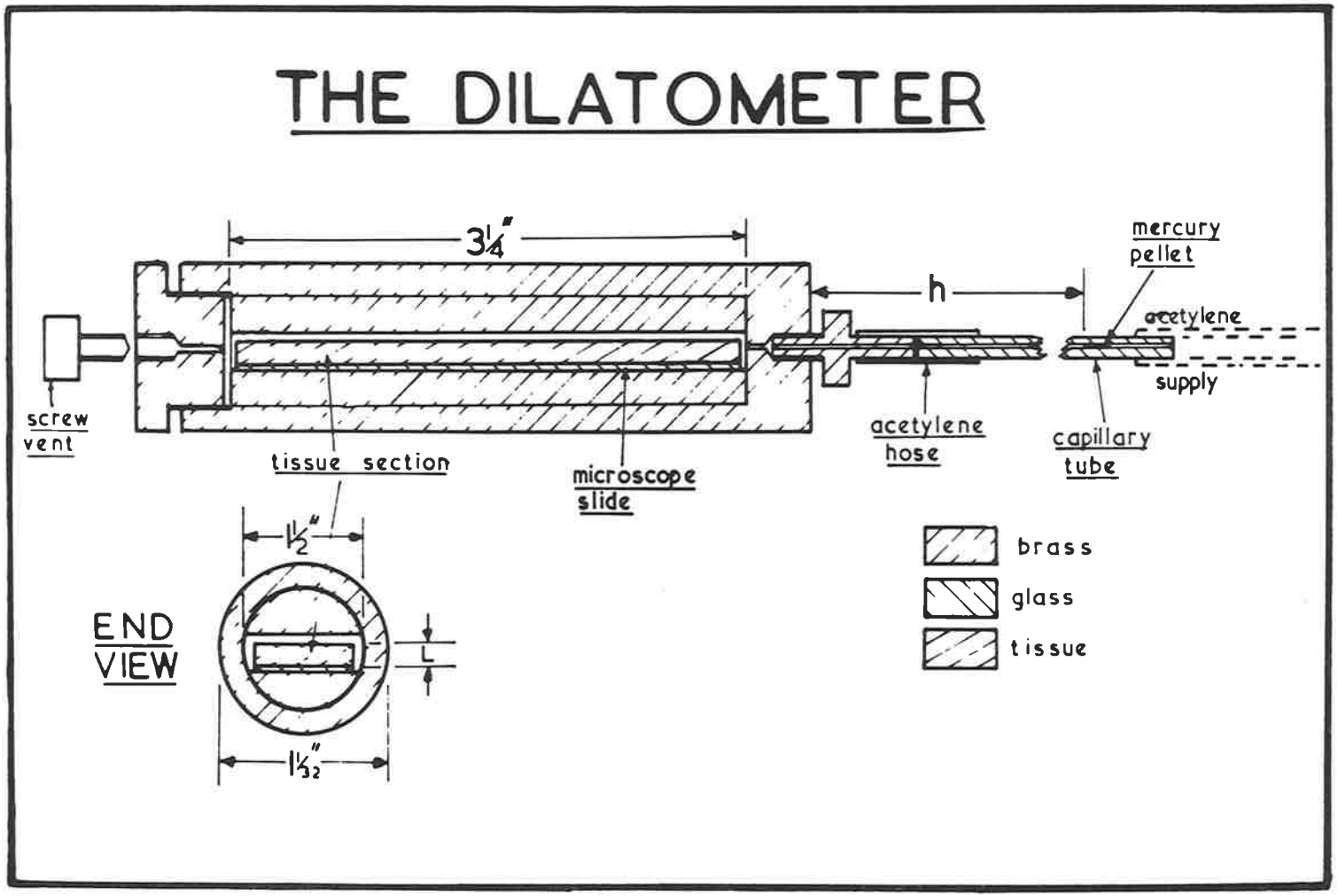

THE DILATOMETER
3¼"
h
mercury pellet
acetylene
supply
screw vent
tissue section
microscope slide
acetylene hose
capillary tube
brass
glass
tissue
END VIEW
1½"
L
1½"

Fig.18

section 5.4. In the first run (I) the degree of anaesthesia was controlled as that for which a slight corneal reflex was just attainable. Nembutal was administered at intervals of 5-15 mins. through the ear.

In the second run (II) upon the same animal, a much deeper degree of anaesthesia was maintained throughout, no particular feature being followed for its control. During a third run the animal died.

6.34 Method for excised tissue

The response analysis described in section 5.48 is greatly dependent upon the geometric accuracy of the sections exposed to the inert gas. In many preliminary trials using various cow, sheep and rabbit muscles, it was found that sections of thickness 1-3 mm. could be cut with a variation of no more than 0.05 mm. over the area of 7.5 × 2.5 cms. required to cover a microscope slide. The technique developed was one of quenching the excised muscles in solid CO_2 and "planing" them down to various thicknesses as they gradually thawed on a freezing microtome. Each was then trimmed square with the microscope slide upon which it was mounted. The above dimensions of the section permitted side effects to be neglected in the mathematical analysis.

Excised within minutes of the death of rabbits of similar age, weight and breed to that infused with krypton, the inner thigh muscles were immediately quenched in solid CO_2. This action was intended to render the nucleation of ice formation so profuse that no individual crystal could grow to a size sufficient to cause undue

mechanical damage to cells or other disarrangement of the micro-geometry. Average thicknesses (L) of the sections were determined by weight difference between the mounted section and the pre-weighed microscope slide. All sections were irradiated with U.V. light to delay the onset of putrefaction, and all runs were started within ½ hr. of the death of the animal to minimise the effects of any autolysis.

The mounted section was slid into the dilatometer shown in fig. 18 and the end replaced. The air was then rapidly flushed out by acetylene, and the vent plug replaced. All screw joints were rendered perfectly gas-tight by previously binding all threads with P.T.F.E. tape. Removing the acetylene connection, the open end of the uniform-bore capillary tube was rapidly sealed by a small pellet (3-5 mm. in length) of mercury inserted by a clean dry hypodermic syringe. The distance (h) of one end of this pellet from some arbitrary mark on the dilatometer was recorded against time. Readings were taken every minute for 4 hours; h_∞ was calculated from solubility data.

It was found that very smooth plots of h vs. time (t) could be obtained if the following precautions were taken:-

(i) The glass capillary was thoroughly cleaned by chromic acid, then alcohol and finally dried with dust-free air.

(ii) Only quadruple-distilled mercury was used as the pellet.

(iii) The dilatometer was mounted horizontally on a vibrating table.

Momentarily switching off the vibration at an exact time, the mercury was permitted to 'stick' just long enough to enable the

ACETYLENE UPTAKE WITHOUT CIRCULATION

$$(h - h_\infty) = A'_1.\exp(-\lambda'_1 t) + A'_2.\exp(-\lambda'_2 t) + A'_3.\exp(-\lambda'_3 t)$$

ANALYSES OF RESPONSES			
Exponential components	Half-saturation times		
	Run III	Run IV	Run V
$\theta'_1 = 0.693/\lambda'_1$ =	52 mins.	40.6 mins.	30.3 mins.
$\theta'_2 = 0.693/\lambda'_2$ =	22 mins.	8.8 mins.	5.6 mins.
$\theta'_3 = 0.693/\lambda'_3$ =	3.1 mins.	3.8 mins.	2.8 mins.
Thickness (L)	2.96 mm.	1.91 mm.	1.05 mm.

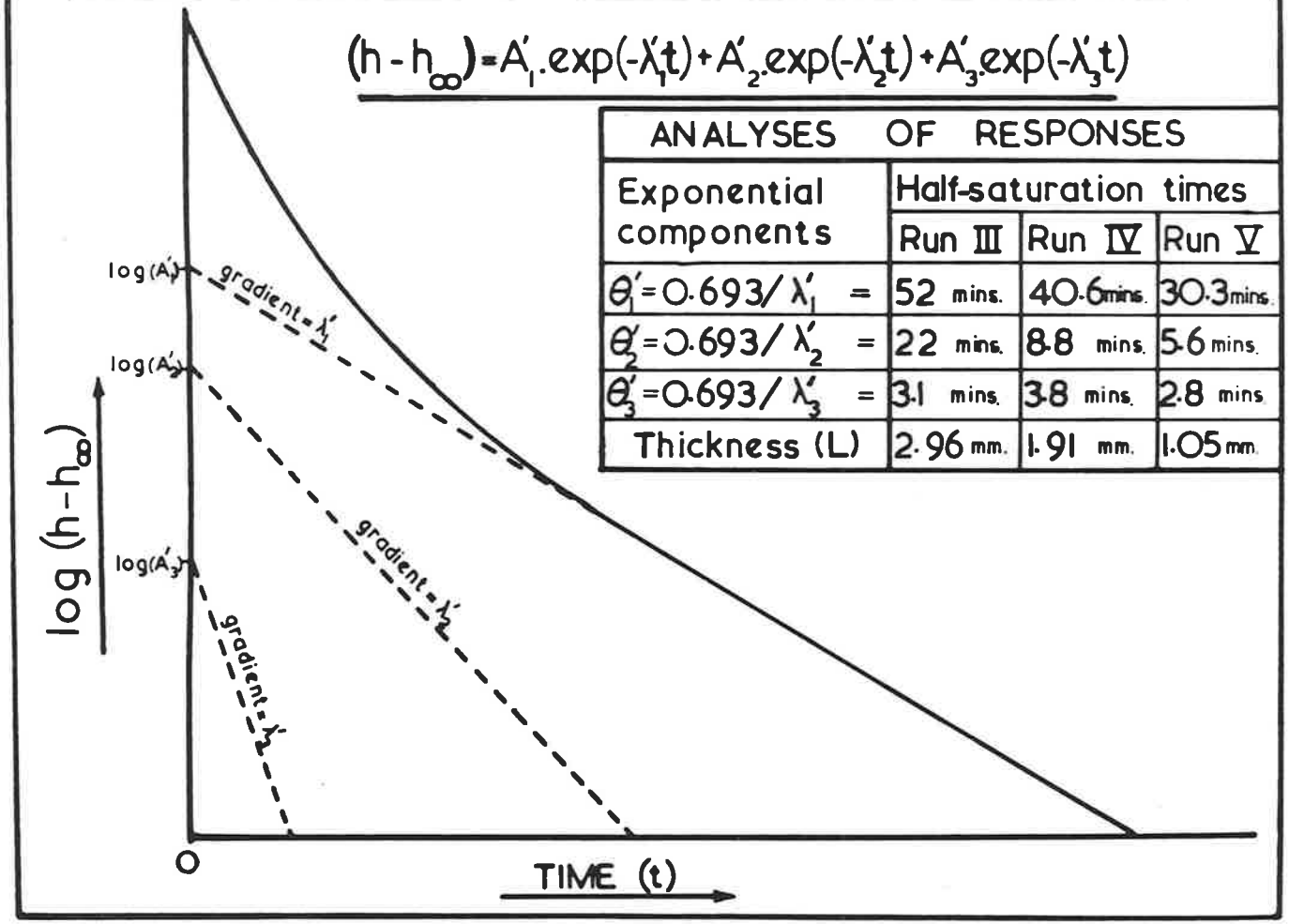


Fig.19

position of the pellet to be measured accurately. Room temperature was controlled at 90 $\pm$ 1 ^{o}F.

The need to minimise 'sticking' of the mercury in the capillary was the feature underlying both the selection of a very soluble inert gas and the design of the dilatometer. In the latter, dead space is kept to a minimum to give the greatest percentage volume change with uptake, and hence the greatest pressure differential forcing the pellet to register the change. Capillaries of diameter less than 1 mm. proved unsuccessful.

The plots of $(h - h_{\infty})$ vs. t show that the response of each tissue section to acetylene can be analysed into three well-defined exponential components (fig. 19). The uncertainties in the exact time of insertion of the mercury pellet detract from any worthwhile information to be gained from extracting intercepts. However, the great advantage of this type of analysis is that such incomplete response data are perfectly adequate for determining the exponential time constants (λ'_1, λ'_2 and λ'_3). The corresponding half-times are designated θ'_1, θ'_2 and θ'_3 in fig. 19.

Analyses of these results and those for krypton are contained in section 5.4.

6.35 Future work

The results recorded in this section are regarded as the bare minimum required to establish that the mathematical model described in section 5.4 is feasible. This conclusion is facilitated by the fact that one is trying to differentiate between values of cellular diffusion coefficients differing by a factor of the order of 10^4.

The work upon excised tissue uptake leaves little doubt that tissue cannot be regarded as a homogeneous diffusion medium. Such a conclusion cannot be disregarded on the grounds of autolysis, or damage caused by cutting the sections, since either process could only serve to render tissue more uniform in its transmission properties.

A more rigorous experimental programme is scheduled which will incorporate the following refinements:-

1. Using ^{85}Kr, and perhaps two isotopes, simultaneously in both cases, i.e. with and without circulation.

2. Taking far more rigorous precautions to minimise autolysis in excised sections.

6.4 THE INHERENT UNSATURATION

6.41 Object

The feature of the hypothesis derived in this thesis is the determination of proximity to marginal symptoms based upon a particular tissue region whose phases are always in thermodynamic equilibrium. This is directly opposed to the conventional postulation that the condition of the critical zone is one of supersaturation following decompression.

Although there would appear to be a strong case in favour of random nucleation, and such a fundamental change of thinking, it is felt that the success or failure of the thermodynamic hypothesis lies in its ability to explain the beneficial effect of staging a diver. This reverts to the basic question of proving the existence of a motive

power for the elimination of gas from tissue regions following phase separation. The theoretical investigation of this alternative to supersaturation (section 5.6 to 5.8) shows how such a driving force for the inert gas can be provided by the inherent unsaturation arising from metabolism.

There would seem little doubt from the published work recorded in section 5.6 that a total tension differential for gases of at least 50-60 mm. Hg exists between tissue and a surrounding atmosphere of air at 760 mm. Hg. Although this is smaller than any which could account for staging, the inherent unsaturation could reach a reasonable magnitude if it varies as predicted theoretically by equation 48.

Thus the specific points to be proven are that the inherent unsaturation

(i) increases linearly with pressure for inhaled gas of constant composition, and

(ii) decreases linearly with mole fraction of the inert gas for constant pressure.

6.42 Design of experiment

The principle adopted for measuring the unsaturation in vivo was that of measuring the total tension of all volatile and gaseous substances as the sum of the partial pressures of those substances in a cavity equilibrated with the tissue. This cavity needs to be non-collapsible, the walls being capable of passing all volatile substances.

One such method described in the literature is that of Lategola (1964) who used a cylindrical capsule with silicone rubber membranes held rigid across the ends. However, his measured unsaturation of 41-48 mm. Hg is open to alternative interpretation in view of his statement that the membranes had "relatively negligible permeability to water vapour". This implies that he could have been simply measuring the vapour pressure of water at body temperature - 46 mm. Hg (equation XVII).

To avoid this uncertainty, the writer used a polyvinyl chloride membrane in the form of a non-collapsible tube whose permeability to nitrogen, oxygen, carbon dioxide and water vapour was proven, in vitro, before implanting in the animal.

While Lategola waited some 5-14 days for the gas in his capsule to reach steady-state, a period of 1-4 months was found necessary by Guyton (1963a) who implanted ping-pong balls with 200 holes, yet full of saline, in dogs. However, his readings are not really relevant to the unsaturation problem since he was measuring a hydrostatic pressure in tissue and not a total gas tension.

Since both Lategola and Guyton took their readings for air at atmospheric pressure only, the time to reach steady-state was not a prime concern. However, a much faster response time is desirable for unnatural environments in which the general health of the animal is likely to deteriorate.

This can be achieved by:-

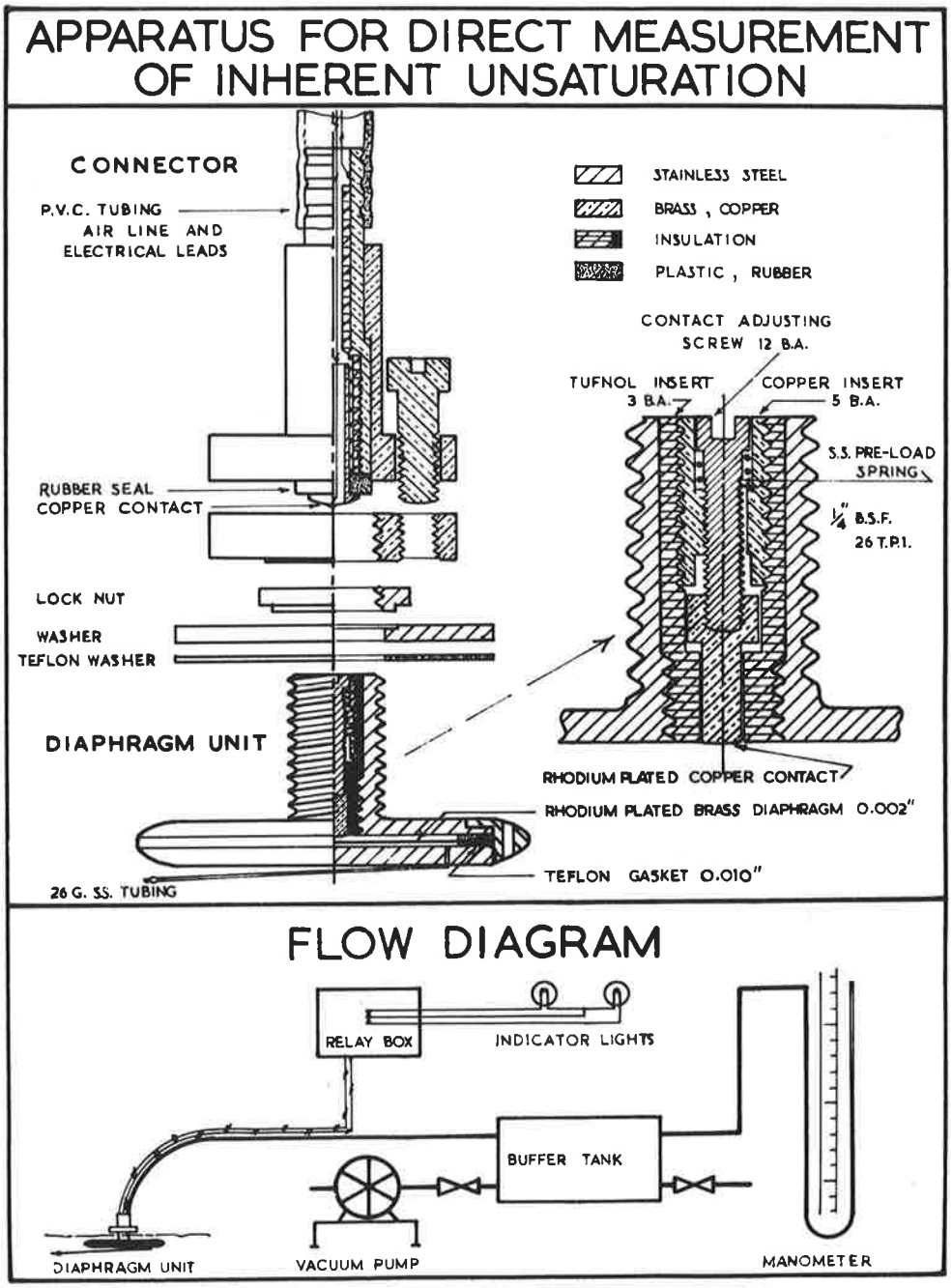

APPARATUS FOR DIRECT MEASUREMENT OF INHERENT UNSATURATION
CONNECTOR
P.V.C. TUBING AIR LINE AND ELECTRICAL LEADS
RUBBER SEAL
COPPER CONTACT
LOCK NUT
WASHER
TEFLON WASHER
DIAPHRAGM UNIT
26 G. SS. TUBING
STAINLESS STEEL
BRASS , COPPER
INSULATION
PLASTIC , RUBBER
CONTACT ADJUSTING SCREW 12 B.A.
TUFNOL INSERT 3 B.A.
COPPER INSERT 5 B.A.
S.S. PRE-LOAD SPRING
1/4" B.S.F. 26 T.P.I.
RHODIUM PLATED COPPER CONTACT
RHODIUM PLATED BRASS DIAPHRAGM 0.002"
TEFLON GASKET 0.010"
FLOW DIAGRAM
RELAY BOX
INDICATOR LIGHTS
BUFFER TANK
DIAPHRAGM UNIT
VACUUM PUMP
MANOMETER

Fig. 20

(i) reducing the gas capacity of the implanted probe to a minimum.

(ii) offering this volume the largest surface area for exchange with the surrounding tissue, the relevant parameter being (surface area/volume).

The above reasoning has led to the selection of a polyvinyl chloride tube 49 cms. in length, 0.8 mm. O.D. and 0.4 mm. I.D. This membrane cavity is closed by means of a sealed diaphragm unit (see fig. 20) which permits the animal to run around free of any connections during the period of equilibration for a particular inhaled atmosphere. Dead space on the membrane side is again reduced to a minimum for the fastest response, the internal pressure reaching at least 95% of the asymptote within 12 hours of any step change in the inhaled partial pressures. All readings were recorded after 24 hours equilibration time.

6.43 The diaphragm unit

The diaphragm unit (fig. 20) is a devide for determining the pressure developed in the membrane (equal to the total tissue tension Σp) by measuring the pressure (P^*) needed to be applied to the other side of the diaphragm to effect a balance.

When a reading is required, the reference pressure lead is attached to the outside compartment of the diaphragm unit by screwing the tapped flange on to the short threaded tube emerging from the skin. The joint is sealed by tightening the flange screws, thereby automatically connecting the electrical leads - one to a contact point and the other to the diaphragm. For convenience these leads are kept

within the reference pressure line until well outside the animal's cage. They carry a very low contact current (3mA.) supplied at a low potential (125 mV.) to minimise arcing between the diaphragm and adjustable contact. Two lights give a simple indication of whether the electrical leads are on 'make' or 'break', i.e. whether the diaphragm is pressed against the fixed contact point or not. It was found necessary to coat all contact surfaces with 0.00025 inches of rhodium to avoid oxidation resistances.

The applied pressure to effect this balance (P^*) may be readily adjusted by balancing a higher against a lower pressure air bleed to a 2-litre buffer tank as shown in the flow diagram in fig. 20. Such a dynamic system minimises the effect of any leaks.

6.44 Surgery

While the foregoing systems were designed by the writer, the experimental testing of the postulated inherent unsaturation was undertaken as a joint project with the Aeromedical Research Unit (Adelaide). The writer is therefore, indebted to their Officer-in-Charge, Dr. D.H. LeMessurier, for his surgical skill in implanting the capsule.

The polyvinyl chloride membrane, attached to the diaphragm unit, was inserted under the skin by means of a trochar comprising a 12 inch 10-gauge stainless steel tube with a removable stainless steel end turned to a very sharp point. Entering the anaesthetised animal at the point from which the screw connection can be seen in fig. 22, the trochar was brought out through the hind quarters level with the pelvic girdle. This deposited the P.V.C. tube subcutaneously as the three loops

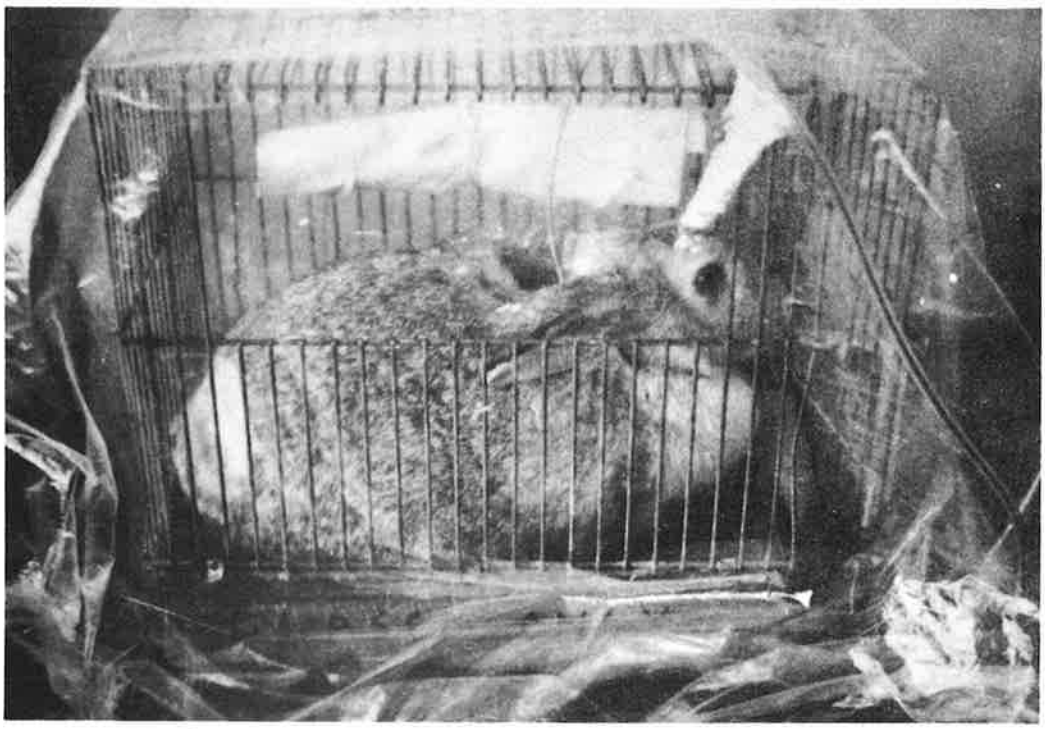


Fig. 21 – THE RABBIT WITH PRESSURE LEAD CONNECTED

Fig. 22 – THE IMPLANTED DIAPHRAGM UNIT DISCONNECTED

in which it was initially packed into the trochar. All equipment was thoroughly sterilised before the operation, and the rabbit was given 2 million units of penicillin to combat any chance infection.

A pathological investigation of one animal which died one month after the insertion showed that fibrous tissue had grown around the membrane. In all readings the number of days following the operation has been recorded, a minimum of two weeks being allowed for recovery.

6.45. Interpretation of pressure readings

The difference between the absolute pressure (P) of the gas mixture inhaled by the animal and the absolute pressure for balance (P^*) exceeds the true inherent unsaturation (Δp) on account of the finite volume displacement of the diaphragm (V_e)

i.e. $P - P^* > \Delta p$.

Since a pressure balance could be obtained in a time far less than the induction period for transmission of any gas through the membrane, the number of moles of gas on the membrane side of the diaphragm would be the same before and after balance. Applying Boyle's law this gives:-

$$V_m . (\Sigma p) = (V_m + V_e) P^*$$

V_m is the membrane volume with the diaphragm pressed against the base of the capsule by the true unsaturation developed while the animal is disconnected. Σp is the total tension of volatile substances in the tissues and hence the final absolute pressure developed in the membrane during the period of disconnection.

The above equation gives the true inherent unsaturation (Δp) as:-

$$\Delta p = P - (\Sigma p) = (P - P^*) - P^* V_e / V_m .$$

Assuming uniform curvature of the diaphragm, and a maximum deflection equal to the thickness of the P.T.F.E. gasket, the dimensions recorded in fig. 20 give:-

$V_e = 2.38 \times 10^{-3}$ in.^{3}

$V_m = 11.30 \times 10^{-3}$ in.^{3} (including diaphragm dead space).

The latter value is obtained by integrating for circular segments over the maximum linear diaphragm displacement.

Hence $\Delta p = P - 1.21\ P^*$ (53)

The form of this equation was verified experimentally, in vitro, by taking readings of P^* after leaving the membrane exposed to known pressures in a sealed unit, i.e. for $\Sigma p = P$.

6.46 Unsaturation vs. gas composition

Atmospheric was selected as the absolute pressure at which to investigate the variation of the inherent unsaturation (Δp) with mole fraction of the inert gas (x). This permitted the animal's cage to be placed in a polythene bag which was flushed with an oxygen/air mixture from a cylinder pre-blended to the approximate composition desired for that run. This is shown in fig. 21 with the pressure balancing lead connected to the diaphragm unit.

Analyses were performed upon each blend using a Lundin nitrogen meter to obtain the mole fraction of inert gas to within $\pm 0.5\%$. Volume fractions of oxygen over the range 20-100% were used.

The particular blend was fed to the cage at the rate of 2 litres/min. until the diaphragm unit and accompanying circuits indicated that a steady pressure had been obtained within the membrane. The polythene was freely vented, and the free end of the manometer was left open to atmosphere. Its final reading was taken as an absolute pressure (P^*) from which the inherent unsaturation Δp can be deduced by equation 53. The time allowed for reaching a steady reading was always in the region of 24-30 hours.

Results for five different gas mixtures are given in table 12, and plotted in fig. 23.

INHERENT UNSATURATION versus GAS COMPOSITION

animal at atmospheric pressure (P = 760 mm. Hg)

Mole fraction of inert gas (x)	Absolute pressure for "make" (P^*) in mm. Hg	Inherent unsaturation (Δp) + in mm. Hg	Time following membrane insertion in days
0	113	628	15
0.42	374	322	16
0.62	471	209	17
0.80	582	79	19
0.80	582	79	29
0.183	216	507	37
0.80	270	94	68

TABLE 12

+ Δp calculated according to equation 53.

6.47 Unsaturation vs. absolute pressure

Air was the most convenient gas mixture for investigating the variation of inherent unsaturation with the absolute pressure of inhaled gas.

Negative pressures, relative to atmosphere, were obtained using a standard decompression chamber given to the Aeromedical Unit by the Royal Australian Air Force. This chamber had an internal power supply and ample space for the cage and all instruments. Moreover, the writer and his associates, could be admitted through an outer air lock to take readings at any time without varying the pressure upon the animal.

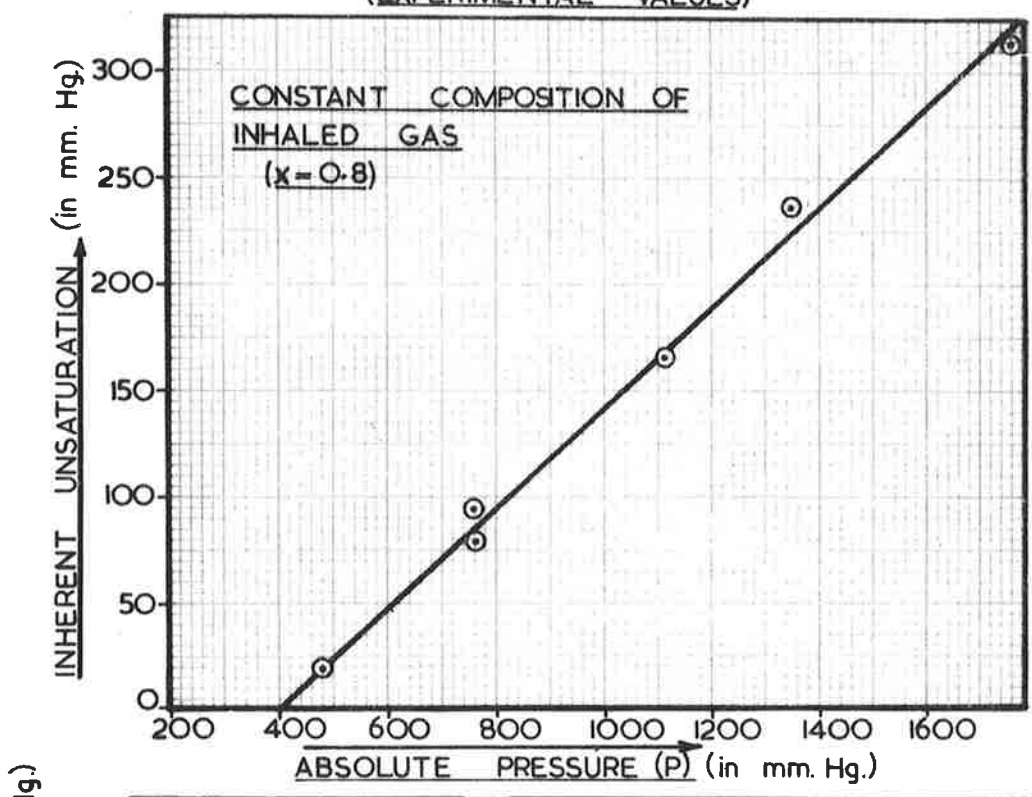
Following a run at an absolute pressure of 460 mm. Hg, it was found that recompression to an ambient atmospheric pressure of 752 mm. Hg, over a period of 5 minutes, caused the manometer to increase its reading by 292 mm. Hg. Moreover, the reading had not changed after a further 10 minutes. This was taken to indicate that the absolute pressure of gases in the membrane had not changed over this period. Such a delay was consistent with the observation that the manometer reading for diaphragm balance was never found to change within 90 minutes of any change of inhaled gas composition.

It is this 'induction' period which rendered it practicable to measure the inherent unsaturation under hyperbaric conditions.

No investigator could be admitted to the high-pressure chamber (described in section 6.82), and the rabbit could not be left with the pressure and electrical leads connected for the 24 hour period previously found to guarantee a steady reading. However, it was found that a well-organised team could take a reading within 5 minutes of decompressing the animal. This was well within the proven induction time of the response of the implanted membrane. The balancing pressure (P^*) was then positive with respect to the open end of the manometer shown in the flow diagram (fig. 20), so a bottle of compressed air was substituted for the vacuum pump.

THE INHERENT UNSATURATION

(EXPERIMENTAL VALUES)



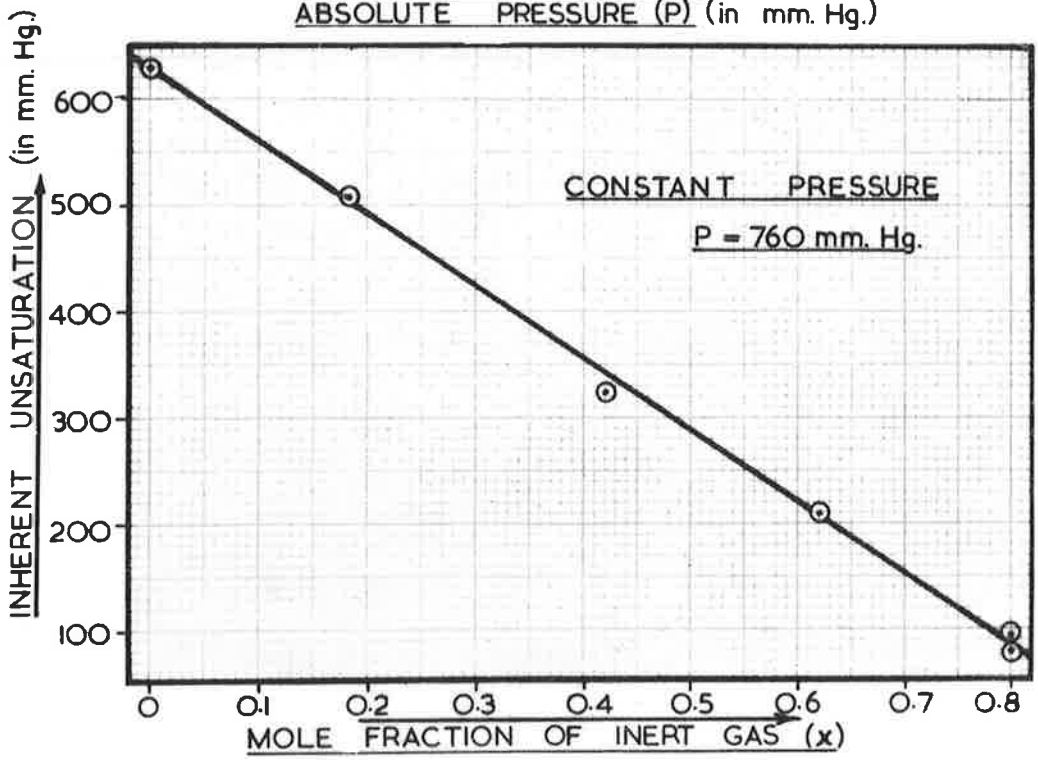


Fig. 23

Manometer readings were checked after a further 10 minutes and, in no instance, were they found to have changed. In view of the much shorter response times recorded for the same membrane in vitro, it would appear that the implanted membrane response is governed by its gas capacity and the resistance of the adjacent tissue, membrane permeability appearing to have little influence in this case.

Results for 6 different pressures are given in table 13, and plotted in fig. 23,

INHERENT UNSATURATION versus ABSOLUTE PRESSURE

(Inhaling air, x = 0.8)

Absolute pressure of inhaled gas (P) in mm. Hg	Absolute pressure for "make" (P*) in mm. Hg	Inherent * unsaturation (Δp) in mm. Hg	Time following membrane insertion (days)
760	582	79	19
760	582	79	27
1349	950	236	28
760	582	79	29
1116	811	166	33
1761	1236	314	40
760	570	94	68
480	395	18	70

TABLE 13

*Diaphragm correction factor given by equation 53.

Air at atmospheric pressure is taken as the control.

6.48 Conclusions

The results, recorded in tables 12 and 13 and plotted in fig. 23, would seem to confirm equation 48 to the extent that the inherent unsaturation:-

(1) increases linearly with absolute pressure for an inhaled gas mixture of constant composition.

(2) decreases linearly with mole fraction of the inert gas in the inhaled atmosphere at constant pressure.

The above relationships hold whatever volume ratio is used in equation 53 to calibrate the diaphragm unit.

The correlation of absolute values is not as good as the above trends. However, all values recorded in table 12 lie within the limits of metabolic activity predicted by equation 48, and all but the value of Δp for the highest pressure recorded in table 13. It is felt that this discrepancy may be partially attributed to the fact that a rabbit is a burrowing animal, while equation 48 is based upon constants derived for man.

All results may be made to fit if an empirical value is assumed for V_e/V_m in equation 53, but the writer can see no justification for this.

A comparison of absolute values may be made for the conditions under which other authors have quoted values for the unsaturation. These are:-

(1) For air at 760 mm. Hg, equation 48 predicts:-

$97 > \Delta p > 57$ mm. Hg

Experimental values for the control runs recorded in tables 12 and 13 show a range of 79-94 mm. Hg, while Piiper (1963a) quotes 57 mm. Hg for dogs.

(2) For 100% O_2 at 760 mm. Hg, equation 48 predicts:-

$668 > \Delta p > 628$ mm. Hg

An experimental value of 628 mm. Hg is recorded in table 12, while Rahn (1961) quotes a value of 600 mm. Hg.

Normally readings were taken during the daytime with the rabbits resting in their cages. However, it was found that values of Δp obtained at night could be some 20-30 mm. Hg lower than those recorded by day with the animal kept active.

It would thus appear that equation 48 represents a realistic mathematical form of accounting for the uncertainties imposed by metabolism.

6.5 THE THERMAL ANALOGUE

6.51 Purpose

The response analysis to gas uptake of the geometric model considered most relevant to decompression sickness (fig. 8) derives the transient tension distribution as the sum of the superposed effects of all the pressure steps experienced by the diver. Despite the mathematical complexity of the expression for a single step (equation VII), computation is still feasible for a dive whose depth vs. time profile is rectangular.

However, most practical dives in the ocean are too irregular to reduce to such a form without gross approximation or treating them as a very large number of steps. The corresponding number of terms soon renders the response expression so cumbersome that calculation is often not feasible. The tediousness of such an approach is greatly increased when the summation of the superposed terms must be repeated for each of some 10 or more different radial locations in order to obtain the instantaneous tension distribution.

Optimisation of a decompression by the method advocated in section 5.9, and expressed quantitatively by equations 51 and 52, require the diver's position to be adjusted continuously such that his absolute pressure coincides with the peak total tension, i.e. $r' = r_1 = r_2$ in fig. 12. Even if the frequency of such adjustment were reduced to one-minute intervals, the burden of computation would be too great, since the depth and peak tensions are mutually dependent variables.

Recourse to use of a digital computer was eliminated for reasons of the complexity of data, e.g. dives in Appendix I, and the failure to find a suitable sub-routine in South Australia for generating Neumann functions. This led to the alternative means of avoiding mathematical approximation by building analogues to simulate the distribution of gases according to the model derived in section 5.5. This approach has the incentive that any such unit proving successful has the possibility of conversion to a practical unit for eventual use 'on deck' as a direct indicator of optimal decompression. While this might sound excessively optimistic, any instrument acting as a check against the use of tables would serve to reduce the chances of human error by the tender.

The first problem in designing an analogue is therefore the selection of a system whose response is exactly analogous to that of the postulated model and mechanism.

6.52 Review of possible systems

The feature of the model which would appear most difficult to simulate, and prominent in determining the proximity to symptoms, is the

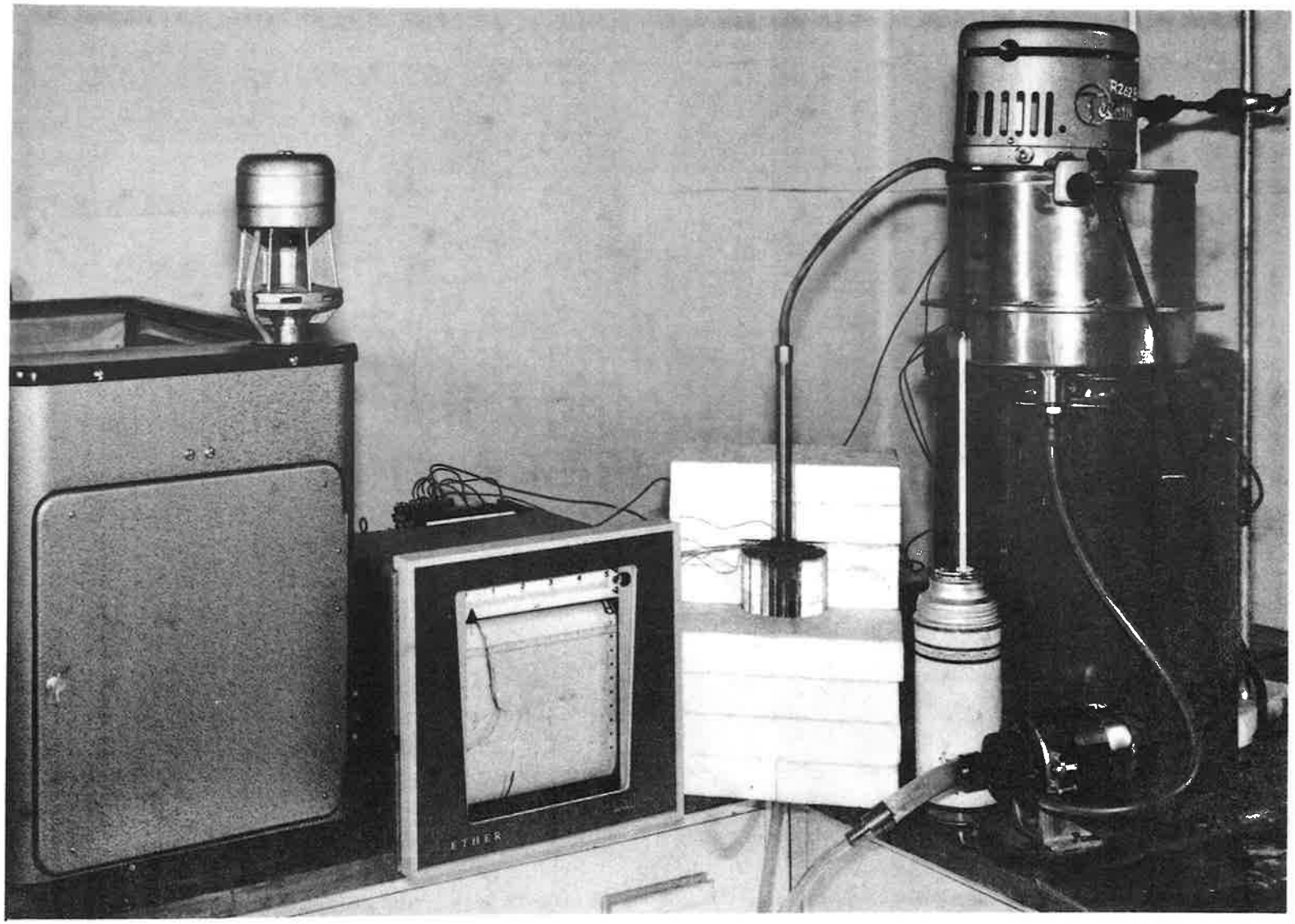


Fig. 24 THE PRELIMINARY THERMAL ANALOGUE

inert gas uptake and distribution. The form of such a transient response would seem to be reproduced most faithfully if:-

1. exact similarity of the geometric layout is retained, and
2. the intensive parameter (Γ) selected to simulate inert gas tension is related to the flow of the corresponding extensive quantity by a law exactly similar to Fick's law of diffusion, i.e. for linear transient flux in the z direction:-

$$\left(\frac{\partial^2\Gamma}{\partial z^2}\right) = \frac{1}{\Omega}\left(\frac{\partial\Gamma}{\partial t}\right) \qquad (54)$$

Possible systems thus include those listed in table 14.

DIFFUSION AND SIMILAR PROCESSES

Process	Diffusion	Thermal conduction	Electrical conduction	Fluid Flow
Intensive parameter	tension (p)	temperature (Θ)	potential	pressure (Π)
Extensive entity	solute	heat	charge	fluid mass
The constant (Ω)	diffusion coefficient (D)	thermal diffusivity (κ)	resistivity	flow resistance

TABLE 14

While electrical analogues are the simplest to construct, it is very difficult to simulate radial transmission. The simple representation of a tissue type by a resistor in series with a capacitor has been used by Mapleston (1963). A grid of resistors and capacitors has been selected by Evans and Naylor (1964) to simulate tissue in their study of its exchange response with respect to blood moving in the capillary. However, it would appear very difficult to obtain a time-base of order similar to that of the critical tissue in the diver unless one used extremely large condensers, or resistors of resistance so high as to be comparable with that of the insulation

A liquid flow system was dismissed as impracticable on the grounds of:-

(a) difficulty of reproducing the geometry without inducing turbulence, and

(b) difficulty of attaining a suitable time base without using a very viscous fluid. Any thixotopy would also cause deviations from equation 54.

While the foregoing difficulties may not be insurmountable, the most suitable system appeared to be thermal conduction - temperature being a parameter which is easily measured with the minimum of disturbance, and without consuming the extensive quantity (heat).

6.53 A preliminary analogue

A preliminary model was made of the worst possible case likely to occur in the critical tissue type (section 5.52). This geometric concept of cytoplasm enveloping a capillary was interpreted by an annulus of outside:inside radii turned in the ratio b/a = 5.29 (section 8.64). The material used was one developed by the writer (Hills, 1965) for transparency and low thermal conductivity, the thermal diffusivity (κ) being determined as $\kappa = 4.13 \times 10^{-4}$ cm^2 min^{-1} using a thermocouple to detect the response of the centre of a cylinder of the material to a sudden step in external temperature. The direct determination of thermal diffusivity by such transient methods is discussed by Tait and Hills (1964).

Circulation was simulated by pumping water from a thermostat bath through the central core at a rate of 10 gals./min. The annulus had an internal diameter of 1 inch, 11 thermocouples placed in 1/16 inch

THE THERMAL ANALOGUE

THE TISSUE MODEL

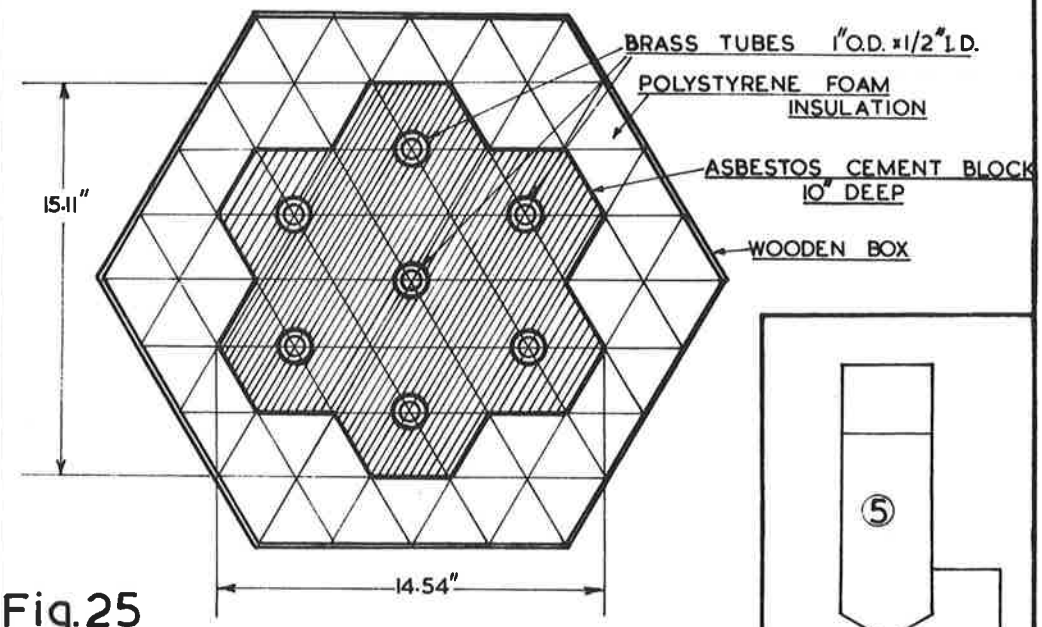


Fig.25

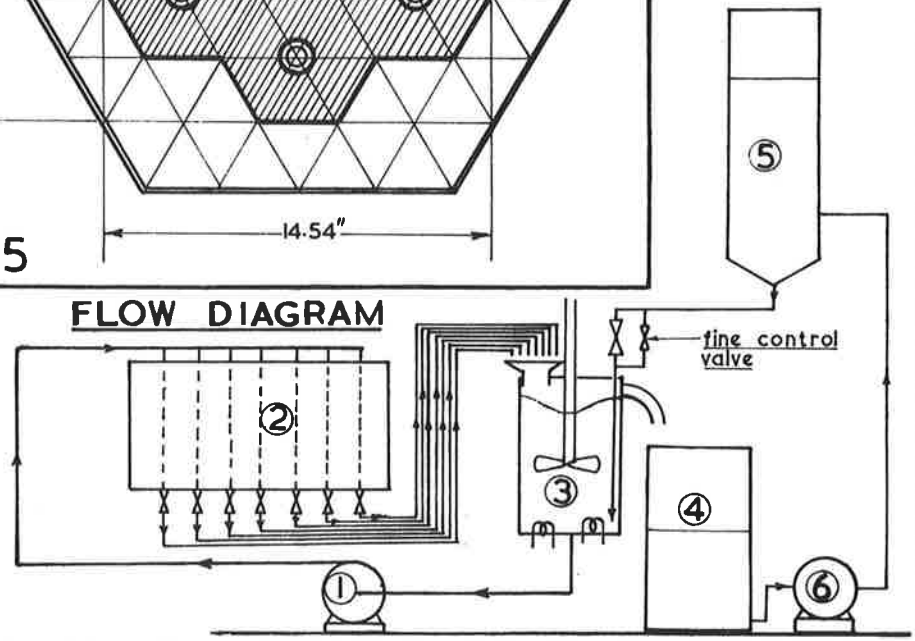


Fig.26

holes at different radial locations appearing to have no effect upon steady-state heat transmission. Maintaining the inside at 60°C and the outside of the annulus at 0°C (stirred ice bath) for 24 hours, it was found that the temperature recorded by each thermocouple differed by no more than 0.5 C° from the theoretical value for its particular location. This was comparable with the recording error. Fig. 24 shows the whole of this preliminary apparatus with a quarter section of foam insulation removed to expose the tissue model. The time base of the annulus appeared to lie within 20% of that for a diver (section 8.65). However, no thermal insulation could be found of conductivity sufficiently lower than that of the plastic to enable the outer boundary condition to be applied effectively i.e. $\partial\theta/\partial r = 0$ at $r = b$ (Appendix II). Even 3 inches of polyurethane foam gave a 10 C° temperature drop across the annulus after maintaining the inside 60 C° above ambient for 24 hours, all thermocouples giving a steady reading after 10 hours.

The conclusions drawn from this preliminary model may be listed as follows:-

1. Placed in 1/16 inch dia. holes, thermocouples made from 0.003 inch chrome/alumel wires appear to cause negligible disturbance of the isotherms.
2. A circulating liquid of boiling point higher than that of water is desirable to increase the temperature range, and hence sensitivity of the analogue.
3. An analogue whose response is up to 5 times faster than the critical tissue would enable details of a dive history to be fed in with no significant loss of faithfulness to the original

record. This would minimise erroneous heat losses since the insulation would be more effective relative to a material of higher thermal diffusivity.

4. For simulated dives of any appreciable duration, an alternative to thermal insulation must be found for imposing the boundary condition for the volume receiving gas from one capillary (r=b).

6.54 The final design

One of the simplest means of overcoming the problem of side heat losses is provided by reverting to the less approximate Krogh model, i.e. taking one central capillary surrounded by six others spaced upon a regular triangular pitch (fig. 8). The hexagonal form of the volume influenced by the central pipe is thus isolated from the exterior by six similar regions in cutting the block to the shape indicated in fig. 25.

The block is composed of 5 × 2 inch layers of a cement/asbestos material of uniform composition, each laminate cut from the same template. This permits holes of diameter no greater than 1/16" to be drilled to an effective depth of 5 inches in the assembled block. These holes, indicated by protruding wires in fig. 27, locate the 11 chrome/alumel thermocouples. Different orientations with respect to the central hexagon minimise the cumulative effect of any disturbance to the heat flow pattern. Radial distances from the centre are selected to permit the temperature distribution to be plotted each time the recorder scans its twelve channels. Eleven points on the curve prove ample for estimating the peak temperature to within 1% of full-scale deflection.

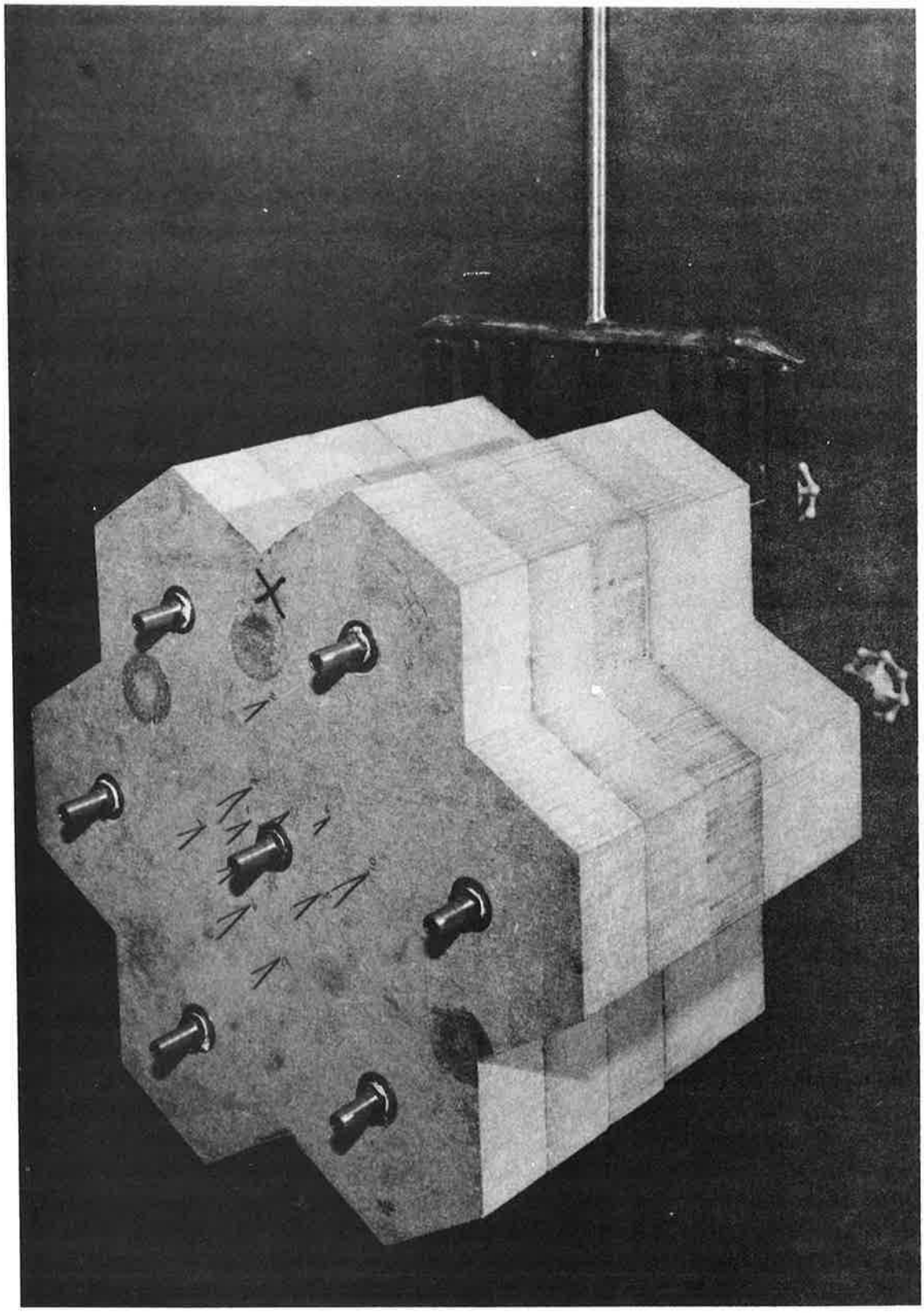


Fig. 27_THE ASBESTOS BLOCK SHOWING THERMOCOUPLE LOCATIONS

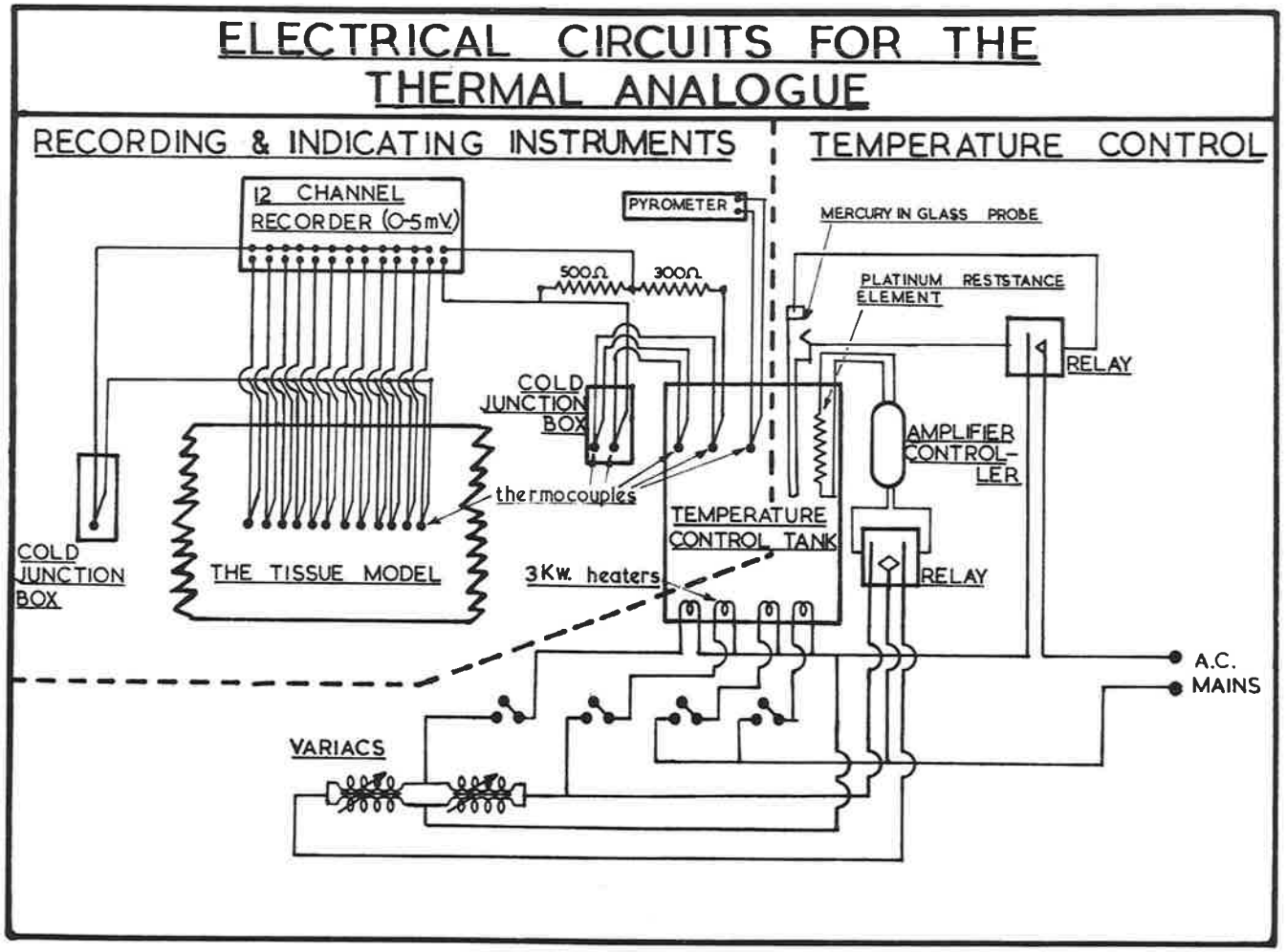

ELECTRICAL CIRCUITS FOR THE THERMAL ANALOGUE
RECORDING & INDICATING INSTRUMENTS
TEMPERATURE CONTROL
12 CHANNEL RECORDER (0-5mV)
PYROMETER
MERCURY IN GLASS PROBE
500Ω
300Ω
PLATINUM RESTSTANCE ELEMENT
RELAY
COLD JUNCTION BOX
AMPLIFIER CONTROL-LER
thermocouples
TEMPERATURE CONTROL TANK
COLD JUNCTION BOX
THE TISSUE MODEL
3Kw. heaters
RELAY
A.C. MAINS
VARIACS

Fig.28

The capillaries are simulated by brass tubes of thermal conductivity so much higher than that of the asbestos (Stoever, 1941), that their outside diameter (a') is the relevant dimension for relating to the capillary radius (a). The distance between centres (2b') is related to the intercapillary distance (2b) such that geometric similarity is preserved if:-

$$(b'/a') = (b/a) = 5.29$$

for the resting condition (section 8.64).
giving $(b'/a') = 5.816$ as the basis of the design of the hexagons. The overall size was fixed by that of the available asbestos cement plates. 10 inches total thickness is sufficient to reduce end effects to less than 1% (Appendix V) if a = 0.5 inches.

Blood is simulated by heat transfer oil (Castrol HT 1402) which does not fume appreciably until heated above 150°C. The viscosity is low enough that the oil is readily circulated by a centrifugal pump.

Individual oil return lines to an open trough draining into the thermostat bath, afford a direct visual check upon the flow in every 'capillary'. Each is fitted with its own valve for manual adjustment in the case of any irregularity in oil distribution (see fig. 29). Mercury-in-glass thermometers at the inlets provide a further check, the overall flow diagram being shown in fig. 26.

6.55 Temperature control

In order to simulate inert gas tension by temperature, one needs accurate thermostatting and rapid response of the 'arterial' oil to a new control position. This control temperature (Θ) can then be varied according to the absolute pressure of the diver (P).

Control to within ± 0.1 C° about any temperature selected by a dial within the range 20-120°C has been obtained using a 2-stage amplifier and relay with a platinum resistance sensing probe. This switches an immersion heater of 3Kw rating in the oil bath between two power inputs independently adjustable by means of separate variacs (see fig. 28). The lower the power differential the better is the control.

Then the heat uptake by the asbestos block is high this differential needs to be increased, even to the extent of including a further 3Kw heater in the 'on' position. The need to change the control temperature very rapidly to simulate normal diver descent rates has led to the following design features:-

1. Further 2 × 3Kw manually operated 'boost heaters' to bring the power input to a possible maximum of 12Kw.
2. Reduction of the thermal capacity of the circulating oil to a minimum by:-
   (a) Using a heat transfer oil (Castrol HT 1402) of low specific heat (0.45 cal./gm. C°).
   (b) Reducing the oil tank volume to the minimum (2½ gals.) required to cover the heaters and contain the 2 × 3" dia. propeller stirrers required to maintain uniformity on account of the rapid external circulation (averaging 4 passes of the oil through the block per minute).

2½ gals. is not large in view of the size of oil immersion heaters whose maximum surface heat flux is severely limited by the flash point of the oil.

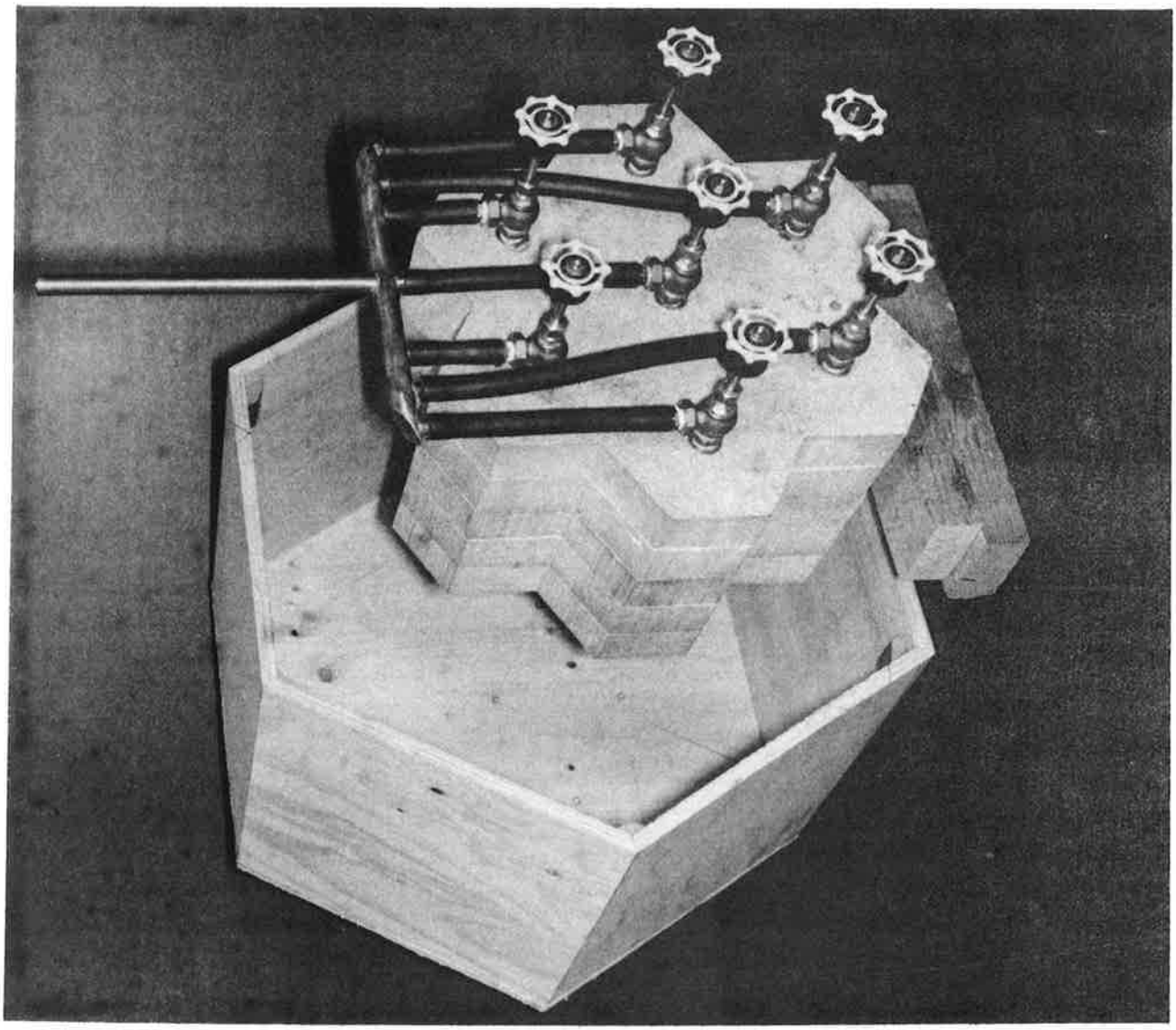


Fig. 29 – THE ASBESTOS BLOCK SHOWING VALVES

Rapid cooling is effected by running cold oil into the bath from a 12 gal. header tank, the mixed oil automatically overflowing through a pipe set at the level for minimal working capacity.

The instrument, heating and emergency cut-out circuits are shown in fig. 28.

6.56 The time base

The response of an annulus to a step in any intensive parameter obeying equation 54, is given by equation XI. This solution is given as the sum of an infinite series of terms each of which can be regarded as composed of two factors:-

(i) a geometric factor, expressed in terms of Bessel and Neumann functions, which can be reduced to a function of relative geometric dimensions, (r/a) or (b/a), and a dimensionless root term $(a\alpha_n)$.

(ii) a response factor $(\exp(-\alpha_n^2\Omega t))$ which can be expressed as $\exp(-(a\alpha_n)^2(\Omega t/a^2))$, the parameter of time occurring in no other form.

The dimensionless root term $(a\alpha_n)$ is defined as the n^{th} solution to equation VIII which can be re-written as:-

$$J_o(a\alpha_n).Y_1((a\alpha_n)(b/a)) = Y_o(a\alpha_n).J_1((a\alpha_n)(b/a)).$$

$(a\alpha_n)$ is thus a function of (b/a) only, and must be the same for all geometrically-similar systems. The secular response of different parameters conforming to equation 54 is therefore invariably expressed in terms of the dimensionless group $(\Omega t/a^2)$. Two systems have reached equivalent stages with respect to time if $(\Omega t/a^2)$ is the same for both. Hence:-

$$\frac{\text{Time base of thermal analogue}}{\text{Time base of critical tissue}} = \frac{D(a')^2}{\kappa(a)^2} \qquad (55)$$

where κ is the thermal diffusivity of the asbestos (= thermal conductivity/ density × specific heat) which has the same dimensions as the diffusion coefficient, i.e. length^2 time^{-1}.

6.57 Response analysis

$\kappa/(a')^2$ has been determined by response analysis for a step in the temperature of the circulating oil. Starting with the asbestos block equilibrated to room temperature (Θ_o), the oil bath was brought to a control temperature of $(\Theta_o + 100)^oC$ with the circulation pump turned off. The temperatures (Θ) at each of the 11 thermocouples were then recorded every 52 seconds for 5 hours. Re-plotting these curves as log $(\Theta_o + 100 - \Theta)$ vs. t, response analyses, such as those performed in figs. 17 and 19 for gas uptake, gave the gradients (k_1) for the slowest exponential component. These are listed in table 15.

$$\left(\frac{\Theta_o + 100 - \Theta}{100}\right) = \Sigma A_n \exp(-k_n t)$$

While the intercepts A_n should be a function of radial location, k_n should not since $k_n = \alpha_n^2 \kappa$ (equation XI) and α_n values are functions of (b/a) only.

The average value of 0.0183 for $\alpha^2\kappa$ gives (κ/a_1^2) = 0.271 min^{-1} since $(a\alpha_1) = 0.26$ for b/a = 5.29 (fig. 42).

The value of (D/a^2) for the critical tissue of a resting man is derived in section 8.65 as $D/a^2 = 0.129$ min^{-1}. Hence from equation 55:-

SLOWEST EXPONENTIAL COMPONENT FOR ANALOGUE RESPONSE

Position	Radial location (r) in cms.	$k_1 = \alpha^2\kappa$ in $min.^{-1}$
1	1.91	0.0217
2	2.26	0.0164
3	2.62	0.0188
4	3.05	0.0237
5	3.49	0.0180
6	4.01	0.0150
7	4.52	0.0215
8	4.96	0.0188
9	5.71	0.0215
10	6.44	0.0129
11	7.40*	0.0136
Average value	-	0.0183

TABLE 15

*Corner of hexagon.

$$\frac{\text{time base of critical tissue}}{\text{time base of thermal analogue}} = 2.16$$

Hence diving data should be fed to the thermal analogue 2.16 times faster than recorded in practice. Conversely, optimisations should be performed in vivo 2.16 times slower than indicated by the analogue.

6.58 Interpretation of absolute pressure

According to section 5.92, the essential feature of optimisation is the relation of the minimum tension required to reach the brink of phase separation (P + 200 mm. Hg, equation IV) relative to the total radial maximum of $x(P_o - 46 + (P - P_o)\Phi(r';t)) + 132$ mm. Hg (equation XIX) where r' is the radial location of the peak.

i.e. $x(P_o - 46 + (P - P_o)\Phi(r;t)) + 132$ relative to $P + 200$

or $(P - P_o)\Phi(r;t)$ relative to $\frac{1}{x}\left((P - P_o) + (P_o + 68 - x(P_o - 46))\right)$ (56)

The temperature range of the eleven thermocouples in the block is set by the room temperature (Θ_o) to which the asbestos block has equilibrated before the run, and the scale for simulation - say 1 mm. Hg $\equiv \eta$ temperature units. With Θ corresponding to P, the dive profile can be fed in to the analogue via the oil bath as a simple linear conversion. If Θ_o corresponds to P_o:-

$$(P - P_o) \equiv \eta\,(\Theta - \Theta_o) \tag{57}$$

Hence the peak total tension versus phase separation criterion, expressed in equivalent temperatures, may be transposed from equation (56) to read:-

$\frac{1}{\eta}(\Theta - \Theta_o)\Phi(r;t)$ relative to $\frac{1}{x}\left((\Theta - \Theta_o)/\eta + (P_o + 68 - x(P_o - 46))\right)$

i.e. $(\Theta - \Theta_o)\Phi(r;t)$ relative to $\frac{1}{x}(\Theta - \Theta_c)$ (58)

where $\Theta_c = \Theta_o - \eta\,((1 - x)\,P_o + 68 + 46x)$ (59)

However, the temperatures from which the peak, $\Theta + (\Theta - \Theta_o)\Phi(r;t)$, is selected are measured by 11 thermocouples, each being ultimately recorded as an e.m.f. If all thermocouple junctions have a sensitivity of ρ electrical potential units per temperature unit, then the peak reading recorded on the chart should be:-

$\epsilon.\Phi(r;t)$ relative to an e.m.f. ϵ_{12}, where ϵ_{12} is the potential fed to the 12^{th} channel of the recorder as representative of the condition for phase separation. This comparison becomes realistic if:-

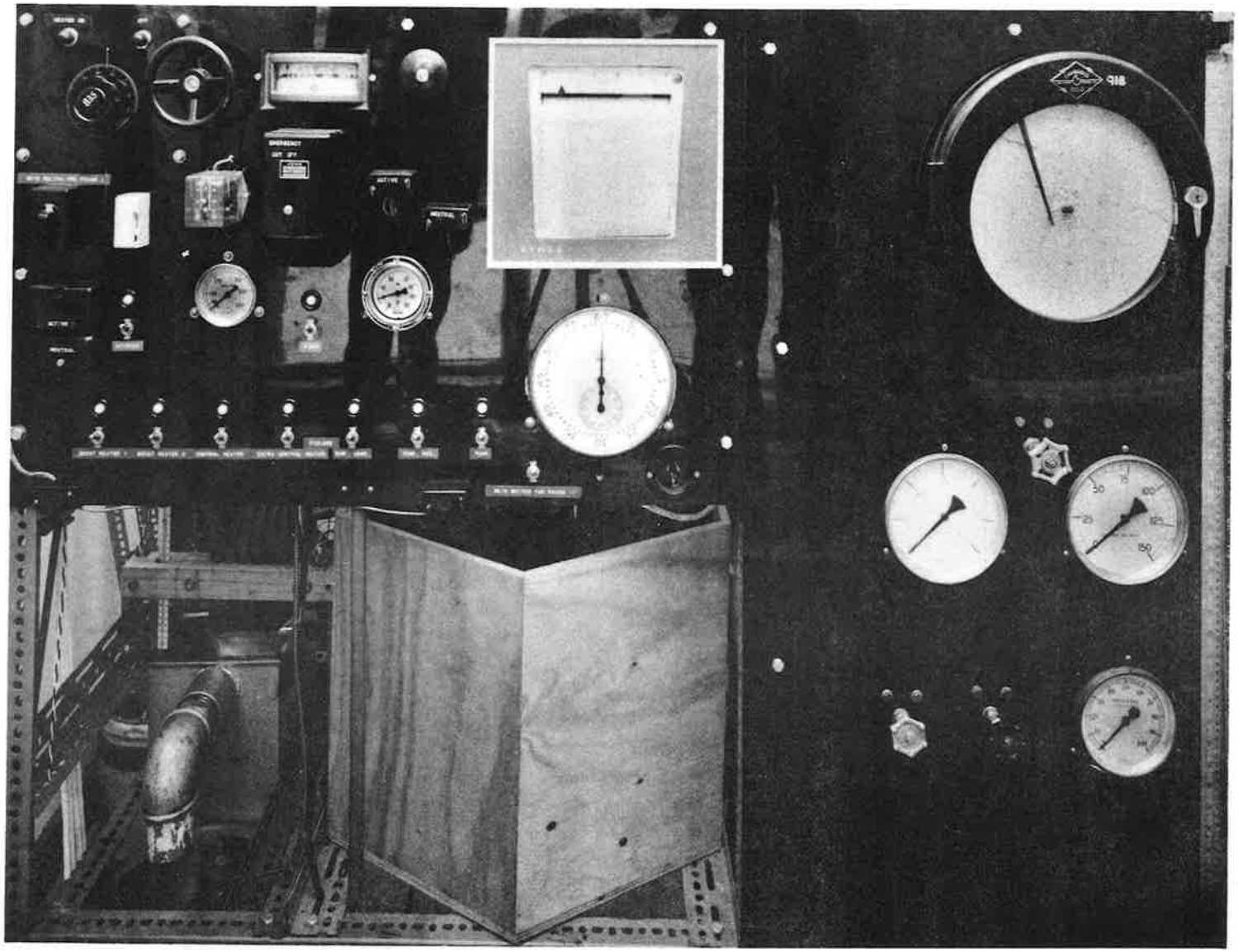


Fig. 30 – THE INSTRUMENT PANEL FOR BOTH THERMAL & PNEUMATIC ANALOGUES

(i) $\epsilon \equiv \rho(\Theta - \Theta_o)$

i.e. the 11 thermocouples in the block have their common cold junction kept at room temperature (Θ_o), and

(ii) $\epsilon_{12} \equiv \frac{\rho}{x}(\Theta - \Theta_o)$

i.e. the cold junction for the 12^{th} thermocouple is kept at a temperature Θ_o given by equation 59, and its e.m.f. increased in the ratio $\frac{1}{x}$:1. Since exact amplification is difficult and costly, it was found to be simpler to duplicate, in series, the thermocouples between the oil tank and the cold junction box maintained at Θ_o. The required reference e.m.f. for the 12^{th} channel can then be obtained as a tapping of $\frac{1}{2x}$ of the resistance to which the doubled thermocouple output is fed. The circuit is shown in fig. 28 with resistance values indicated for the particular case of simulating nitrogen uptake from air inhalation.

The 12^{th} channel should thus automatically register the conditions for possible phase separation relative to the transient tensions simulated by the readings of the 11 channels recording directly from the asbestos block. The recorder scans the channels once every minute, which is of the order of the delay to be attributed to the circulation. Hence this would seem a convenient interval for making adjustments in determining an optimal decompression.

6.59 Decompression optimisation

The dive arbitrarily selected for decompression optimisation was 40 minutes at 150 feet of sea water upon air. Taking 10° as equivalent to 2 feet of sea water, this gives a working temperature range of 75°, i.e. maximum temperatures would not exceed $110^{\circ}C$ for an Adelaide

temperature which can often reach 35°C for Θ_o. For $x = 0.8$, $\frac{1}{2x}:1 = 500:800$, so the 12th channel potential was obtained by taking a tapping from a 500 ohm resistor in series to 300 ohms with respect to the duplicated thermocouples. Taking P_o = 760 mm. Hg as equivalent to 33 feet of sea water, equation 59 gives:-

$$\Theta_c = (\Theta_o - 5.6)\ ^\circ C.$$

For a day when the ambient temperature is Θ_o, the optimisation would consist of the following steps:-

1. Switching on the circulation pump with the oil bath maintained at a constant temperature of $(\Theta_o + 75)^\circ C$ (corresponding to 150 feet).
2. Maintaining this temperature for 40/2.16 = 19 mins., applying the time base correlation factor of 2.16 derived for nitrogen in section 6.57.
3. Rapidly quenching to $(\Theta_o + 58.5)^\circ C$ which is equivalent to H_ϵ = 117 ft. (s.w.g.) determined by equation 49.
4. Continuously cooling the bath from $\Theta_o + 58.5^\circ C$ to below $\Theta_o + 14.5^\circ C$ (corresponding to H_s in section 5.9), adjusting the rate of temperature fall every minute such that the plot of the 12th channel (ϵ_{12}) coincides with the peak of the other 11 direct thermocouple potentials.

The optimal decompression schedule for the particular dive selected (40 mins. at 150 feet) is suggested as that given in fig. 37. This is the average profile given by 3 runs on the thermal analogue, no points varying by more than 1% from the mean.

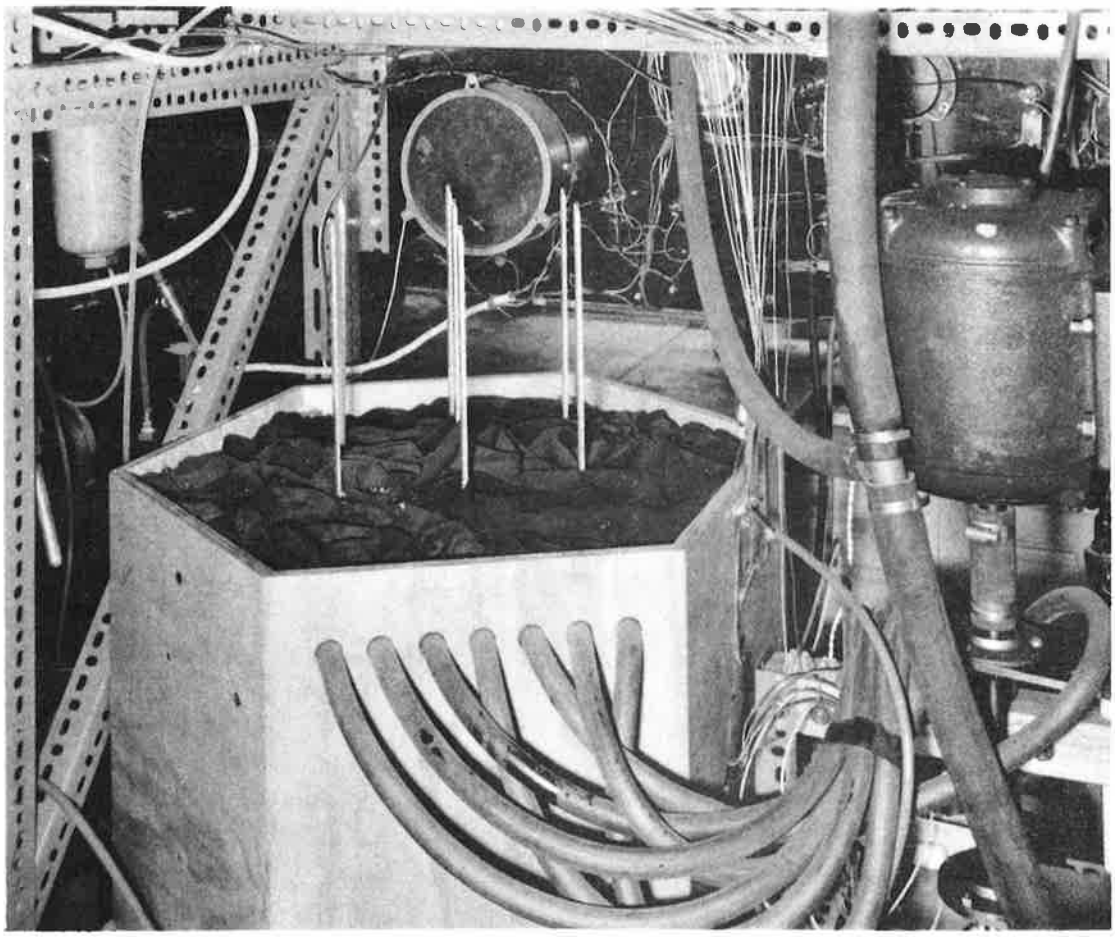


Fig. 31 — THE THERMAL ANALOGUE

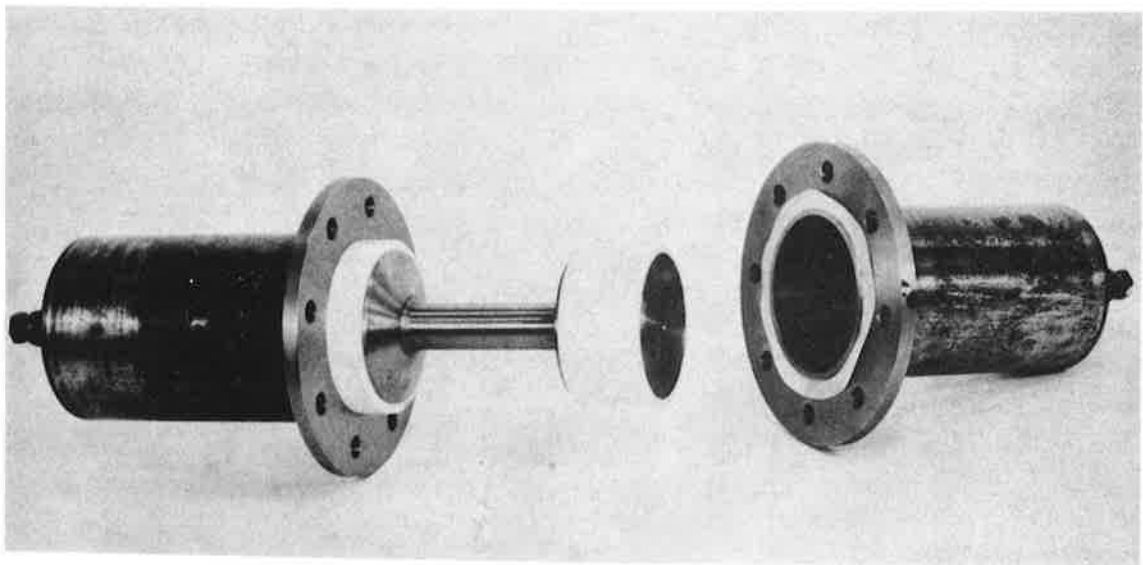


Fig. 32 — PRESSURE TRANSDUCER

6.6 THE PNEUMATIC ANALOGUE

6.61 Reason

If the hypothesis is correct, the thermal analogue would seem well suited to the derivation of optimal decompressions since these should never cause gas to separate from solution until the point is reached for the final rapid ascent to the surface. By this time the unit has fulfilled its purpose.

However, neither the thermal analogue, nor any other of which the writer is aware, can account for a phase change.

6.62 Principle

It is only gas in true physical solution which can contribute to the driving force for gas transport in tissue. The problem is therefore one of selecting a system in which the intensive parameter, simulating total gas tension, cannot exceed the value corresponding to the absolute pressure of gas separated from solution in tissue. This would seem feasible if the transit medium selected for the analogue is a compressible fluid contained in a transport model whose retaining boundaries may expand. If the resistance to this expansion is the actual hydrostatic pressure, then movement would occur until the internal gas pressure was reduced to the external value. This displacement would represent the total gas which could separate from solution at the corresponding region in the tissue if total tension were simulated by the internal pressure of the system. Moreover, the volume displacement of the model would be directly proportional to the volume

of separated gas in tissue if the compressible fluid used is a gas, i.e. Boyle's law is automatically applied in the analogue as it is to bubbles forming in vivo.

The writer could find no method of obtaining a continuous expansion of the model with respect to location, i.e. exactly simulating ξ vs. r in section 5.73, without changing transport resistances within the model. However, there would seem little approximation in permitting the gas to expand at the nearest of 27 separate points, each equivalent to a different radial distance from the capillary. At each of these points, the expansion can be very simply accommodated by connecting the system to a cylinder in which the hydrostatic pressure is applied to the remote side of the piston. Starting with the 27 pistons fully retracted, their presence should have no influence upon the response of the model until conditions for phase separation are exceeded. Moreover, the use of individual cylinders means that the compressible fluid in excess of equilibrium is retained at the same radial location, and ensures that it is eventually returned to the transport system at the same point. This would simulate the need for separated gas to be re-dissolved at its site of deposition from solution in order to be eliminated from tissue via the capillary.

While this overall model is able to account for a phase change, the problem is now one of designing a basic transport system to copy radial diffusion in which the transit medium is a gas.

6.63 Simulation of radial diffusion

The response characteristics of any system conforming to equation 54 are a function of capacity and resistance, their relative magnitude and distribution. In the case of radial diffusion the substrate may be

regarded as an infinite number of annuli, each of whose capacity and resistance lie in series with each other and with those of the other radial segments. If the n^{th} segment has an internal radius r_n and external radius r_{n+1} :-

(i) inert gas capacity of the n^{th} segment $= \pi S(r_{n+1}^2 - r_n^2)$ (60)

(ii) diffusional resistance of the segment

$$= \frac{1}{2\pi D} \log (r_{n+1}/r_n) \qquad (61)$$

Radial diffusion from a capillary may thus be simulated exactly by an infinite number of chambers of volume proportional to $(r_{n+1}^2 - r_n^2)$ separated from the next by a tube whose resistance to flow is proportional to $\log (r_{n+1}/r_n)$. Reverting to finite numbers, it would be most convenient if each of the 27 points suggested for simulating phase separation were a chamber. Equivalent to replacing the true transient radial distribution curve by the closest histogram, this could introduce little error when taking as many as 27 steps.

In view of the uncertainties in estimating gas flow in tubes, on account of end effects etc., any errors should be minimised by using identical lengths of hypodermic tubing as representing equal resistances. According to equation 61 this implies equal ratios of r_{n+1}/r_n for all values of n. Thus taking $r_{n+1}/r_n = \rho^2$ (a constant), and V_n as the volume of the n^{th} chamber, equation 60 indicates that:-

$$V_n \propto r_{n+1}^2 - r_n^2 = r_n^2(\rho^4 - 1)$$

But $r_1 = a$ (the capillary radius), $r_2 = a\rho^2$ etc., such that $r_n = a\rho^{2(n-1)}$, giving:-

$$V_n \propto a^2(\rho^4 - 1)\rho^{4(n-1)}$$

or
$$V_n/V_1 = \rho^{4(n-1)} = r_n^2/r_1^2 \qquad (62)$$

The above equation gives the relative volumes of successive chambers, separated by equal resistances, required to obtain the closest approximation to the form of a true radial response. The absolute volumes, however, are set by the time base.

6.64 Volume of chambers

The greatest approximation in fitting a histogram to the tension distribution curve should occur for the larger radial steps, i.e. for the greatest value of $(r_{n+1} - r_n)$. For steps of equal resistance, this should occur for the higher values of n. To reduce the error in this region it would therefore be necessary to reduce the capacity and hence the interconnecting resistance of those chambers.

Retaining the principle of keeping all resistance tubes identical, the use of two in parallel would halve the resistance and thus enable the volumes of the adjacent chambers to be halved. For m chambers with single interconnecting tubes in series with m' interconnected by two tubes (halved resistances), the greatest error should be reduced to a minimum if $V_m = V_{m+m'}$. However, gas reaching the chambers more remote from the source must pass through those in between. The chambers and resistance tubes of lower value of n thus exert a greater influence upon the transmission. A somewhat arbitrary compromise was therefore reached in halving the resistance between the 15^{th} and 16^{th} chambers, and all subsequent resistances, such that

$r_{n+1}/r_n = \rho$ according to equation 62 and the definition of ρ. Hypodermic tubes connecting the 15th to the 16th and all subsequent chambers were duplicated in parallel - see fig. 33. Hence, by a derivation exactly parallel to that of equation 62,

$$V_n/V_{15} = r_n^2/r_{15}^2 = \rho^{2(n-15)} \qquad (63)$$

for $n \geq 15$.

For $n = 27$, $r_{27}/r_{15} = \rho^{12}$

Equation 62 still holds for $1 \leq n \leq 15$, giving:-

$$r_{15}/r_1 = \rho^{28}$$

Hence, $r_{27}/r_1 = \rho^{40} = b/a = 5.29$ (section 8.67)

since $r_1 = a$ and $r_{27} = b$. Thus $\rho = 1.035$ for the resting condition.

Having determined this constant, the relative volumes of chambers 1 to 14 can be determined from equation 62, while chambers 15 to 27 are given by equation 63.

The absolute volume is set by the capacity of the hypodermic syringes used as the best source of transparent cylinders of precision bore. The largest available in Australia has a nominal capacity of 50 c.c., or practical maximum of 62.7 c.c. Allowing 2.4 as the maximum pressure ratio for bends pain, the same expansion ratio on the analogue would limit the volume of the largest (27th) chamber to 44.84 c.c.

Chamber capacities and dimensions calculated upon this basis are given in table 16.

CHAMBER VOLUMES & DIMENSIONS

Single interconnecting tubes					Double tubes (half resistance)				
Chamber No.	Volume (c.c.)	Nominal hypo-dermic	Chamber internal diam.	Length	Chamber No.	Volume (c.c.)	Nominal hypo-dermic	Chamber internal diam.	Length
1	3.899	2 c.c.	1/4"	2.42"	15	17.28	50 c.c.	1/2"	2.69"
2	4.570	5 c.c.	1/4"	2.84"	16	18.73	50 c.c.	1/2"	2.91"
3	5.357	10 c.c.	1/4"	3.33"	17	20.26	50 c.c.	1/2"	3.15"
4	6.278	20 c.c.	1/4"	3.90"	18	21.94	50 c.c.	1/2"	3.41"
5	7.359	20 c.c.	3/8"	2.03"	19	23.74	50 c.c.	1/2"	3.69"
6	8.626	20 c.c.	3/8"	2.38"	20	25.73	50 c.c.	1/2"	4.00"
7	10.11	20 c.c.	3/8"	2.79"	21	27.83	50 c.c.	1/2"	4.33"
8	11.85	50 c.c.	3/8"	3.27"	22	30.15	50 c.c.	1/2"	4.69"
9	13.89	50 c.c.	3/8"	3.84"	23	32.62	50 c.c.	1/2"	5.07"
10	16.28	50 c.c.	3/8"	4.50"	24	35.34	50 c.c.	1/2"	5.49"
11	19.08	50 c.c.	3/8"	5.27"	25	38.23	50 c.c.	1/2"	5.94"
12	22.36	50 c.c.	1/2"	3.48"	26	41.42	50 c.c.	1/2"	6.44"
13	26.21	50 c.c.	1/2"	4.07"	27	44.84	50 c.c.	1/2"	6.97"
14	30.73	50 c.c.	1/2"	4.78"	Total	564.8			

TABLE 16

6.65 The resistances

In deriving the above dimensions of the gas chambers such that the system has a response format exactly similar to radial diffusion into an annulus of dimensions b/a = 5.29, it has been assumed that all interconnecting tubes represent an equal resistance. However, in conforming to equation 54, this presumes equal molar flow rates per unit pressure gradient whatever the pressure range.

According to standard textbook derivations, e.g. Coulson and Richardson (1957), the flow of a compressible fluid in a smooth horizontal pipe may be expressed as:-

$$\left(\frac{W}{A}\right)^2 \log\left(\frac{P_1}{P_2}\right) + \frac{P_2^2 - P_1^2}{2P_1 v_1} + 4\,(Fr)\,\frac{1}{d}\left(\frac{W}{A}\right)^2 = 0$$

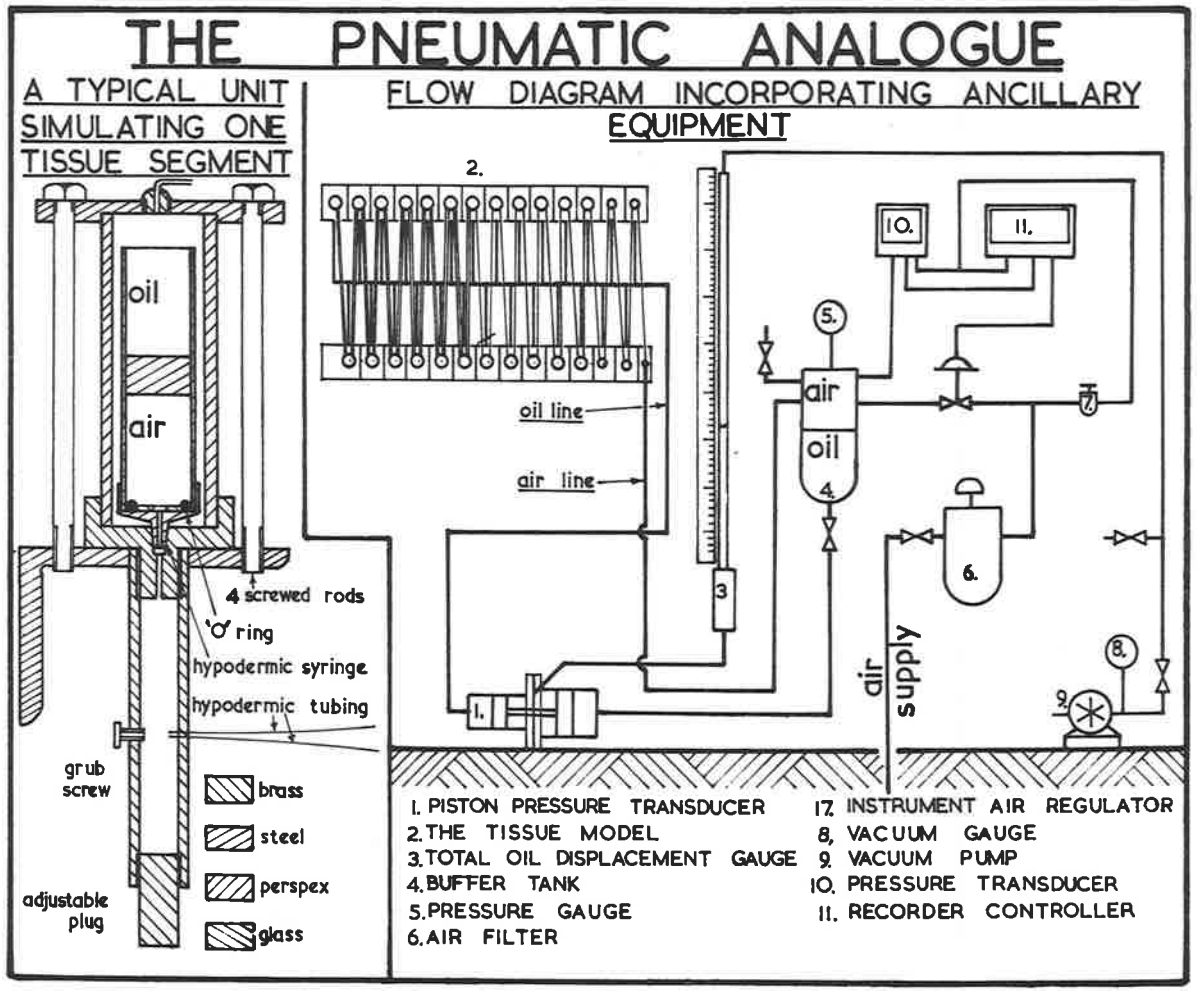

THE PNEUMATIC ANALOGUE
A TYPICAL UNIT SIMULATING ONE TISSUE SEGMENT
FLOW DIAGRAM INCORPORATING ANCILLARY EQUIPMENT
oil
air
4 screwed rods
'O' ring
hypodermic syringe
hypodermic tubing
grub screw
adjustable plug
brass
steel
perspex
glass
2.
oil line
air line
3
1.
5.
air
oil
4.
6.
7.
8.
9.
10.
11.
air supply
1. PISTON PRESSURE TRANSDUCER
2. THE TISSUE MODEL
3. TOTAL OIL DISPLACEMENT GAUGE
4. BUFFER TANK
5. PRESSURE GAUGE
6. AIR FILTER
17. INSTRUMENT AIR REGULATOR
8, VACUUM GAUGE
9. VACUUM PUMP
10. PRESSURE TRANSDUCER
11. RECORDER CONTROLLER

Fig. 33

where Ξ is the mass flow per unit time, l is the tube length, d the diameter, v_1 the volume occupied by unit mass at pressure P_1, and (Fr) is a dimensionless friction factor. Taking long narrow tubes, i.e. l/d large, the term $(\Xi/A)^2 \log(P_1/P_2)$ can be ignored giving:-

$(\Xi/A)^2 \propto (P_2^2-P_1^2)/(Fr)$, since $P_1 v_1$ = constant for isothermal conditions.

While (Fr) is often assumed constant in pipes, it is felt that any resistance tubing used in the analogue must be tested experimentally. The required relationship is:-

$$(\Xi/A) \propto (P_1 - P_2) \qquad (64)$$

Various porous plugs were tried over the pressure range 0-100 p.s.i. and found to be totally unsatisfactory.

The closest approximation to the desired variation of mass flow rate with pressure difference was found using 18" lengths of 27-gauge hypodermic tubing. The times (t_a) required to collect 1 litre of transmitted air in a graduated flask are recorded in table 17.

PRESSURE DROP vs. FLOW RATE IN RESISTANCE TUBES

Pressure drop (ΔP) in p.s.i.	Collection time (t_a) in secs.	$10^{-3}(\Delta P)t_a$
99.5	222	22.1
75.5	300	22.6
50.0	435	24.0
26.5	837	22.2
Average		22.7
Maximum deviation		5.7%

TABLE 17

Since $E \propto 1/t_a$, the values of $(\Delta P)t_a$ are sufficiently constant to claim that the condition expressed by equation 64, and hence equation 54, is satisfied and the tubing used for the experiment summarised in table 17 is suitable for simulating resistance.

6.66 The overall design

In the final design the resistance presented by radial diffusion is simulated by the 18" lengths of hypodermic tubing described earlier, each connecting chambers of the net volumes indicated in table 16. These represent the simultaneous resistance and capacity effects, the overall layout being shown in figs. 33 and 34.

The net chamber volumes are those available for gas storage with the pistons pressing against the 'O' rings at the base of the cylinders. This form of seal is found necessary to prevent oil leaking into the chambers when their internal gas pressure is far below that of the oil. For any other position of the pistons, gas and oil pressures are equal and oil seepage is no problem.

The chambers are made $\frac{1}{2}$" longer than the lengths given in table 16 and the end 1" is tapped. The net volume is attained, before drilling the holes for the resistance tubes, by pouring the corresponding volume of liquid into the chamber and adjusting the end-plug until the liquid is just level with the top of the 'O' ring.

The plugs are then marked and removed. After withdrawing the liquid these end-plugs are returned to the same mark, all threads being well bound with P.T.F.E. tape to avoid gas leaks.

Several methods of operating the analogue have been tried. In the most successful, gas is fed to the end chamber at a pressure reduced in proportion to the mole fraction (x) of the pressure of the diver. This feed pressure is then raised by a factor of $(\frac{1}{x})$ for application to the oil which now corresponds to the depth of the diver. This conversion is performed automatically by a pressure transducer consisting of two opposed pistons of areas in the ratio 0.8:1 (for air) - see fig. 32. It is not practicable to adopt the alternative method of feeding the diver's pressure direct to hydraulic main and obtaining a reduced pressure source for the end chamber. This arises from the fact that the gas fed to the chambers must far exceed the total oil displacement such that the latter alternative would require a far greater piston capacity for the transducer.

Information is fed to the analogue via the recorder-controller which varies the balance between a high-pressure air feed for the buffer tank and a continual bleed. The control system is outlined in the flow diagram shown in fig. 33. To ensure fidelity to the data analysed, the pressure in the buffer tank is recorded on a chart upon which the depth-time profile of the dive has been previously traced after correction for the time base. If the two plots are not closely superimposed the result of the analysis by the analogue is disregarded.

6.67 Allowance for minor corrections

In analysing the extent of phase separation one is primarily concerned with the total separated gas pressure before coalescence (P + 10) mm. Hg (section 5.77) relative to the total gas tension (xP - 46x + 132 mm. Hg) - taking the venous limit of equation 48. Corrections for

surface tension, elastic deformation and the metabolisable gases may be applied very simply by adjustment of the pressure (Π) applied between the transducer pistons - via the oil in the total displacement indicator (item 3 in fig. 33).

For piston areas in the ratio 1:x, the correct tension: absolute pressure relationship is preserved if:-

$$x = \frac{\text{Net load on small piston}}{\text{Net load on large piston}} = \frac{xP - 46x + 132 - \Pi}{P + 10 - \Pi}$$

$$\text{i.e. if} \qquad \Pi = \frac{132 - 46x - 10x}{(1 - x)} \text{ mm. Hg}$$

For air ($x = 0.8$), $\Pi = 435$ mm. Hg.

The volume indicator tube was thus kept under a vacuum of 325 mm. Hg by means of the pump shown.

A feature of the analogue is the automatic integration of the simulated separated gas afforded by measuring total piston displacement as the net discharge from the hydraulic main. This is measured indirectly in the plastic tube through which the pressure (Π) is applied to the backs of the transducer pistons.

The common oil supply to all hypodermic pistons has the desired effect of 'cutting off' the tension distribution curve as illustrated in fig. 12. Visual observation of the glass cylinders shows a piston displacement corresponding to a histogram of the theoretical separated gas distribution, i.e. ξ vs. r in equation XXII. The total oil displacement is thus the integral of this curve with Boyle's law automatically applied such that it should be directly proportional to the total volume of gas separated in the region influenced by one capillary. It is thus a direct indication of the proximity to marginal symptoms if the hypothesis is fundamentally correct.

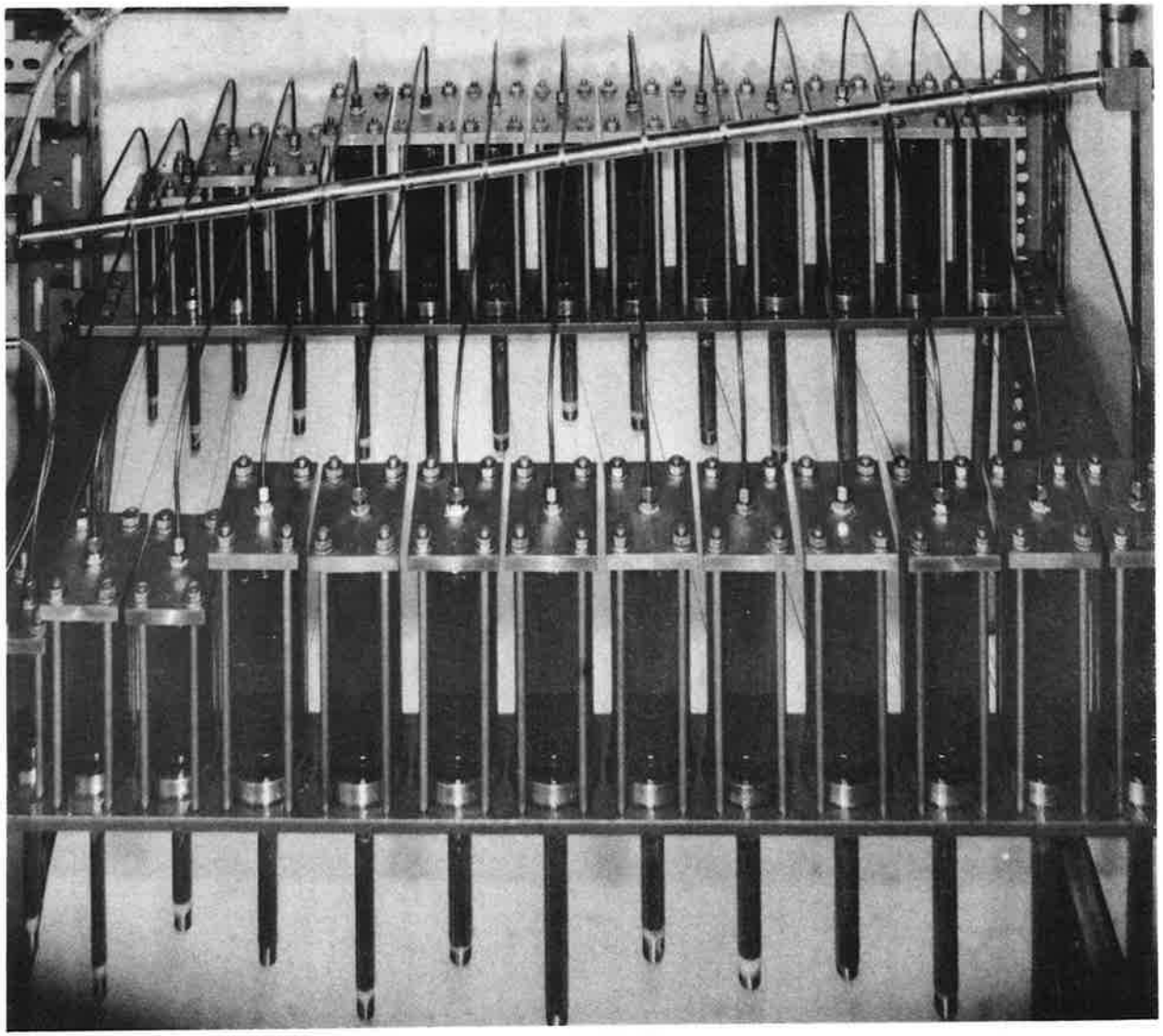


Fig. 34 — THE PNEUMATIC ANALOGUE

6.68 The time base

Although the time base could be estimated theoretically, it was considered more realistic to determine it experimentally.

A pressure gauge was fitted to the 27th chamber and a constant pressure of 90 p.s.i. applied to the 1st chamber. The oil was kept at 100 p.s.i. to ensure all pistons were seated firmly on the '0' rings, since the time base required was that of the basic transport system corresponding to tissue without phase separation. Various leaks were stopped until the last chamber read 90 p.s.i.

This gauge was then replaced by an end-plug, correctly located, and the whole system of chambers left for 12 hours to reach a steady 90 p.s.i. throughout. The connection to the first chamber was then suddenly cut and the free end placed under the neck of a large measuring cylinder inverted in water. The cumulative volume of gas (G) evolved from the analogue was then recorded against time. A final value (G_{∞}) was taken after 12 hours. A semi-log plot of ($G_{\infty} - G$) vs. t confirmed that ($G_{\infty} - G$) may be expressed as the sum of a number of exponential terms - as illustrated in figs. 17 and 19.

The predominating first term gave a time constant of:-

$$\lambda_1 = 0.0174 \text{ min.}^{-1}$$

In section 8.65, D/a^2 is derived from dive analysis as:-

$$D/a^2 = 0.129 \text{ min.}^{-1}$$

For $b/a = 5.29$, fig. 42 or equation VIII gives:-

$$a\alpha_1 = 0.26$$

Hence, according to equation VII, the first time constant of the critical tissue type (resting) is given by:-

$$k_1 = \alpha_1^2 D = (D/a^2)\ (a\alpha_1)^2 = 0.00872 \text{ min.}^{-1}$$

$$\therefore \quad \frac{\text{Time base of tissue}}{\text{Time base of analogue}} = \frac{\lambda_1}{k_1} = \frac{0.0174}{0.00872} = 1.99$$

This experimental value is remarkably close to the factor of 2 used in design.

Hence data must be fed to the analogue 1.99 times faster than the dive was performed in practice.

6.69 Preliminary trials

The pneumatic analogue is really an analytical tool permitting estimations to be obtained in cases where the transition points introduced by phase separation render conventional mathematical methods almost impracticable. Results of such analyses are not recorded here but in the context relevant to the particular dive.

However, a general qualitative description of a typical run may serve to illustrate the adherence of the instrument to the hypothesis proposed. At maximum pressure, equal to the 'bottom depth' of the dive to be analysed, air enters the end chamber and gradually flows further into the system. The oil is at a greater pressure, corresponding to that of the diver, so all pistons are kept pressed against the 'O' rings. Each chamber is thus reduced to its minimum effective volume necessary to simulate radial diffusion according to table 16.

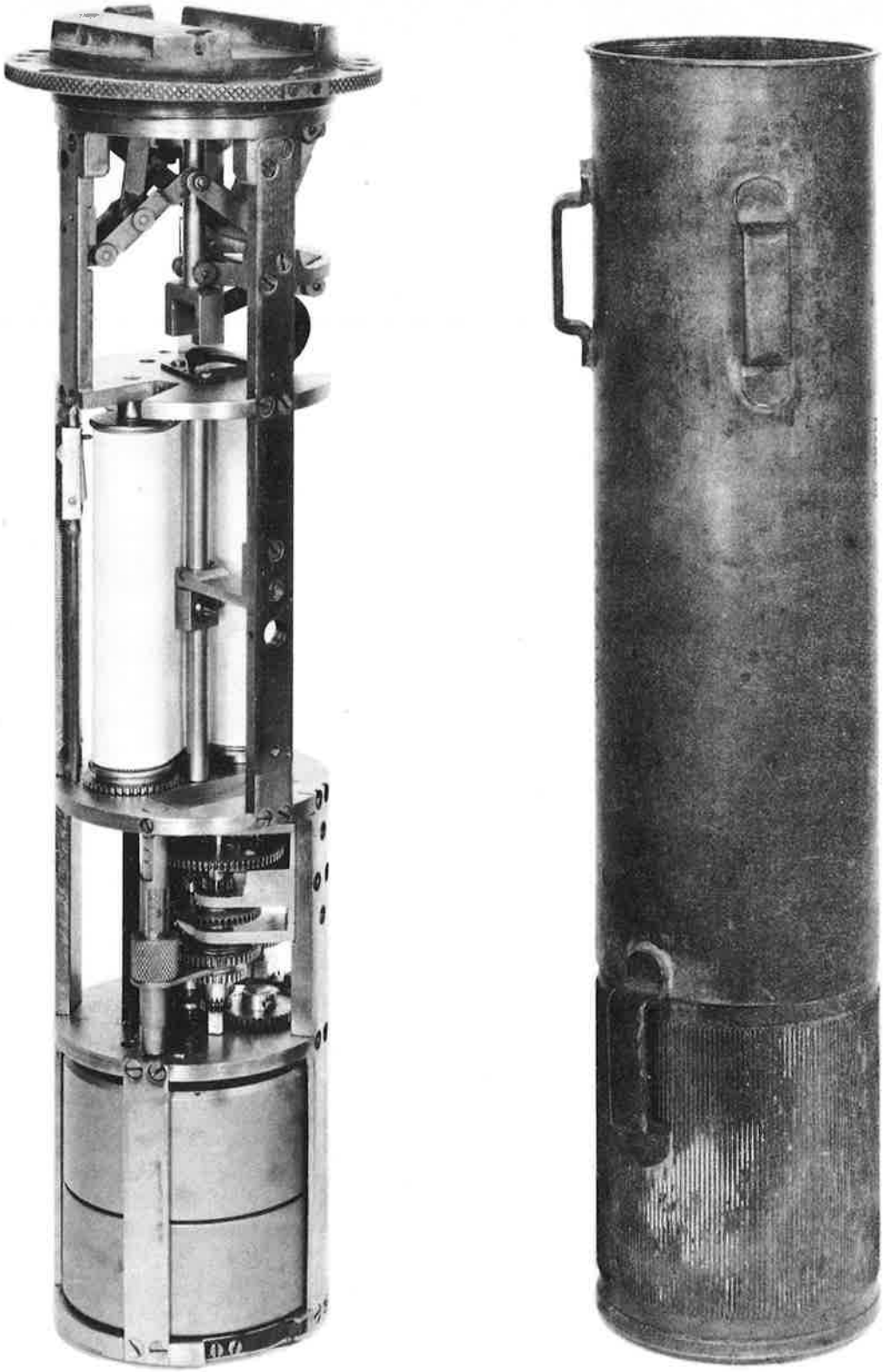


Fig. 35 — THE DEPTH RECORDER

The greater the pressure applied to the buffer tank, the greater the differential between the oil and the pressure of gas fed to the end chamber. This corresponds to the inherent unsaturation increasing with depth (equation 48).

Upon decompression the gas transport process is reversed unless it is so rapid that the delay in air passing through the hypodermic tubes is such that the pressure of gas in one or more chambers exceeds that of the oil. The pressure differential in each chamber is then rapidly dissipated by the pistons moving in the corresponding cylinders.

If left at a certain pressure the displacements are eliminated in turn starting with the cylinders closest to the source simulating the capillary. One piston must be completely returned before the next starts to move - just as required by the hypothesis and illustrated in fig. 12 (graph 3).

6.7 FIELD WORK

6.71 Scope

The ultimate test of any quantitative hypothesis of decompression sickness is its ability to predict the outcome of dives actually performed in the ocean. Most sets of published dives refer to decompressions styled upon a Haldane-type of approach, their similarity of form rather limiting the advantages of using such a volume of data in acceptin or rejecting any hypothesis.

However, a startling contrast to Naval-style decompression is provided by empirical techniques regularly practised by pearl divers operating off the coast of Australia. Fortunately, these include the two types of dive most difficult to correlate by conventional theories, viz:-

1. Long and deep dives, as performed regularly in the Torres Strait - see Appendix I, and

2. Repetitive dives, as performed regularly in the shallow waters around Broome, Western Australia.

A visit to Broome was arranged as a joint venture with the Aeromedical Unit (Adelaide) for the purpose of placing the local diving technique on record.

6.72 Instrumentation

The methods normally used for measuring depth on board of the pearling luggers, viz. marks on the life-line or tank pressures, were considered far too inaccurate. The instruments selected were ex-Naval torpedo 'depth-and-roll' recorders (U.S. Navy, 1922), with the following modifications:-

1. Duplicated springs to extend the depth range to 150 feet.

2. Modified governors and gearing to permit the chart to run for 1 hour upon 1 winding of the clock springs.

The unit was thus completely self-contained and housed in a casing made to resist salt water. The modified unit is shown in fig. 35. Its submersed weight of 11 lbs enabled it to replace the lead weight normally strapped to the back of the conventional diving suit.

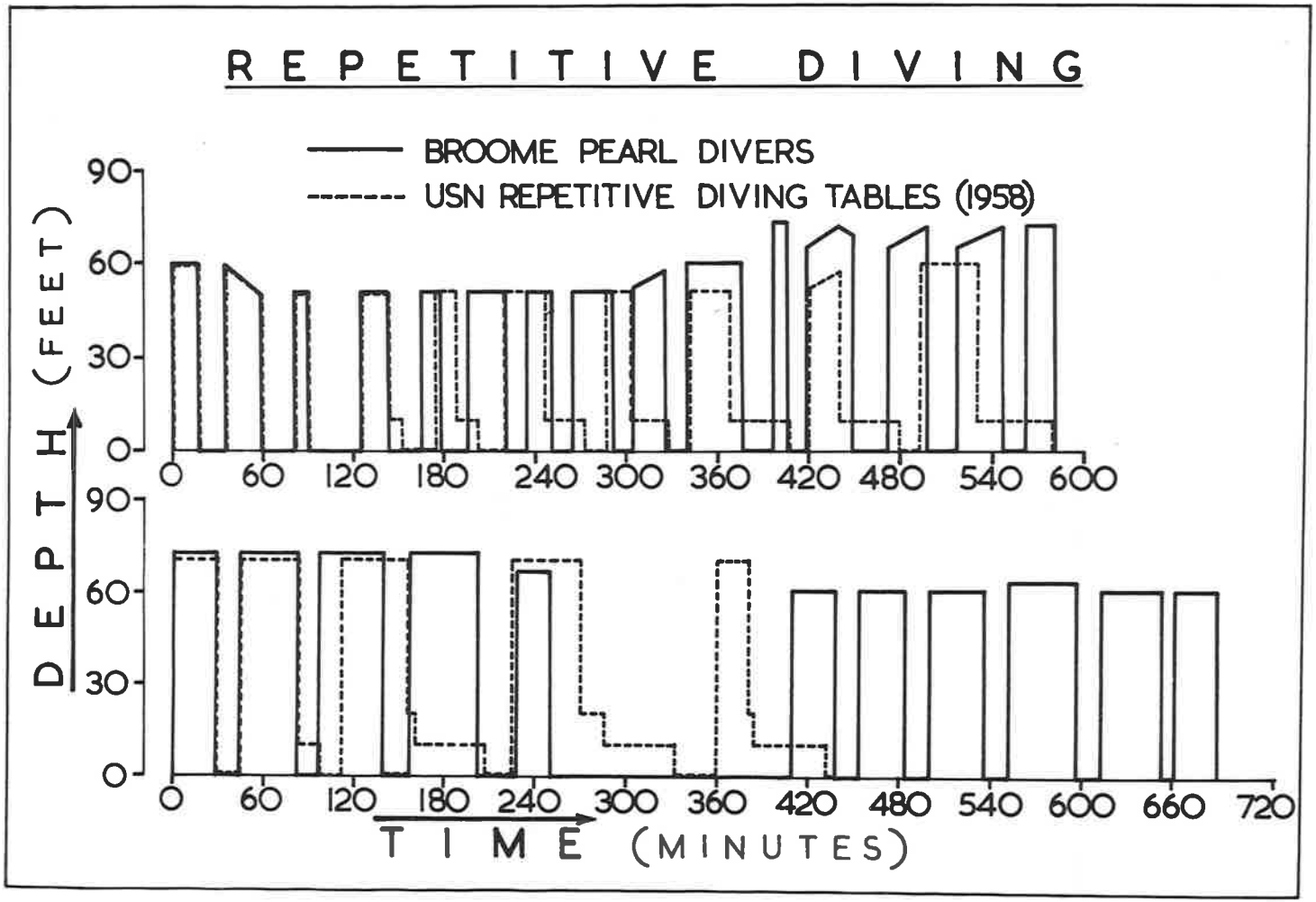

REPETITIVE DIVING
BROOME PEARL DIVERS
USN REPETITIVE DIVING TABLES (1958)
DEPTH (FEET)
90
60
30
0
0 60 120 180 240 300 360 420 480 540 600
90
60
30
0
0 60 120 180 240 300 360 420 480 540 600 660 720
TIME (MINUTES)

Fig. 36

6.73 Visit to Broome

One month was spent aboard the "Kuri Pearl" which is a 240 ton motor vessel used to service a fleet of 5-8 luggers oyster fishing on the Continental Shelf off the North-west coast of Australia. November-December was selected as the end of the season when S.E. winds normally turn the shallower water green, forcing the 'stronger' divers to venture to depths of 20 fathoms and above. However, this had not occurred in December 1964 so most of the value of this visit was lost.

The divers in Broome were all aware of Naval decompression tables but would not use them for economic reasons, their own empirical methods returning the diver to the surface in far shorter times.

Despite the unfortunate timing of the visit, two records of a day's diving were obtained which proved safe, yet were outside the limits permitted by Naval tables. These are shown in fig. 36, and analysed in section 8.56.

6.8 DECOMPRESSION OPTIMISATION TESTED IN VIVO

6.81 Object

If the hypothesis is correct, it would predict an appreciable reduction in total decompression time, the greatest uncertainty being the depth for direct surfacing. A most pertinent test of the hypothesis, and its possible value to diving, would consist of 'titrating' the time of direct surfacing of an animal which has undergone the optimal decompression format derived by the thermal analogue (section 6.52). The whole of the dive arbitrarily selected (40 mins. at 150 feet) and decompression format (fig.

37), needs to be repeated upon each occasion that one reduces the total decompression time, i.e. advances the time for rapid decompression to atmospheric pressure. Such trials must be separated by intervals of at least 2 days to avoid retention of any effects from the previous run.

The animals selected were goats since these are of comparable body mass to men and have proven of similar susceptibility to decompression sickness (section 1.42). Davidson et al (1950) and Hempleman (1960) describe the advantages of using these animals.

6.82 Equipment

Pressurisation is effected in the chamber shown in figs. 38 and 39 by dry warm air supplied from the compressor and ancillary equipment shown in fig. 40. Three bottles of compressed air are used to boost the rate of compression to permit simulation of a diver descending at the conventional rate of 60 feet per minute.

The tank can be programmed for any reasonable pressure-time relationship by means of the program transmitter and associated transducers shown in fig. 41. The desired decompression is plotted in radial co-ordinates on a brass sheet and then cut out as a cam - just visible in the right-hand instrument case shown in fig. 39. This guarantees repetition of the same decompression for successive runs of a 'titration'.

A uniform flow of fresh air is supplied to the animals by means of a manual by-pass for the automatic inlet control valve. A decompression can be terminated at any time by venting the tank air through the manual exhaust valves shown in series with the rotameter in fig. 41.

OPTIMAL DECOMPRESSION FOR A DIVE OF 40 MINUTES AT 150 FEET

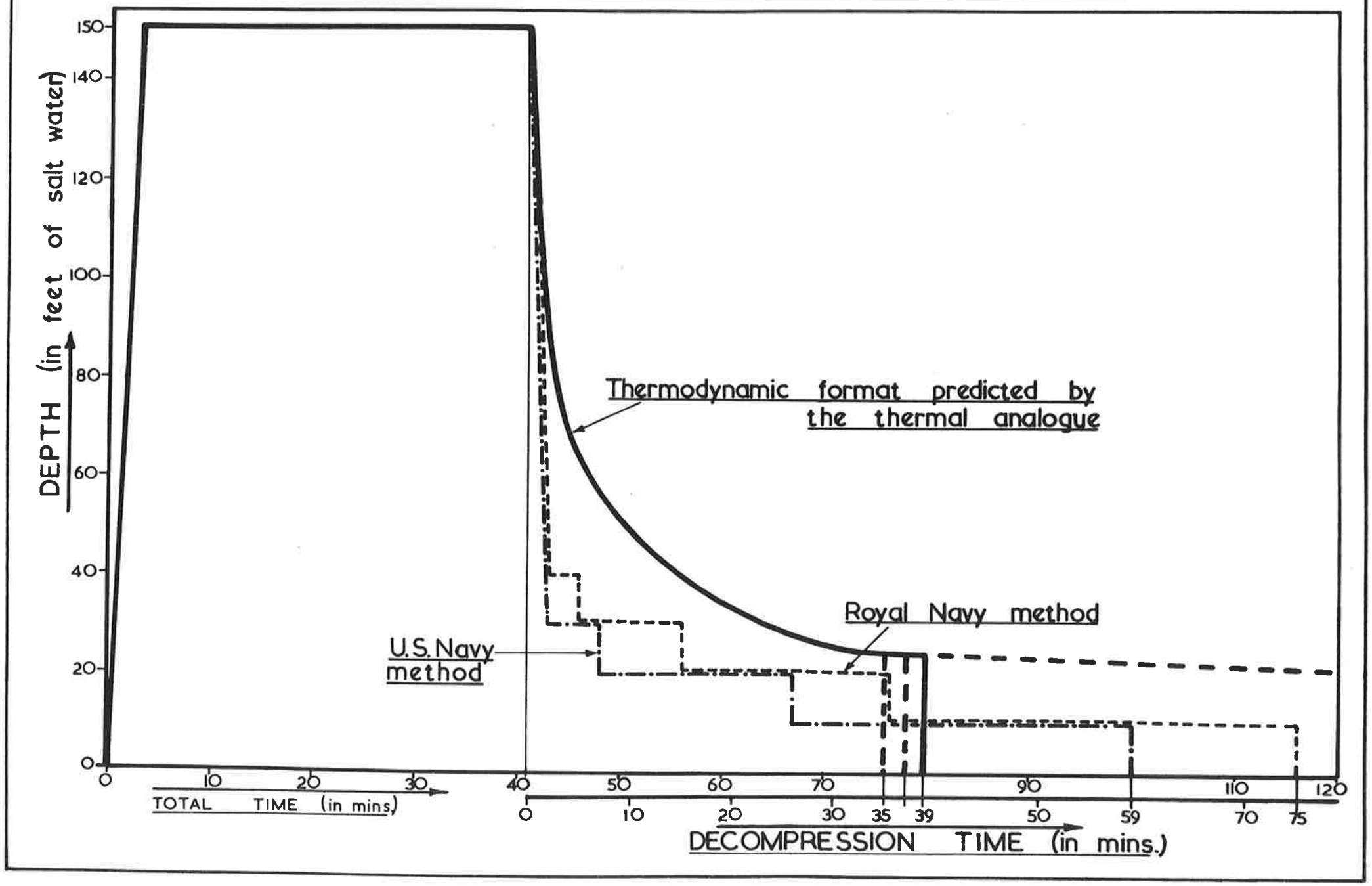


Fig. 37

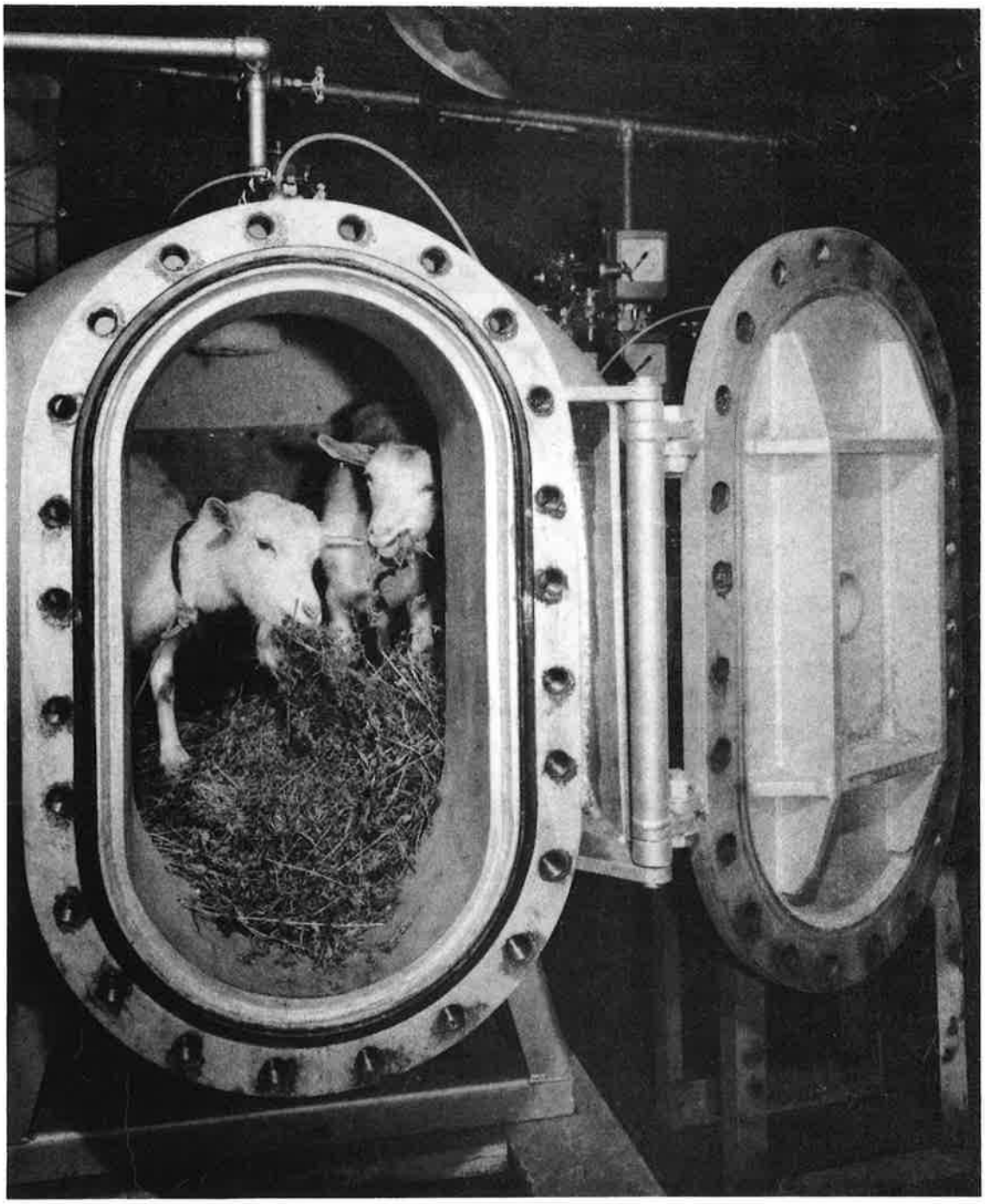


Fig. 38 – GOATS "A" & "C"

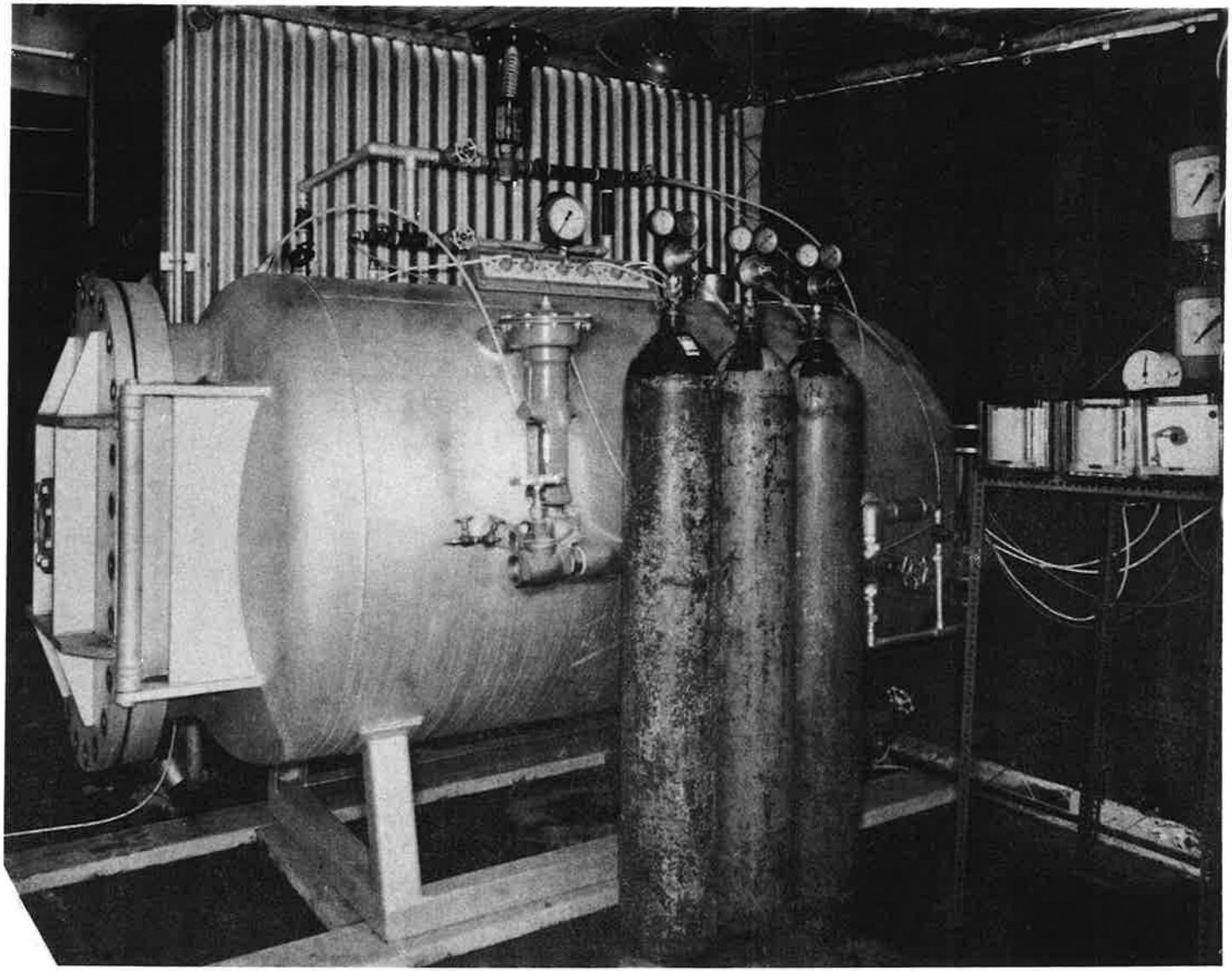


Fig. 39 — THE PRESSURE CHAMBER & INSTRUMENTATION

6.83 Procedure

One or two of the three female goats were used at a time. These were designated A, B and C and had the following weights:-

A - 74 lbs.

B - 66 lbs.

C - 54 lbs.

The goats would be placed in the chamber on a tray containing dry earth, and permitted to eat as much hay as they wished. After bolting the door, pressure would be applied, the timing of the dive starting from the moment of attaining half the maximum gauge pressure, i.e. at 75 feet (s.w.g.). Upon reaching the equivalent of 150 feet, the pressure would be automatically maintained constant by means of the recorder-controller set at the appropriate control position. After 40 mins. the latter unit would be switched to the program generator containing the cam for the particular decompression format scheduled for that run.

When the total decompression time had expired, all exhaust valves would be opened fully and the gauge pressure brought to zero within 10-15 seconds. The animals would then be watched, through any of the four windows in the tank, for the next five hours to see if symptoms developed. Cases of bends were easily recognized by the animal lifting a hoof. With the door bolts still in place, the writer would wait a further two minutes to see if the other goat developed symptoms and would then recompress both animals to 30 feet (s.w.g.) upon 100% oxygen. This invariably alleviated all symptoms. This treatment would be continued for several hours to minimise the effect of the run upon subsequent runs.

6.84 Results

Runs using the 'thermodynamic' type of decompression derived from the thermal analogue (section 8.67) were interspersed with 'control' runs for which standard U.S. Navy or Royal Navy tables were used. All three types of decompression are plotted in fig. 37 for the same exposure of 40 mins. at 150 feet. The results are given in table 18. All runs except No. 2 were performed under resting conditions.

SUMMARY OF GOAT TRIALS

Decompression format	Total decom-pression time	Runs			Number of symptoms	Total animal decom-pressions	% with symptoms
		total	safe	% safe			
Thermodynamic	35 mins.	1	0	0	1	1	(100)
Thermodynamic	37 mins.	4	2	50%	2	6	33%
Thermodynamic	39 mins.	4	4	100%	0	8	0
U.S. Navy	59 mins.	4	0	0	6	8	75%
Royal Navy	75 mins.	1	1	(100)	0	2	0

TABLE 19

6.85 Conclusions

The following features of tables 18 and 19 would seem to justify comment:-

1. Symptoms appear much sooner using U.S. Navy tables.

2. Every run proved unsafe using the U.S. Navy tables.

3. All three goats experienced bends, at some time using the U.S. Navy tables.

These facts would indicate that the goats used were more susceptible to decompression sickness than the pre-selected U.S. Navy diver.

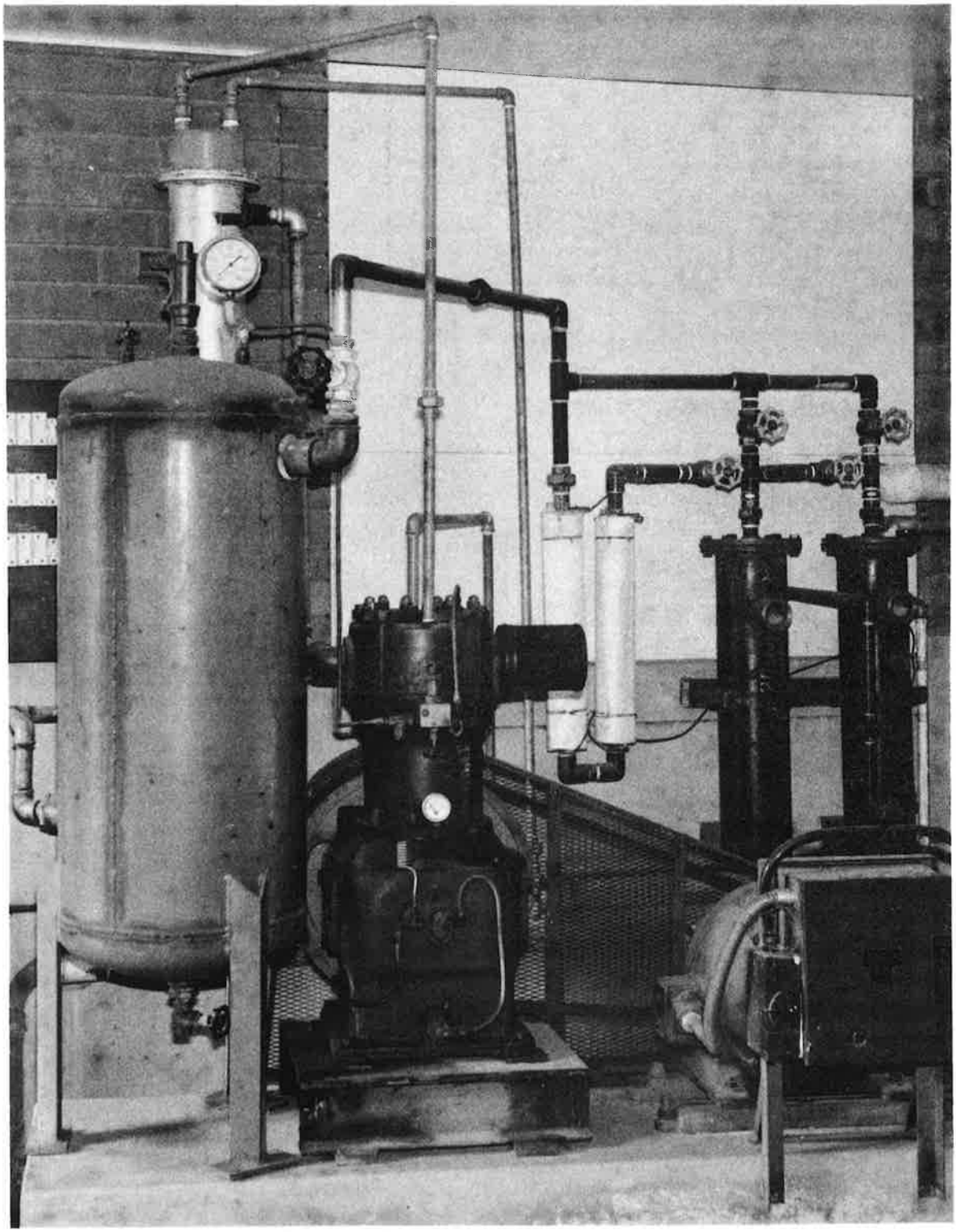


Fig.40 – COMPRESSOR, AIR HEATERS & DRYERS

SYMPTOMS RECORDED IN GOATS DECOMPRESSED BY VARIOUS METHODS

Run No.	Date	Symptoms recorded			Decompression format used	Total decompression time	Number of cases			Total decompressions
		Goat A	Goat B	Goat C			severe	mild	total	
1	7/6/'66	No symptoms	-	-	Thermodynamic	40 mins.	0	0	0	1
2	9/6/'66	Mild bends in L.F.+ (35 mins.)	No symptoms+	-	Thermodynamic	35 mins.	0	1	1	2
3	14/6/'66	No symptoms	No symptoms	-	Thermodynamic	37 mins.	0	0	0	2
4	16/6/'66	Severe bends in L.F. (1 min.)	Mild bends in L.H. (2 mins.)	-	U.S. Navy	59 mins.	1	1	2	2
5	21/6/'66	No symptoms	Mild bends in L.H. (2 mins.)	-	U.S. Navy	59 mins.	0	1	1	2
6	23/6/'66	No symptoms	No symptoms	-	Royal Navy	75 mins.	0	0	0	2
7	28/6/'66	No symptoms	Hyperpathia* R.H. (29 hours)	-	Thermodynamic	37 mins.	1	0	1	2
8	5/7/'66	No symptoms	-	-	Thermodynamic	37 mins.	0	0	0	1
9	7/7/'66	Mild bends in R.H. (48 mins.)	-	-	Thermodynamic	37 mins.	0	1	1	1
10	14/7/'66	No symptoms	-	No symptoms	Thermodynamic	39 mins.	0	0	0	2
11	19/7/'66	Severe bends in R.F. (1 min.)	-	No symptoms	U.S. Navy	59 mins.	1	0	1	2
12	21/7/'66	No symptoms	-	No symptoms	Thermodynamic	39 mins.	0	0	0	2
13	26/7/'66	Mild bends in L.H. (1 min.)	-	Severe bends in R.F. (< 1 min.)	U.S. Navy	59 mins.	1	1	2	2
14	28/7/'66	No symptoms	-	No symptoms	Thermodynamic	39 mins.	0	0	0	2
15	4/8/'66	No symptoms	-	No symptoms	Thermodynamic	39 mins.	0	0	0	2

TABLE 18

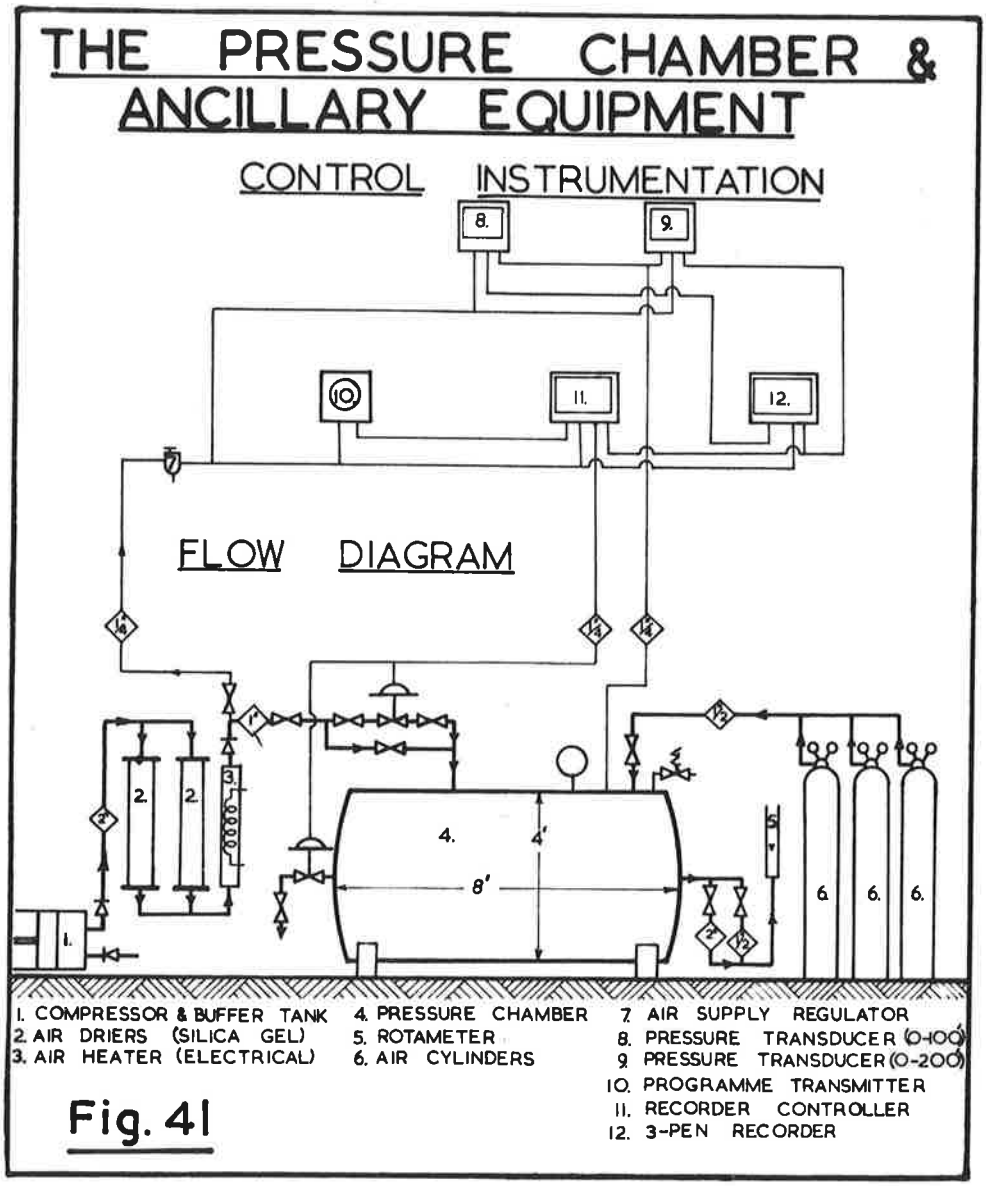
R.H. right hindleg
L.H. left hindleg
R.F. right foreleg
L.F. left foreleg

* A pathological investigation failed to reveal whether the trouble was decompression or other injury - the goats had been climbing trees that day.

\+ Goats were fighting at pressure - exercise conditions.

Figures in parentheses indicate the time of onset of symptoms following return to sea-level pressure.

THE PRESSURE CHAMBER & ANCILLARY EQUIPMENT



1. COMPRESSOR & BUFFER TANK
2. AIR DRIERS (SILICA GEL)
3. AIR HEATER (ELECTRICAL)
4. PRESSURE CHAMBER
5. ROTAMETER
6. AIR CYLINDERS
7. AIR SUPPLY REGULATOR
8. PRESSURE TRANSDUCER (0-100)
9. PRESSURE TRANSDUCER (0-200)
10. PROGRAMME TRANSMITTER
11. RECORDER CONTROLLER
12. 3-PEN RECORDER

Fig. 41

The 'thermodynamic' decompression equivalent to the 59 mins. advocated by the U.S. Navy is probably in the region of 36 ± 2 mins. for goats.

The very much longer onset time recorded for cases following the thermodynamic format would support the theoretical postulations that:-

1. Gas has separated from solution long before the U.S. Navy would return their diver to the surface.

2. Separated gas must be given time to congregate before it can become manifest as symptoms.

6.86 Future work

While the above results refer to goats only, they hold the implication that the same mathematical expressions may also prove realistic for decreasing decompression times for divers. Since trials upon men cannot be undertaken by a Faculty of Engineering, the writer has made tentative arrangements to further such work during a visit to the Royal Naval Physiological Laboratories.

CHAPTER 7

THE HYPOTHESIS

7.1 General

7.2 Salient Features

CHAPTER 7

THE PROPOSED HYPOTHESIS

7.1 GENERAL

The foregoing experimental work would not seem at variance with any features of the hypothesis derived from fundamental physical and physiological parameters in chapters 2-5. In fact, the results support the three major deviations from conventional theory which are:-

1. Random nucleation by decompression in vivo.
2. An inherent unsaturation in tissue which increases with depth.
3. Cellular diffusion coefficients several orders lower than generally presumed from steady-state determinations.

The above features are combined with others, which have been described previously, to give a quantitative hypothesis which may be summarised qualitatively by the list of salient points enumerated below.

7.2 SALIENT FEATURES

1. Quantitative analyses of decompressions should be based upon the 'worst possible' combination of physical and physiological parameters rather than the average likely to occur in the critical tissue type.

2. Nucleation of tissue supersaturated by decompression is a random process, the 'worst possible' zones being those in their most stable thermodynamic state, i.e. where there is complete phase equilibration at all times. In such regions, all gas in excess of saturation must be presumed to have separated from solution.

3. The diffusion coefficients of gases in cellular material are several orders less than the corresponding values in blood or interstitial fluid. These must be determined by a truly transient method.

4. The 'worst possible' regions for blood:tissue exchange occur where two or more irregularly-shaped cells completely envelop a capillary. The mathematical transport model for the worst possible case is thus one of radial gas diffusion from a cylindrical capillary into cytoplasm.

5. There is a driving force for re-dissolving and transporting separated inert gas to the capillary. This arises from metabolism and increases linearly with pressure, becoming appreciable for any depth from which decompression may provoke symptoms.

6. Gas separating from solution is initially deposited as very fine bubbles or films, preferentially located at any direct lipid-aqueous phase boundaries which may exist within the critical tissue type. The coalescence of these films, or congregation of the bubbles, can be accelerated by movement of the tissue.

7. Pain, or other symptoms of decompression sickness, can become manifest when the gas-tissue pressure differential is sufficient to cause a nerve ending to be bent or otherwise distorted beyond a critical threshold. This can occur when a local concentration of mechanical stress arises by virtue of the random congregation of bubbles described above.

8. The criterion for the threshold to be exceeded can be expressed quantitatively by one equation (XXX) for any conditions.

CHAPTER 8

ASSESSMENT OF THE HYPOTHESIS

8.5 Analyses of Dives with Staging

8.6 Fundamental Interpretation of Constants

ASSESSMENT OF THE HYPOTHESIS

8.1 QUALITATIVE ASSESSMENT

8.11 General approach

Decompression sickness is mentioned a minimum number of times during the derivation of the hypothesis in chapters 3, 4 and 5 in order to attain a more fundamental approach. Having finalised these deductions (chapter 7), the task is now one of testing the compatibility of this postulated theory with the many phenomena recorded in the literature which are specific to decompression sickness.

This initial qualitative assessment takes the form of a comparison of this hypothesis with the published theories on the broad issues of:-

(a) the mechanism - phase equilibration or supersaturation, or theories of bubbles whose growth is limited by inter-phase gas transfer.

(b) transport - radial diffusion or blood perfusion as rate-limiting.

The aspects specific to the development of symptoms are listed below and classified where feasible into the following sections:-

8.12 Random phenomena

Two of the most striking features of decompression sickness are the variable onset time and the random occurrence of symptoms when the safety limits for any decompression format have been exceeded (section 1.25). Most theories avoid these issues as irrelevant to the

calculation of the safety limits. However, it is felt that any random observation must be the manifestation of at least one random physical or physiological process, and that no theoretical approach is comprehensive unless the model or mechanism postulated has at least one stage demanding statistical interpretation. The specific points to be correlated may thus be listed as follows:-

(i) Random occurrence which is compatible with the thermodynamic hypothesis on the grounds of random nucleation (section 4.34), no metastable limit being postulated as implied by the theories based upon a critical limit to supersaturation. This effect is enhanced by the irregular nature of tissue geometry postulated (section 5.4) in which only a few regions would conform to the worst possible transport case of two cells enveloping a capillary. The probability of any one of these zones of the critical tissue type being sufficiently nucleated to acquire phase equilibration should thus be of the same order as the fraction of cases recorded in marginally unsafe decompressions (table 26). A more quantitative correlation is not possible without knowing the tissue type responsible.

(ii) Increased incidence of symptoms with increasing decompression which is noted when the safety limits have been exceeded. This is illustrated by Bateman (1951) for aerial decompressions to altitudes in excess of a threshold in the region of 22,000 feet (section 1.31). The increased incidence of symptoms in the same individuals with greater altitude is compatible with the increasing probability of gas phase initiation occurring for greater decompressions. This can hold only if the metastable zone implied by supersaturation theories were really one of random nucleation.

(iii) Random onset time of symptoms (section 1.25), which is compatible with the random nature of gas coalescence or the congregation of bubbles into a region where their integrated mechanical stress may cause symptoms (section 4.4).

This phenomenon would seem more difficult to correlate with supersaturation theories, most of which imply that the mere presence of the gas phase provokes symptoms. This opinion is enhanced by the observation that nucleation invariably occurred within a minute or so of very rapid decompressions in vitro (section 4.2). This is an order or two different from the onset time for symptoms (table 1).

If the rate of transfer of nitrogen from tissue fluid to the gas phase were the critical mechanism one would anticipate far less scatter in the time during which the bubble would reach a critical size under identical external conditions. This would tend to detract from the theories of Nims and Bateman as interpreted in section 1.67.

More significant is perhaps the effect of exercise upon onset time.

8.13 Stimulation

The effects of stimulation upon the incidence of symptoms differ according to the form of the stimulation and the stage of application, i.e.

(iv) Exercise following decompression decreases the onset time of symptoms (section 1.46). This observation is compatible with the hypothesis since the mechanical action of exercise should hasten the congregation of gas separated from solution.

Mechanical strain imparted by exercise is put forward by many advocates of limited supersaturation theories as an additional source of decompression (section 4.42). However, one would then expect phase separation to occur with the first straining movement giving instantaneous nucleation and hence immediate symptoms.

While the foregoing items concerning onset times would favour the thermodynamic hypothesis, there would be nothing to prevent the concept of coalescence being incorporated into other theories.

(v) Exercise at depth increases the incidence of symptoms (section 1.46). This observation is readily explained by increased uptake of inert gas and can be thus claimed as compatible with all theories. Mathematically, this may be expressed for the thermodynamic hypothesis as a decrease in the (b/a) ratio in Equation VII.

(vi) Exercise during pre-oxygenation tends to reduce the incidence of symptoms (section 1.46). This is again readily interpreted by all theories on the basis of increased venting of inert gas prior to decompression

(vii) Increased temperature following decompression tends to reduce the incidence of symptoms. This may be similarly interpreted by all theories in terms of increased blood:tissue exchange.

The effects listed in items v, vi and vii might seem too small to be interpreted by the corresponding increase in blood flow to the overall regions contracting symptoms. Jones (1951) discusses the marginal effects of exercise. However, advocates of circulation-controlling transport processes would seem to have an explanation consistent with their

model in attributing such apparent discrepancies to heterogeneous perfusion producing a marginal increase in blood flow to the unidentified critical tissue type.

(viii) Exercise during decompression increases the chances of symptoms occurring (section 1.46). This would appear contrary to all theories in which any degree of supersaturation is postulated in estimating the proximity to symptoms; exercise could only accelerate tissue desaturation if no phase change has occurred.

According to the thermodynamic hypothesis, however, this increased loss of inert gas via the capillary should be directly opposed to the other effect of exercise in simultaneously promoting coalescence. The relative predominance of these processes should depend upon the quantity of separated gas present during decompression. Hence the thermodynamic hypothesis predicts that exercise during decompression would not be advocated by the U.S. Navy (1964). They make a very long first 'pull' from the bottom during which much gas should separate from solution. This could then coalesce during the remainder of the decompression to a form less condusive to re-solution in later stagings. It is Naval experience to avoid exercise during decompression - Behnke (1951).

On the other hand, adherence to the optimal conditions proposed in section 5.9, in which no phase change should occur, would indicate that exercise during decompression should reduce the incidence of symptoms. In this respect it is interesting to note that caisson workers appeared no more susceptible to bends by walking during the 'deep' stagings used by Japp (1909).

8.14 X-ray data

Ferris and Engel (1951) state that the first X-ray studies of decompression sickness, made by Evelyn (1941) and Boothby et al (1940), demonstrate the presence of bubbles or accumulations of gas in joint and tendon sheath spaces. Subsequently, Webb et al (1943) and Blankenhorn and Ferris (1944) have found that gas occurs in three forms:-

(a) In the joint where there is no correlation with pain.

(b) As discreet round gas bubbles in the periarticular tissues about the knee joint, usually seen just behind or lateral to the neck of the femur in the popliteal fat pad.

(c) Fine longitudinal streaking in the popliteal fossa which appears to be distributed along tendon or muscle bundles. Stereoscopic studies of these lesions reveal them to be "wide, flat ribbon-like shadows" presumably of finely dispersed gas particles. They can be seen only when the angle of the X-rays to the band is obtuse.

Webb et al found that streaking could predict 74 out of 85 cases of decompression sickness correctly. 6 cases were found displaying streaking but no bubbles or pain. The occurrence of a phase change without pain has been confirmed by Thomas and Williams (1944). In view of the observations of Ryder et al (1945), who found the first indications of streaking to occur at an altitude of 12,000 feet, it would seem that the "flat ribbon-like shadows" are an initial stage in the formation of bubbles - possibly the gas films predicted thermodynamically (section 7.2).

While all theories would agree with the correlation between bends and recognisable bubbles, the points which offer a more critical comparison are:-

(ix) Streaking of X-ray plates, which may be observed with or without the simultaneous occurrence of symptoms. This is one of the strongest points in favour of the thermodynamic hypothesis since it provides direct evidence of the presence of separated gas prior to its coalescence or congregation into a bubble of sufficient size to provoke pain. This practical observation is very difficult to interpret by any theory opposed to the concept of "silent bubbles".

(x) Minimum altitude for streaking, which implies the decompression needed to initiate phase separation. The altitude range of 10,000-12,000 feet, as the point at which changes occur in X-ray photographs and the fluid volume of the spinal column etc., is discussed quantitatively in section 8.24.

The above data is incompatible with any decompression ratio or fixed ΔP of the order envisaged by advocates of limiting supersaturation theories. Moreover, such a threshold is difficult to envisage from the mathematical expressions of Nims, Bateman or Albano (sections 1.66 and 1.67) which imply that growth of the gas phase should start for any decompression from ambient.

8.15 The effects of increased oxygen

The effects of increasing the mole fraction of oxygen in the inhaled gas mixture invariably reduces the likelihood of symptoms.

However, the relative extent of protection is not obvious and leads to the following aspects requiring correlation:-

(xi) Oxygen wash-out before decompression, which reduces the probability of symptoms occurring later - whether applied prior to aerial ascent (section 1.54) or for a short time immediately before rising from depth (section 1.53). This phenomenon can be readily explained by all theories on the general basis of 'washing out' the inert gas although few, if any, derive quantitative expressions showing that oxygen does not replace the inert gas in the critical tissue type. Quantitative account of this phenomenon can be taken by the thermodynamic hypothesis in the form of equation XII, where decreased x (higher O_2 mole fraction) decreases g and hence the proximity to symptoms (equation XXX).

(xii) Increase in the minimum depth for symptoms, which is found with breathing gas with a higher mole fraction of O_2 (section 1.53). According to equation 48 increased partial pressure of inhaled oxygen should correspond to the increase in inherent unsaturation, permitting men to surface directly from greater depth. Quantitative correlation is contained in section 8.25.

(xiii) Improved treatment of symptoms by using increased oxygen during recompression, which is a technique found advantageous by Goodman and Workman (1966). According to the thermodynamic hypothesis this again corresponds to a greater value for the driving force (Δp) for inert gas re-solution (equation XXI).

(xiv) Decreased advantage of preoxygenation at altitude (see section 1.54). According to the thermodynamic hypothesis this observation is compatible with a lower value of Δp in equation XXI, or driving force for inert gas elimination, for a smaller value of P. This phenomenon is difficult to explain by any supersaturation theory since the tension differential providing the driving force for inert gas 'wash-out' by 100% O_2 should be the same for any absolute pressure. According to such theories no phase change should occur until higher altitudes are reached.

8.16 Other gases

The variation of the proportion of gases other than oxygen leads to the following points for correlation:-

(xv) The substitution of other inert gases for nitrogen, particularly helium which is less soluble in both aqueous and lipid phases. The advantages of using He for dives of long duration are compatible with all theories qualitatively, the relevant expression for the thermodynamic hypothesis being equation XII.

(xvi) Increased inhaled carbon dioxide, which has a negligible effect upon bends incidence (see section 1.44). According to the thermodynamic hypothesis the substitution of CO_2 for inert gas in the atmosphere should cause almost the same change in the corresponding cell tensions. However, total cell tensions would hardly change, and since this is the relevant parameter determining the extent of phase separation, there should be negligible effect upon the incidence of symptoms.

This observation would seem incompatible with theories of critical supersaturation if one accepts the experimental acetylene results (fig. 19). These indicate that substitution of a more soluble for a less soluble gas should greatly increase the probability of cavitation for the same tissue tensions and extent of decompression.

According to theories in which gas transfer across the bubble-fluid interface is rate-limiting, one would again expect the higher solubility of CO_2 to increase bends incidence.

8.17 Parameters of the individual

The factors which may influence individual susceptibility to decompression sickness are listed as follows:-

(xvii) Obesity, in which susceptibility increases with the more corpulent individuals (section 1.3). This observation would seem equally well interpreted by all theories on the basis of a higher fat content of the overall body being reflected as a higher lipid content in the critical tissue type, i.e. increased S in equations XII and XXX.

(xviii) Water balance, in which a high natural fluid turnover has proved an indicator of individual susceptibility (section 1.33). The writer could find no fundamental interpretation of this phenomenon inthe literature, Jones (1951) describing it as "puzzling".

However, Macfarlane (1965) has shown a definite increase in water turnover rate with the water content of cattle grazing in different parts of Australia. Moreover, many references are quoted by Keys and Brozek (1953) illustrating the reciprocal nature of water and fat contents

of the human body. Without going more deeply into this aspect it would seem that higher natural water turnover is an indication of a lower inherent lipid content, and hence lower susceptibility to decompression sickness. This would again be equally acceptable according to all theories.

Possible justification for the assumption that the overall fat content of the body is a reflection of the lipid content of the critical tissue type is provided by Gersh et al (1944). They find a definite correlation between average fat and the lipid content of tendon in guinea pigs.

(xix) Age, where advancing years increases susceptibility (section 1.32). This would correspond to increasing elastic moduli according to equation II. Moreover, the direct proportionality expressed in this equation transposes a linear increase of tissue modulus with age to one of susceptibility with age (section 4.16).

8.18 Miscellaneous phenomena

Miscellaneous aspects of decompression sickness which further illustrate the diverse nature of phenomena to be correlated include:-

(xx) The diurnal bends effect. This is only recordedfor negative gauge pressures and is far more pronounced at greater altitudes (section 1.42). It is readily interpreted by the thermodynamic hypothesis on the basis of the diurnal shift in metabolic rate. This is confirmed by Stevens et al (1947) on the basis of oxygen consumption measured during decompression trials in which there was found to be no change in the elimination rate of inert gas. Quantitatively, equation 38 would predict that in the afternoons the metabolic rate (M) would be greater and hence $(p_o + p_c)$ would be smaller

than in the mornings. Hence the total tension of all volatile cell components should be smaller and so there should be a lower incidence of symptoms in afternoon trials. The extent of this tension change could not exceed the 40 mm. Hg maximum differential set by metabolism (equation 48). Moreover, this difference between the limiting values only becomes appreciable relative to absolute pressure at high altitudes. Hence the increase in the diurnal bends effect with increasing altitude is offered as one of the major points supporting the more pronounced role of the reactive gases. In the conventional theories no reference could be found to a quantitative assessment of the effects of metabolism upon decompression sickness.

(xxi) The decreasing tolerance of pilots to successive aerial decompressions (described in section 1.54). It would seem inconsistent with all supersaturation theories that a pilot should be restricted to successively lower altitudes despite breathing 100% O_2 from the start of the first decompression. If no phase separation had occurred in the earlier safe 'flights' one could only presume that he must have lost inert gas and so be capable of more, and not less decompression the next time. With growth-limiting theories one could only visualise bubbles receding with further 'wash-out' time.

According to the thermodynamic hypothesis, the driving force for inert gas desaturation (Δp in equation XXI) is very small for low absolute pressures. With successive decompressions one should get increased coalescence or congregation of gas whose total quantity is only decreasing slowly. Hence it is compatible with the hypothesis that a pilot's tolerance should decrease with successive flights.

(xxii) Post-decompression sickness (see section 1.56). This very rare phenomenon of symptoms first occurring after return of a pilot to ground level would seem irreconcilable with all theories including the thermodynamic hypothesis. However, the latter does predict that a phase change can occur without symptoms so that recompressed bubbles could congregate or coalesce following recompression. It is very difficult to find any explanation on the basis of theories of limited supersaturation where no symptoms at altitude imply no phase separation. There would also be no driving force for bubble growth to continue after recompression, so coalescence is again indicated as the final process for the mechanism of inducing symptoms.

(xxiii) Surface decompression, which is the name given to the process whereby a diver may be rapidly brought to the surface, immediately recompressed on deck, and then decompressed as though still at depth (Behnke, 1951).

The fact that the same decompression format may be used is exactly contrary to all theories postulating a critical degree of supersaturation, since the system must have been nucleated during the initial 'pull' to the surface. On the other hand, adherence to the concept of thermodynamic equilibrium implies that the large initial phase separation would greatly reduce the driving force for inert gas redistribution during ascent to the chamber on deck. Provided the divers were recompressed before appreciable coalescence of the separated gas could occur, the inert gas distribution should be little different when maximum pressure is re-attained (e.g. fig. 12, graph 4). Hence the same subsequent decompression procedure should hold - whatever its theoretical basis.

The thermodynamic hypothesis would thus interpret the transfer time from depth to surface chamber as limited by the induction period for the creation of the critical local pressure differential by coalescence of a volume of separated gas in excess of the minimum required to provoke eventual symptoms. This would infer that the diver should take the very minimum of exercise during the transfer in order to delay the process of gas congregation. The latter prediction is in agreement with the practical findings of Gouze (1944).

While the foregoing points are qualitative, it is felt that the true test of the thermodynamic hypothesis lies in its ability to correlate experimental data quantitatively.

8.2 QUANTITATIVE CORRELATIONS INDEPENDENT OF TIME

8.21 Constants

Hitherto no numerical values have been given to the constants in the quantitative expressions derived to describe the proximity of the individual to marginal symptoms. From the equations summarised in section 5.84, it may be seen that the number of constants may be reduced to three groups. These are as follows:-

1. (F_c/SP_o), which is dimensionless and characteristic of the susceptibility of the individual for a given inert gas. The vital parameter (F) has a critical value (F_c) independent of the inert gas, and hence its solubility (S).

2. (b/a), which is a dimensionless group defining the relative geometry of the transport model, and hence the dimensionless term $(a\alpha_n)$

according to equation VIII. It is essentially a parameter characterising the vascularity of the critical tissue type.

3. (D/a^2), which has the dimensions of $(\text{time})^{-1}$, is the factor complimentary to (b/a) in determining the transient response of the system, since the time constants $\alpha_n^2 D$ (equation XI) may be expressed as $(D/a^2)(a\alpha_1)^2$.

It is felt that the reduction of the effective number of constants to three decreases the number of 'degrees of freedom', such that the analysis of data constitutes a more rigorous test of the hypothesis.

This number may be reduced to one in those aspects of decompression sickness where time is no longer a relevant variable and where (b/a) and (D/a^2) are not involved. These are the cases in which the body is brought to a steady-state before decompression, and include the following:-

8.22 Minimum depth for symptoms

In section 1.31 the opinion has been expressed that the best quantitative assessment of susceptibility is afforded by the minimum depth from which the individual can surface safely without staging. This statement was based upon the belief that such a value is independent of any analysis of transients and the assumptions associated with any transport model.

Referring to the distribution of values described in section 1.31, it would seem reasonable to base calculations upon two levels of susceptibility:-

1. A minimum 'no-stage' depth for 'weak' divers which has been set by Duffner et al (1959) at 33 feet for breathing air.

2. A corresponding value for divers preselected for their natural tolerance to decompression sickness, for which 38 feet (Behnke, 1951) is probably a conservative estimate.

Combining equations XII and XXX, symptoms can occur if:-

$$\frac{x(P_b - P_o)\Psi(\theta) - (g'/S) + x(P_o - 46) - (P+74)}{(P + 74)} = \frac{F}{SP_o} > \frac{F_c}{SP_o} \qquad (65)$$

A minimum bends depth (H_{∞}), corresponds to the particular case of:-

1. An infinite exposure, i.e. $H_{\infty} = P_b - P_o$ for $t = \infty$, when $\Psi(\theta) = 1$ according to equation XIII.

2. No staging, i.e. $g' = 0$.

3. Return of the diver to the surface, when $P = P_o = 760$ mm. Hg.

4. For air $x = 0.8$.

Making the foregoing substitutions in equation 65, bends can occur if:-

$$H_{\infty} > 1042.5(F_c/SP_o) + 329 \text{ mm. Hg.} \qquad (66)$$

For $H_{\infty} = 38$ feet (876 mm. Hg), $(F_c/SP_o) = 0.525$

while for $H_{\infty} = 33$ feet (760 mm. Hg), $(F_c/SP_o) = 0.413$

Thus for pre-selected divers $(F_c/SP_o) = 0.525$ (67)

while for 'weak' divers $(F_c/SP_o) = 0.413$ (68)

While the above calculations constitute no test of the hypothesis in themselves, they set the critical values (F_c/SP_o) to be anticipated for the parameter (F/SP_o) which is the most 'sensitive' in differentiating between potentially safe and unsafe cases.

8.23 Minimum altitude for symptoms

Rapid aerial decompressions without pre-oxygenation correspond to the particular case of:-

1. An effectively infinite sojourn at ground level before decompression, i.e. $P_b = P_o = 760$ mm. Hg.

2. No staging, i.e. $g' = 0$.

3. Having previously inhaled air, $x = 0.8$.

4. For decompression to the minimum bends pressure (P_s), $P = P_s$.

Making the foregoing substitutions in equation 65, symptoms can occur if:-

$$(F/SP_o) = \frac{(497 - P_s)}{(P_s + 74)} > (F_c/SP_o) \qquad (69)$$

Taking the value for pre-selected divers (equation 67) of $(F_c/SP_o) = 0.525$, the above expression gives:-

$$P_s = 300 \text{ mm. Hg.}$$

This absolute pressure corresponds to an altitude of 23,000-24,000 feet which is close to the 25,000 feet generally recognized as the lower limit of altitude potentially dangerous to pre-selected pilots. (See section 1.31). Taking the value for 'weak' divers (equation 68) of $(F_c/SP_o) = 0.413$ equation 69 gives:-

$$P_s = 330 \text{ mm. Hg.}$$

It is regarded as most significant that this value lies well within the limits of 321-335 mm. Hg corresponding to the altitude range of 21,000-22,000 feet at which the 'weakest' subjects were found to develop symptoms (section 1.31).

8.24 Minimum altitude for a phase change

In section 5.68 three pieces of evidence from six groups of workers have been presented which strongly indicate 10,500-12,000 feet as the altitude for the onset of a phase change for a man decompressed from ground level. This corresponds to a threshold pressure range of 483-512 mm. Hg.

The point of phase separation is that for which the volume fraction of separated gas (F) becomes finite,

i.e. $F \geq 0$ or $(FS/P_o) \geq 0$.

Making this substitution in equation 69, since this expression refers to decompression from 'air equilibration' at ground level, one obtains the critical pressure for phase change (P'_s) as:-

$$P'_s = 497 \text{ mm. Hg}$$

It is regarded as most significant that this value lies in the middle of the experimental range of 483-512 mm. Hg indicated by techniques varying from X-rays to fluid volume measurements on the spinal column.

8.25 Minimum unsafe depth with increased oxygen

The maximum depth from which a diver may be decompressed safely with no staging following a very long exposure, corresponds to the particular case where:-

1. there is an effectively infinite exposure, i.e. $\theta = \infty$, giving $\psi(\theta) = 1$ (equation XIII).
2. decompression to the surface, i.e. $P = P_o = 33$ feet.
3. no staging, i.e. $g' = 0$.

Converting equation 65 to pressure units of feet of salt water, and incorporating the above conditions, symptoms can occur if:-

$$\frac{x(P_b-2) - 36.2}{36.2} > (F_c/SP_o)$$

The Micoperi Company (Pellegrini, 1963) have claimed that men can work for 7 hours at 25 m. (82 feet), breathing an increased proportion of oxygen, and surface directly without symptoms developing.

For P_b = 115 feet the above equation gives:-

x = 0.489 for pre-selected divers for whom F_c/SP_o = 0.525 (equation 67)

x = 0.453 for 'weak' divers for whom F_c/SP_o = 0.413 (equation 68).

These compositions correspond to oxygen partial pressures of 1.84 and 1.72 Kgm. cm^{-2} respectively for a depth of 82 feet. This is consistent with the range of 1.6-1.8 Kg. cm^{-2} used by Pellegrini in practice.

8.26 Minimum unsafe depth with helium

For a predominantly aqueous tissue type, such as that believed to be the site of bends pain, the solubility of helium in water (S' = 0.0087 cc. He/c.c. H_2O atmos.) can be substituted for that of nitrogen in water (S = 0.0127 c.c. N_2/c.c. H_2O atmos.), when $(F_c/S'P_o) = 0.413 \times \frac{0.0127}{0.0087} =$ 0.603. For weak divers equation 68 gives $(F_c/S'P_o)$ = 0.413. The above values of solubilities are quoted by Behnke (1951) for body temperature.

After substituting $(F_c/S'P_o)$ = 0.603 for F_c/SP_o, equation 66 gives the maximum depth from which a weak diver may surface safely without staging, following a 'saturation' exposure upon 80% helium, as 960 mm. Hg or 41.6 feet.

This lies within the range of 37-43 feet quoted by Duffner et al (1959) as the values recorded in practice for the weakest divers breathing 80% He + 20% O_2.

8.27 The decompression ratio

No theory could be accepted unless it predicts a roughly constant decompression ratio (P_1/P_2) for the onset of marginal symptoms in the same individual. If P_1 is the absolute pressure at which the subject spends an effectively infinite time before direct decompression to a lower absolute pressure (P_2) at which he is observed over a period of several hours, (P_1/P_2) is the decompression ratio. Despite the original postulation by Haldane (section 1.62), that this ratio should be constant, it is comparatively recentl that it has been confirmed experimentally. This very fundamental issue has bee clarified by Hempleman (1957) in a most painstaking piece of experimental work using goats.

Equation 65 may be re-written with feet of salt water replacing mm. Hg as the units expressing quantities of the same dimensions as pressure, i.e. symptoms can occur if:-

$$\frac{F}{SP_o} = \frac{x(P_b-P_o)\psi(\theta)-(g'/S)+x(P_o-2)-(P+3.2)}{(P+3.2)} > \frac{F_o}{SP_o} \qquad (70)$$

The foregoing definitions of P_1 and P_2 would refer to the particular case where:-

(a) the duration of the compression is effectively infinite, i.e. $\theta = \infty$, when $\psi(\theta) = 1$ (equation XIII).

(b) $P_b = P_1$, and the pressure for symptoms (P) = P_2.

(c) no staging, i.e. $g' = 0$.

Hence equation 70 becomes:-

$$\frac{x(P_1-2)-(P_2+3.2)}{(P_2+3.2)} > \frac{F_c}{SP_o}$$

This can be rearranged to give the critical value for (P_1/P_2) as:-

$$\frac{P_1}{P_2} = ((F_c/SP_o)+1) + \frac{(3.2(F_c/SP_o)+5.2)}{P_2} \qquad (71)$$

i.e. (P_1/P_2) is approximately constant for appreciable depths where $P_2 >> 3.2(F_c/SP_o) + 5.2 \approx 6.2$ feet, the latter value being obtained by substituting for (F_c/SP_o) according to equation 68.

However, there would be no approximation in stating that equation 71 would predict P_1 as a linear function of P_2 and that (P_1/P_2) should decrease slightly for greater values of P_2. This small predicted deviation from the ratio rule would seem in good agreement with the following experimental facts:-

a. The appreciably higher decompression ratios for symptoms to be incurred by aerial decompression (section 8.23) where tensions of the order of 6.2 feet become significant relative to the absolute pressure (P_2) - equation 71.

b. The slightly lower decompression ratio with higher P_1 or P_2 for the particular goat which Hempleman titrated to as many as four bends points in 12 decompressions. The writer disagrees with the manner in which Hempleman has drawn a straight line through those points assuming it to be concurrent with $P_1 = P_2 = 0$. A

complete differentiation between 'bends' and 'no bends' points can be achieved by a straight line having a positive intercept of 5-10' on the P_1 axis. This is predicted by equation 71.

Taking values from Hempleman's graph for the two terminal bends points of his line:-

Point 1: $P_1 = 233'$, $P_2 = 104'$, $P_1/P_2 = 2.24$, and $(1+(F_c/SP_o)) = 1.724$

Point 2: $P_1 = 82'$, $P_2 = 33'$, $P_1/P_2 = 2.48$, and $(1+(F_c/SP_o)) = 1.768$

Equation 71, with a 1.3% variation in $(1+(F_c/SP_o))$ from the mean, would thus appear to offer a better correlation of the data than a constant ratio for which (P_1/P_2) has a 5.3% deviation from the mean.

Data recorded by Hempleman for the other goats are in general agreement with an approximately constant ratio but, with no more than 7 decompressions, do not permit such rigorous analyses.

8.3 QUANTITATIVE ANALYSES INVOLVING TIME

8.31 Decompression to the surface

The foregoing correlations have been effected to test the fundamental adequacy of the hypothesis to aspects other than those involving time. The next step in the assessment is therefore directed at the transport model and the analysis of dives of finite duration which have been performed in practice. These almost invariably refer to the case where any symptoms have developed after return to the 'deck', i.e. where:-

a. symptoms develop at $P = P_o = 33$ feet

b. 80% inert gas has been inhaled, i.e. $x = 0.8$

c. bottom depth $(H_b) = P_b - P_o$

Hence equation 70 predicts that symptoms can occur under these conditions if:-

$$\frac{H_b\Psi(\theta)-(g'/0.88)-14.3}{36.2} > \frac{(F_c/SP_o)}{0.8} \qquad (72)$$

8.32 No-stage dives

One of the major features of the thermodynamic hypothesis is phase equilibration and its effect upon transport - as manifested by the very different nature of the quantitative expressions describing inert gas uptake and its elimination by staging (equations XII and XXIV). Taking the former alone, the most critical test is probably afforded by no-stage decompressions to the surface. This is the particular case where $g' = 0$, such that for $x = 0.8$, equation 72 implies symptoms for:-

$$H_b\Psi(\theta) = 45.3(F/SP_o) + 14.3 > 45.3(F_c/SP_o) + 14.3 \qquad (73)$$

However, the features of no-stage diving is the remarkable correlation of data attained by the $\sqrt{t}$ effect for dives of short duration (see section 1.65).

8.33 $\sqrt{t}$ relationship

No theory of decompression sickness would be acceptable quantitatively unless it predicted the $\sqrt{t}$ effect for small values of t which has been demonstrated by Hempleman (1952).

In Appendix II, it is shown that $\Psi(t)$, as expressed by equations XIII and VIII, have many approximate forms whose faithfulness to the original expression all increase with decreasing values of t. The last of these approximations is given by equation 220 as:-

$$\Psi(t) = \frac{G}{\pi(b^2+a^2)SP_A} \approx \frac{4a\sqrt{Dt}}{(b^2+a^2)}$$

Hence, for a dive of duration given by $t = \theta$ equation 73 would predict symptoms if:-

$$\frac{4H_b\sqrt{(D/a^2)\theta}}{((b/a)^2-1)} > 45.3(F_c/SP_o) + 14.3 \text{ feet} \qquad (74)$$

Since (D/a^2), (b/a) and (F_c/SP_o) are constants, equation 74 implies bends if $H_b\sqrt{\theta}$ exceeds a constant, which Crocker and Taylor (1952) have taken as 475 feet $\text{min}^{\frac{1}{2}}$ for safe conditions or 500 feet $\text{min}^{\frac{1}{2}}$ for marginal symptoms. These values refer to weak divers working at depth.

Hence the thermodynamic hypothesis would predict the $\sqrt{t}$ effect as the final degree of approximation, valid for dives of short duration only ($\theta < 25$ mins.).

Taking $(F_c/SP_o) = 0.413$ corresponding to the weaker divers (equation 68), equation 74 would give for working dives:-

$$0.0165 < \frac{\sqrt{(D/a^2)}}{((b/a)^2-1)} < 0.0174 \qquad (75)$$

(for a correlation see section 8,65).

8.34 Constants used for dive analyses

The fact that the critical tissue type cannot be positively identified offers the greatest obstacle to any synthetic approach when it comes to attributing numerical values to the basic constants. In the case of the dimensionless group (F_c/SP_o), one set of practical data has been sacrificed as a 'degree of determinancy' in using the minimum depth for symptoms for its

initial determination (section 8.22). However, there are sufficient other cases to verify the value selected.

In the case of (b/a) and (D/a^2), the ranges of possible values derived from fundamental parameters are too wide to warrant their use in the more exact mathematical expressions employed here. However, it was found that a correlation of symptoms could only be obtained for a very narrow range of values for each parameter. The procedure has therefore been adopted of:-

1. Quoting the constants derived empirically,
2. Presenting the analyses of dives using those values,
3. Showing that the constants used for the correlations offered lie well within the limits anticipated by fundamental reasoning for a tissue type likely to be responsible for marginal symptoms of decompression sickness.

8.35 Values of constants

The following values of (b/a) have been selected empirically according to three convenient levels of physical activity:-

1. Resting: (b/a) = 5.29 (76)
2. Swimming easily ('scuba' diving), b/a = 4.91 (77)
3. Working: (b/a) = 4.73 (78)

It is interesting to note that the above values are consistent to the extent that they imply increased vascularity (a lower b/a ratio) for increased exercise.

The other transient parameter (D/a^2) should be independent of the degree of activity if it is accepted that the capillary radius (a) is determined by the dimensions of the red cell.

The value used throughout the following analyses is:-

for nitrogen: $(D/a^2) = 0.129 \text{ min}^{-1}$ (79)

Applying Graham's law to obtain the diffusion coefficient of helium in cytoplasm (D'); $D'/D = \sqrt{28/4}$. Since erythrocytes should not change dimensions for different inert gases:-

for helium: $(D'/a^2) = 0.340 \text{ min}^{-1}$ (80)

Having fixed the values of the two groups (b/a) and (D/a^2), it is now possible to determine the overall response of the system according the general transport model adopted.

8.36 Response of the system

The transient uptake of inert gas, without phase separation, is defined by equation XIII. Having fixed (b/a) for different degrees of activity, the corresponding values of $(a\alpha_n)$ may be obtained from equation VIII. The first term of the series in equation XI predominates so $(a\alpha_1)$ is required with greater accuracy than higher terms. Values of $(a\alpha_1)$ are quoted by Bogert (1951). Values of the higher roots ($a\alpha_2$ to $a\alpha_6$) may be obtained, with adequate accuracy, from the graphical presentation of the solutions to equation VIII published by Jahnke et al (1960). Bogert's values have been plotted in fig. 42 as the two dimensionless quantities $(a\alpha_1)$ versus (b/a). From this graph the relevant values of $(a\alpha_1)$ have been taken for the three exercise levels arbitrarily selected in the preceding section. These are given in table 20 together with the values of $(a\alpha_2)$, $(a\alpha_3)$ and $(a\alpha_4)$ taken direct from the smaller-scale graphs of Jahnke et al.

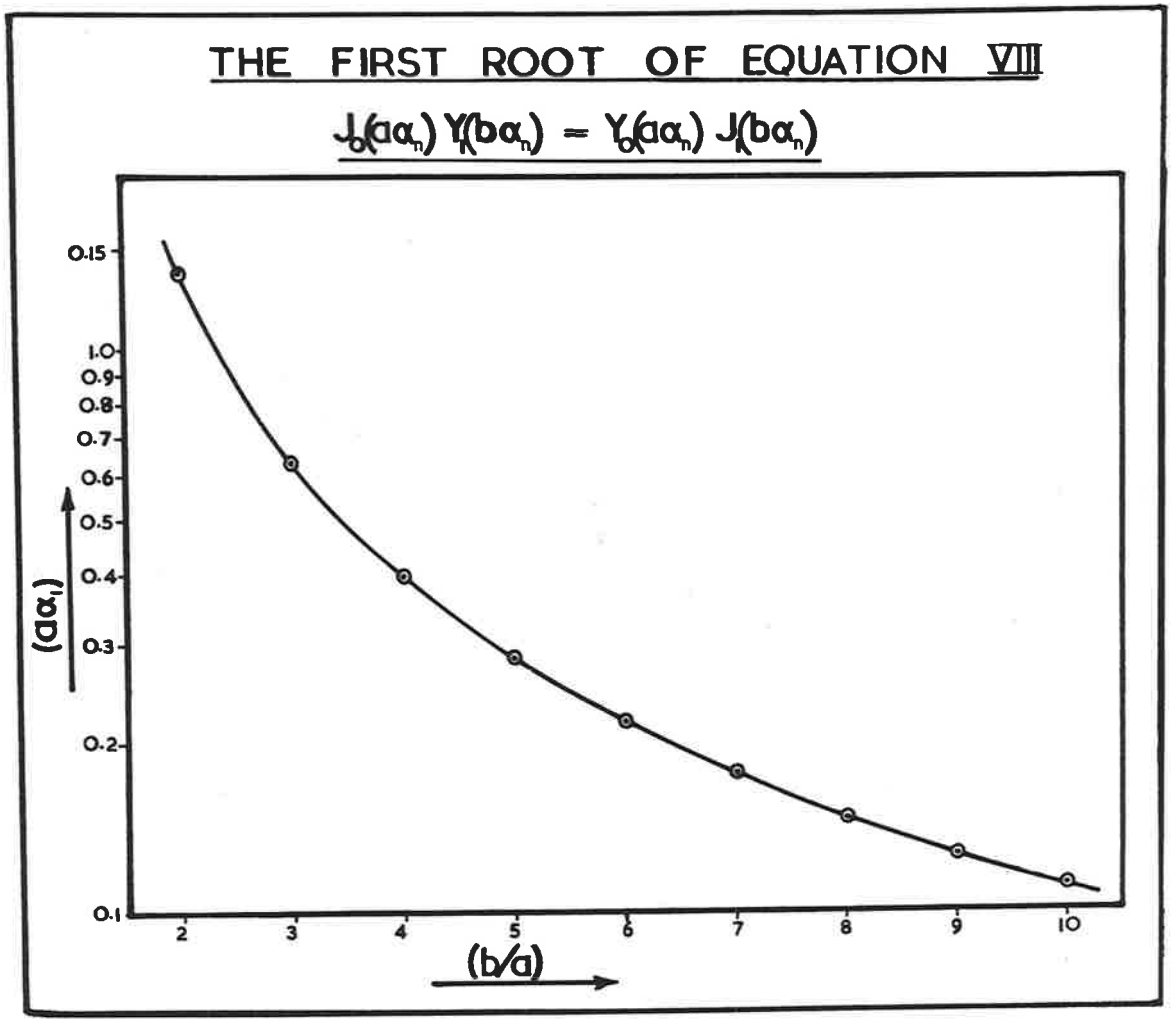

THE FIRST ROOT OF EQUATION VIII
$J_0(a\alpha_n)\,Y_1(b\alpha_n) = Y_0(a\alpha_n)\,J_1(b\alpha_n)$
0.15
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
$(a\alpha_1)$
2
3
4
5
6
7
8
9
10
(b/a)

Fig. 42

Re-writing equation XIII in the form:-

$$\psi(t) = 1 - \sum_{n=1}^{\infty} R_n \cdot \exp\left(-(a\alpha_n)^2 (Dt/a^2)\right) \qquad (81)$$

where $R_n = \dfrac{4}{((b/a)^2-1)(a\alpha_n)^2 \left[(J_0(a\alpha_n)/J_1(b\alpha_n))^2 - 1 \right]}$

the values of k_n and $(a\alpha_n)$ relevant to each exercise level are quoted in table 20.

RESPONSE CONSTANTS

Exercise level	(b/a)	First root		Second root		Third root		Fourth root	
		$(a\alpha_1)$	R_1	$(a\alpha_2)$	R_2	$(a\alpha_3)$	R_3	$(a\alpha_4)$	R_4
Resting	5.29	0.260	0.934	1.060	0.034	1.806	0.012	2.545	0.005
Cruising	4.91	0.289	0.931	1.274	0.035	2.055	0.013	2.846	0.006
Working	4.73	0.304	0.930	1.333	0.036	2.154	0.013	2.948	0.006

TABLE 20

The uptake response of the critical tissue type to changes in arterial tension of the inert gas is conveniently expressed as a plot of two dimensionless groups: $\psi(t)$ versus (Dt/a^2). Taking $D/a^2 = 0.129\ \text{min}^{-1}$ (equation 79), the values derived in table 20 for the respective (b/a) ratios may be substituted in equation 81 to give the basic gas uptake functions for each of the three exercise levels arbitrarily selected. These are derived in table 21 and plotted in fig. 43. They represent the final product of the mathematical analysis. These graphs may then be used for assessing the proximity of any dive to conditions for marginal symptoms with no more than arithemetic substitution.

UPTAKE RESPONSE FOR THREE EXERCISE LEVELS

(Application of equation 81 to the data in table 20)

$(\alpha_1^2 Dt)$	b/a = 5.29		b/a = 4.91		b/a = 4.73	
	(Dt/a^2)	$\Psi(t)$	(Dt/a^2)	$\Psi(t)$	(Dt/a^2)	$\Psi(t)$
0.1	1.479	0.148	1.197	1.151	1.082	0.183
0.2	2.959	0.234	2.395	0.237	2.164	0.248
0.4	5.917	0.374	4.789	0.376	4.327	0.379
0.7	10.36	0.536	8.378	0.538	7.573	0.539
1.0	14.79	0.656	11.97	0.657	10.82	0.658
1.5	22.19	0.792	17.96	0.792	16.23	0.793
2.0	29.59	0.874	23.95	0.874	20.91	0.874
2.5	36.98	0.923	29.93	0.924	27.04	0.924
3.0	44.38	0.353	35.92	0.954	32.45	0.954
4.0	59.17	0.983	47.89	0.983	43.27	0.983

TABLE 21

The above figures are used to plot the response curves illustrated in fig. 43.

8.4 ANALYSES OF 'NO-STAGE' DIVES

8.41 'Scuba' divers breathing air

The most comprehensive set of experimental no-stage dives which the writer could find were those of Albano (1962). These include over 1,000 submersions at an exercise level carefully controlled as that relevant to a 'scuba' diver cruising at depth. They were, in fact, performed in the ocean by free-swimming divers. Albano has titrated the exposure time for each of nine depths and recorded both the safe and unsafe values.

Taking the response curve relevant to a cruising diver, (i.e. b/a = 4.91 in fig. 43), table 22 contains the analysis of his results according to equation XXX, or its re-expression in equation 73, for tension units of feet and the particular case of air.

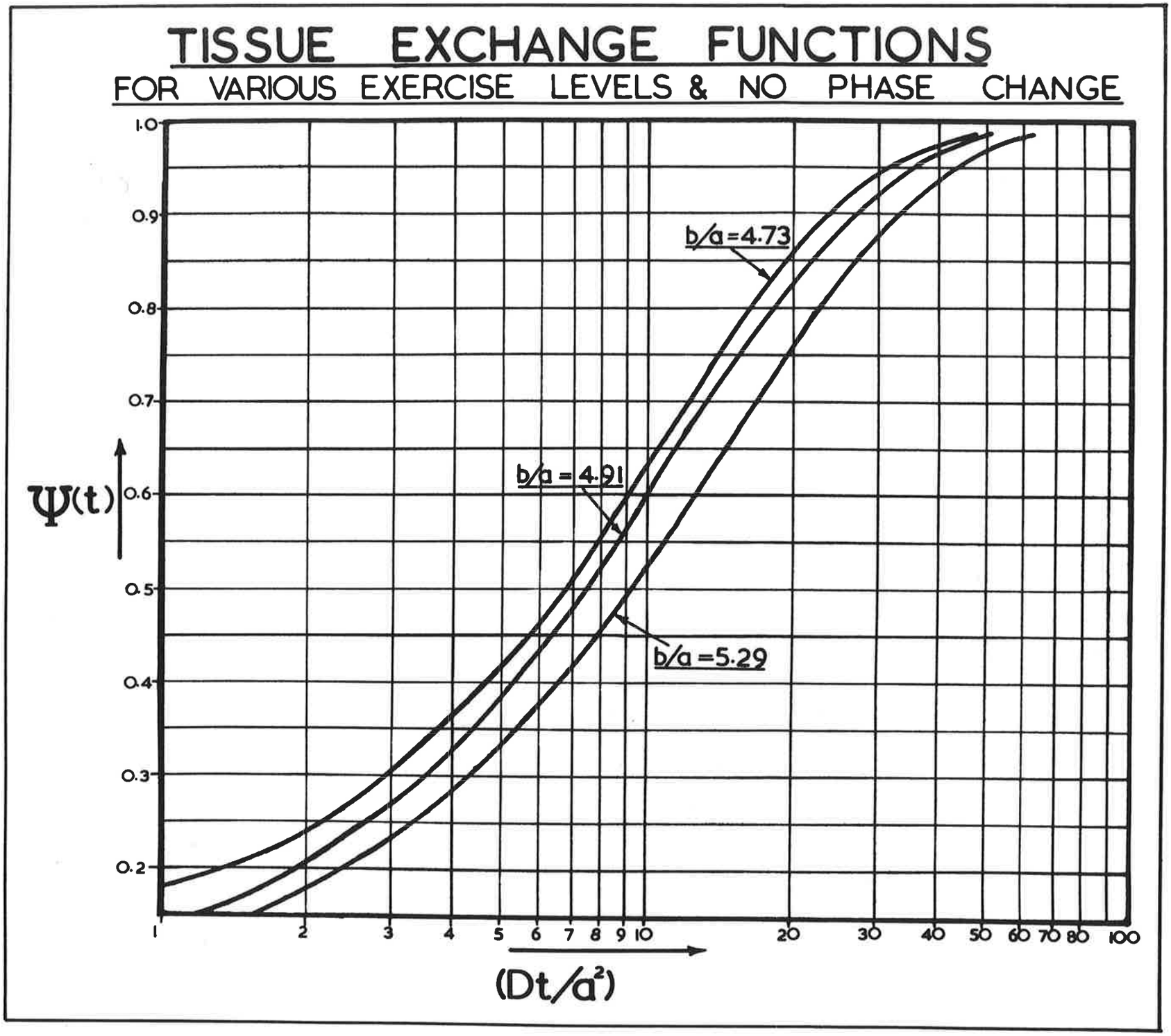

TISSUE EXCHANGE FUNCTIONS
FOR VARIOUS EXERCISE LEVELS & NO PHASE CHANGE
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
Ψ(t)
b/a = 4.73
b/a = 4.91
b/a = 5.29
1
2
3
4
5
6
7
8
9
10
20
30
40
50
60
70
80
100
(Dt/a²)

Fig. 43

TITRATED 'BOUNCE' DIVES - CRUISING 'SCUBA' DIVERS

(Data from Albano, 1962).

Titration No.	Bottom depth (H_b) in feet	Duration of dive (θ) in mins.	$D\theta/a^2$ = 0.129θ	$\psi(\theta)$ (fig. 43)	$H_b\psi(\theta)$ in feet	(F/SP_o) (eqn. 73)	PRACTICAL RESULT
1	213.4	10	1.29	0.155	32.9	0.411	safe
	213.4	10.5	1.35	0.161	34.2	0.439	unsafe
2	197	11.5	1.48	0.167	32.9	0.411	safe
	197	12	1.55	0.171	33.7	0.428	unsafe
3	180.5	12.5	1.61	0.177	31.9	0.389	safe
	180.5	13	1.68	0.183	33.0	0.413	unsafe
4	164	14.5	1.87	0.196	32.1	0.393	safe
	164	15	1.94	0.202	33.1	0.415	unsafe
5	148	17	2.19	0.221	32.7	0.406	safe
	148	17.5	2.26	0.224	33.2	0.417	unsafe
6	133	20	2.58	0.246	32.7	0.406	safe
	133	21	2.71	0.254	33.8	0.430	unsafe
7	115	24	3.10	0.277	31.9	0.389	safe
	115	25	3.23	0.287	33.0	0.413	unsafe
8	98.6	31	4.00	0.330	32.5	0.401	safe
	98.6	32	4.13	0.336	33.1	0.415	unsafe
9	82	42	5.42	0.402	33.0	0.413	safe
	82	43	5.55	0.414	33.9	0.432	unsafe

TABLE 22

(b/a) = 4.91 (equation 77). The practical results can be correlated for a critical value of (F/SP_o) given by (F_c/SP_o) = 0.413.

It can be seen from table 22 that selection of (b/a) = 4.91 as characteristic of the exercise undertaken by cruising scuba divers (equation 77) suggests a critical limit for (F/SP_o) identical to that found for weak divers in the other cases correlated in section 8.2, i.e. (F_c/SP_o) = 0.413 (equation 68).

8.4.2 Titrated working dives

The writer was not able to obtain a copy of the article by Van der Aue (1951) in which he is reported to have titrated divers breathing air and working at depth. However, selected points from this military report are quoted by Duffner et al (1959). Both the safe and unsafe conditions quoted are analysed in table 23 according to equation 73, taking the value of b/a = 4.73 corresponding to working conditions (equation 78).

ANALYSIS OF NO-STAGE AIR DIVES (WORKING)

(Data from Duffner et al, 1959).

Titration No.	Bottom depth (H_b) in feet	Duration of dive (θ) in mins.	$D\theta/a^2$ = 0.129θ	$\psi(\theta)$ (fig. 43)	$H_b\psi(\theta)$ in feet	(F/SP_o) (eqn. 73)	PRACTICAL RESULT
1	150	11	1.42	0.205	30.8	0.364	safe
	150	13	1.68	0.220	33.0	0.413	unsafe
2	100	26	3.35	0.330	33.0	0.413	safe
	100	28	3.61	0.343	34.3	0.441	unsafe
3	50	105	13.5	0.738	36.9	0.498*	safe
	50	113	14.6	0.762	38.1	0.525	unsafe
4	33	∞	∞	1.000	33.0	0.413	safe

TABLE 23

The only result which does not conform* to the critical value of (F_c/SP_o) = 0.413 found previously is titration No. 3. However, in this case, it is noted that the diver is supposed to have maintained the same very high exercise level for 105 mins. which would appear to be a very large strain upon any man. If, in fact, the rate of working had dropped and this case were marginal, then F/SP_o = 0.413 giving $\psi(\theta)$ = 0.660. This corresponds to $(\alpha_1^2 D)$ = 1.02 according to equation VIII. However, $(105D/a^2)$ = 13.55 giving

$(a\alpha_1) = 0.275$. From fig. 42 it can be seen that this corresponds to $(b/a) = 5.06$, or a vascularity characterised by a tissue volume/blood volume $\approx (b/a)^2 = 25.6$ compared with 22.4 for hard work ($b/a = 4.73$) or 27.9 for rest ($b/a = 5.29$).

While there would seem to be adequate grounds for discounting the one discrepancy in table 23 on the grounds of unsustained effort, it should be noted that the Royal Navy recommend staging for this particular dive. (Miles, 1962).

8.43 Miscellaneous unsafe dives

Shilling et al (1935) record the details of 46 cases arising from 2,143 no-stage air dives for 5 depths ranging from 100 to 200 feet. The lowest unsafe exposure for each of these is given in table 24 and the dives analysed for working conditions.

UNSAFE 'NO-STAGE' AIR DIVES

(Data from Shilling et al, 1935).

No. of dive Shilling et al	Bottom depth (H_b) in feet	Duration of dive (θ) in mins.	$D\theta/a^2 = 0.129\theta$	$\psi(\theta)$ (fig. 43)	$H_b\psi(\theta)$ in feet	(F/SP_o) (eqn. 73)
1	100	34	4.39	0.383	38.3	0.529
14	150	18½	2.39	0.262	39.3	0.550
36	167	17½	2.26	0.253	42.3	0.617
42	185	12½	1.61	0.216	40.0	0.567
45	200	13	1.68	0.220	44.0	0.566

TABLE 24 (analysed for b/a = 4.73)

It is interesting to note that all values of (F/SP_o) lie well in excess of the critical value of $(F_c/SP_o) = 0.413$ (equation 68).

8.44 Helium dives

The only experimental data which the writer could find for 'no-stage' helium dives were those of Duffner et al (1959). These authors do not record the exact depth-time parameters of each set of dives numerically, but plot them using axes which are not quite perpendicular and omit the grid. The best information to be extracted for comparative purposes is probably Duffner's "probable safe He:O_2 minimal decompression curve" since this is experimental in origin and would tend to minimise the following objections to the data:-

(a) The intermittent nature of the exercise employed,

(b) the scatter of 'bends' and 'no bends' cases, probably arising from

(c) the use of any two of a group of 17 divers for the determination of each point.

Seven points have been taken from the above curve as well as the restricted presentation permits. These exposures are analysed in table 25, taking the helium value of $(D'/a^2) = 0.340\ min^{-1}$ (equation 80) and the 'working' value of $(b/a) = 4.73$ (equation 78).

While Duffner et al call their curve one of "probable safe minimal decompression" at least 10 out of the 42 points from which it is constructed, represent conditions which proved unsafe and yet lie within their 'safe' zone or on the boundary. Thus it is not surprising that values of $(F/S'P_o)$ lie well in excess of any value of $(F_c/S'P_o)$ to be anticipated for helium on the basis of $(F_c/SP_o) = 0.413$ for air - if the critical tissue type is predominantly aqueous.

COMPARATIVE 'NO-STAGE' DIVES ON 80% He:20% O_2

(Data from Duffner et al, 1959)

No.	Bottom depth (H_b) in feet	Duration of dive (θ) in mins.	$D'\theta/a^2$ = 0.340θ	$\psi(\theta)$ (fig. 43)	$H_b\psi(\theta)$ in feet	$(F/S'P_o)$ (eqn. 73)
1	80	60	20.4	0.865	69.2	1.20
2	100	35	11.9	0.696	69.6	1.21
3	120	25	8.50	0.583	70.0	1.22
4	140	19	6.46	0.485	67.9	1.18
5	160	15	5.10	0.421	67.5	1.17
6	180	12½	4.25	0.377	67.8	1.17
7	200	10½	3.57	0.340	68.0	1.18

TABLE 25

Whatever the composition of the tissue, Duffner's curve probably represents dives of comparable safety, in which case it is regarded as significant that equation 73 gives values of $(F/S'P_o)$ whose deviations from the mean do not exceed a maximum of 2.5%.

8.45 "Oxygen bends"

One of the facets of decompression sickness most difficult to correlate quantitatively with any theory is the phenomenon which Donald (1954) describes under the title of "oxygen bends". In practice, these were instances in which insufficient inert gas could have been taken up to cause symptoms according to any reasonable method of calculation. However, the presence of a large external partial pressure of oxygen seems to have contributed sufficient O_2 to the separated gas to induce pain in certain instances. Justification for attributing this critical increment to oxygen is provided by the transient nature of the symptoms described, severe bends disappearing within 30 mins. of their onset.

Each of the eight exposures described have consisted of 60 mins. at 150 feet. From the point of view of the incidence of symptoms, however transient, Donald's work may be regarded as a titration of mole fraction of inert gas. The critical oxygen content would thus appear to lie between 63.0% and 63.1%. Taking x = 0.369 as the critical value, the test of any quantitative hypothesis lies in the prediction of a reasonable value for increased tissue oxygen tensions.

The derivation of equation XXX is based upon the presumption that, with normal dives, the decompression plus onset times are sufficiently long to enable the cellular oxygen tensions to reach values commensurate with the final pressure. However, in this particular case, there is no staging and the partial pressure of oxygen is well above the level regarded as safe from the standpoint of convulsions (section 1.45). For this case, which is well outside the practical exposure limits to which one would subject men, one cannot retain the assumption that cellular O_2 and CO_2 tensions have an approximately constant total. Hence equation XX should be modified to read:

$$p_o + p_c + p_w = 126 + \Delta p_o \text{ mm. Hg.}$$

where Δp_o is the additional cellular oxygen tension introduced by virtue of the large increase in external oxygen partial pressure. According to equation 38, this should equal the rise in venous oxygen tension for the same metabolic rate.

Repeating the derivation of equation XXX with the above modification, symptoms can occur if:-

$$\frac{g - g' + 0.8(P_o - 46)S - (P + 74 - \Delta p_o)S}{(P + 74 - \Delta p_o)} > \frac{F_c}{P_o} \qquad (82)$$

for an animal living in air at ground level before compression.

Donald's goat experiments refer to the particular case where:-

(a) there is no staging, i.e. $g' = 0$

(b) the goats are returned to 1 atmosphere (absolute), i.e. $P = P_o = 760$ mm. Hg.

(c) the inert gas is nitrogen, i.e. $(F_c/SP_o) = 0.413$ (equation 68)

(d) the uptake corresponding to 60 mins. at 150 feet (3456 mm. Hg) is given by:-

$$g = xSH_b\Psi(\theta) = 0.369 \times 3456S\Psi(60)$$

taking the critical value from Donald's results of $x = 0.369$.

Substitution of the above conditions in equation 82 gives the critical condition as:-

$$\frac{1272\Psi(60) + 571}{834 - \Delta p_o} = 1.413$$

Taking $(D/a^2) = 0.129$ according to equation 79, fig. 43 gives $\Psi(60) = 0.450$ for the curve $b/a = 5.29$, since the animal was probably resting in the tank at pressure, and this represents the most conservative estimate of uptake in any case.

Placing $\Psi(60) = 0.450$, $\Delta p_o = 24$ mm. Hg.

A rise in venous oxygen tension of 24 mm. Hg would seem quite consistent with a rise in arterial oxygen tension from 100 mm. Hg (breathing air at 1 atmosphere) to $(3456 + 760 + 46)(1 - 0.369) = 2635$ mm. Hg for a tissue whose blood oxygen content was reduced according to the average for the whole body. It is certainly consistent with the hyperbaric tension measurements of Lambertsen et al (see section 5.69).

More specific calculations seem hardly justified when the metabolic rate and circulation in the critical tissue type remain unknown for lack of positive identification.

8.5 ANALYSES OF DIVES WITH STAGING

8.51 Staging

The most comprehensive test of any theory of decompression sickness lies in its ability to correlate the practical results of dives followed by staged decompressions.

The gas lost by staging (g') would seem best estimated using the pneumatic analogue described in section 6.6. However, for the conventional Naval type of decompression, where the thermodynamic hypothesis would predict a large initial separation of gas from solution, an approximate analytical method may be employed - as expressed by equation XXIV. This may be re-written as:-

$$\frac{g'}{S} \approx \frac{2(1-x)(D/a^2)\Sigma\tau_m(P_m-(132-46x)/(1-x))}{((b/a)^2-1)\log(\bar{r}/a)}$$

for the usual case of decompression to the surface (P_o = 760 mm. Hg).

Defining the depth of the m^{th} stage as $H_m = P_m - P_o$, and reverting to pressure units of feet, the above equation for air ($x = 0.8$) becomes:-

$$g'/S = \Lambda.\Sigma(\tau_m(H_m + 12.6)) \qquad (83)$$

where Λ is a constant defined by:-

TITRATED STAGING - RESTING DIVES

(Data from Duffner et al, 1959)

Dive No.	Series	Dives	Cases	Duration of dive (θ) (mins.)	Bottom depth (H_b) (ft.)	Gas intake			First Stage			Second Stage			Gas Elimination				Net gas uptake			PRACTICAL RESULT	Analogue result	
						$(D\theta/a^2)$ $=0.129\theta$	$\psi(\theta)$ (fig. 43)	$H_b\psi(\theta)$	Depth (H_1) (ft.)	Time (τ_1) (mins.)	$H_1\tau_1$	Depth (H_2) (ft.)	Time (τ_2) (mins.)	$H_2\tau_2$	Total Time $\Sigma\tau_m$	$12.6\Sigma\tau_m$	$\Sigma H_m\tau_m$	$12.6\Sigma\tau_m + \Sigma H_m\tau_m$ (A)	$A(\Delta)$ $=0.0241A$ $=g'/xS$	$(g-g')/xS$ $=H_b\psi(\theta)$ $-0.0241A$	(F/SP_o) (eq. 86)		Total piston displacement (ΔV) in c.c.	Average $\frac{(\Delta V)}{((b/a)^2-1)}$
1	A	2	0	34	110	4.39	0.304	33.4	10	4	40	-	-	-	4	50	40	90	2.2	31.2	0.373		-	-
2		4	0	34	110	4.39	0.304	33.4	10	3	30	-	-	-	3	38	30	68	1.6	31.8	0.386		87.2	3.23
3		2	0	34	110	4.39	0.304	33.4	10	2	20	-	-	-	2	25	20	45	1.1	32.3	0.397		89.5	3.31
4	B	2	0	40	110	5.16	0.340	37.4	10	12	120	-	-	-	12	151	120	271	6.5	30.9	0.366		-	-
5		2	0	40	110	5.16	0.340	37.4	10	10	100	-	-	-	10	126	100	226	5.4	32.0	0.391		87.5	3.26
6		2	0	40	110	5.16	0.340	37.4	10	9	90	-	-	-	9	114	90	204	4.9	32.5	0.402		89.9	3.33
7		2	0	40	110	5.16	0.340	37.4	10	8	80	-	-	-	8	101	80	181	4.4	33.0	0.413		92.0	3.40
8		6	3	40	110	5.16	0.340	37.4	10	5	50	-	-	-	5	63	50	113	2.7	34.7	0.450	Bends	100.8	3.73
9	C	4	1*	47	110	6.06	0.380	41.8	10	21	210	-	-	-	21	265	210	475	11.4	30.4	0.355	Mild symptom*	81.1	3.00
10		2	0	47	110	6.06	0.380	41.8	10	19	190	-	-	-	19	239	190	429	10.3	31.5	0.380		85.6	3.17
11		2	0	47	110	6.06	0.380	41.8	10	18	180	-	-	-	18	227	180	407	9.8	32.0	0.391		87.2	3.23
12		2	0	47	110	6.06	0.380	41.8	10	17	170	-	-	-	17	214	170	384	9.3	32.5	0.402		90.6	3.35
13		4	2	47	110	6.06	0.380	41.8	10	16	160	-	-	-	16	202	160	362	8.7	33.1	0.415	Bends	92.4	3.42
14	D	6	3	40	130	5.16	0.340	44.2	20	3	60	10	11	110	14	176	170	346	8.3	35.9	0.477	Bends	105.6	3.91
15	%	6	2	47	130	6.06	0.380	49.4	20	9	180	10	11	110	20	252	290	542	12.1	36.3	0.486	Bends	107.8	3.99

TABLE 25

b/a = 5.29

*One mild symptom not requiring recompression - nature not specified, but dismissed by Duffner et al in their titration. In this case the above results are consistent with a critical value of (F/SP_o) given by $(F_c/SP_o) = 0.413$.

$$\Lambda = \frac{0.4(D/a^2)}{((b/a)^2-1)\log(\bar{r}/a)} \qquad (84)$$

assuming $\bar{r}$ is constant. This would seem to introduce no greater approximation than already contained in this approach, and should be reasonable for dives other than those involving extreme exposure.

Since staging is invariably undertaken in the resting state, (b/a) should be the same for all decompressions upon air. Hence a single value of Λ should apply to all air decompressions, the value selected empirically being:-

$$\Lambda = 0.0241 \text{ feet/min.} \qquad (85)$$

Incorporating equation 83 into equation 70, the general condition for symptoms to occur after return to the surface from an air dive is given by:-

$$H_b\psi(\theta)-\Lambda(\Sigma H_m\tau_m+12.6\Sigma\tau_m) = 45.3(F/SP_o) + 14.3 > 45.3(F_c/SP_o) + 14.3 \qquad (86)$$

This expression is a form of equation XXX convenient for analysing staged dives by the approximate method.

8.52 Titrated staging

Duffner et al (1959), describe three dives upon air in which the 10 foot stage has been titrated, and two others which include a 20 foot stage. These authors have dismissed the mild symptoms occurring in the series designated* in table 25 in carrying out their titration. With no specific note of the exercise level, it is presumed that the divers were resting at depth, in which case equation 76 gives (b/a) = 5.29. Using the corresponding curve in fig. 43, the analyses are contained in table 25. From

this it can be seen that the approximate analytical method gives a good correlation of symptoms if one takes the critical value of (F/SP_o) as that which has proven critical in previous cases, i.e. $(F_c/SP_o) = 0.413$.

8.53 Working dives

One of the most comprehensive sets of data for testing any theory is provided by the ocean trials of the tables published by Crocker (1957). Whether one is in agreement with his method of formulation or not, the practical results cover over 200 dives performed under carefully supervised conditions of continuous heavy exercise. For working conditions equation 78 gives $(b/a) = 4.73$. The corresponding curve in fig. 43 is then used for the correlation of practical results in table 26 by the approximate analytical method. It is considered most significant that the safety of each series can be correlated with a critical value of (F/SP_o) which is the same as that determined for all previous quantitative aspects of decompression sickness, i.e. $(F_c/SP_o) = 0.413$.

Only one dive (No. 17) does not conform, and this is a case of itching. Such symptoms which are open to auto-suggestion are regarded by Crocker as difficult to ascertain.

8.54 Miscellaneous wreck dives

While the preceding section is regarded by the writer as a crucial test of the thermodynamic hypothesis, a few more dives are recorded by Crocker (1957) in which the exercise level has not been controlled. Since these were dives to actual wrecks it may be assumed that the men were working at depth. In this case all constants are the same as those used in the

ANALYSES OF WORKING DIVES - Standard exercise

(Data from Crocker, 1957)

Dive No.	Series No.	Dives	Cases	Duration of dive (θ) (mins.)	Bottom depth (H_b) (ft.) (s.w.g.)	Gas intake: $D\theta/a^2 = 0.129\theta$	Gas intake: $\psi(\theta)$ (fig. 43)	Gas intake: $H_b\psi(\theta)$	First stage: Depth (H_1) (ft.)	First stage: Time (τ_1) (mins.)	First stage: $H_1\tau_1$	Second stage: Depth (H_2) (ft.)	Second stage: Time (τ_2) (mins.)	Second stage: $H_2\tau_2$	Third stage: Depth (H_3) (ft.)	Third stage: Time (τ_3) (mins.)	Third stage: $H_3\tau_3$	Gas elimination: Total time $\Sigma\tau_m$	Gas elimination: $12.6\Sigma\tau_m$	Gas elimination: $\Sigma H_m\tau_m$	Gas elimination: $12.6\Sigma\tau_m + \Sigma H_m\tau_m$ (A)	Net gas uptake: $A(A) = 0.0241A$	Net gas uptake: $F/SP_o = H_b\psi(\theta) - 0.0241A$	Net gas uptake: (F/SP_o) eqn. 86	PRACTICAL RESULT	Analogue result: Total piston displacement (ΔV) in c.c.	Analogue result: Average $\frac{\Delta V}{((b/a)^2-1)}$
1	1	1	0	85	50	11.0	0.660	33.0	-	-	-	-	-	-	-	-	-	-	-	-	-	0	33.0	0.413		73.2	3.42
2		18	0	60	60	7.74	0.543	32.6	-	-	-	-	-	-	-	-	-	-	-	-	-	0	32.6	0.404		71.5	3.34
3	2	2	0	20	100	2.58	0.278	27.8	-	-	-	-	-	-	-	-	-	-	-	-	-	0	27.8	0.298		-	-
4		8	0	17	110	2.19	0.250	27.5	-	-	-	-	-	-	-	-	-	-	-	-	-	0	28.5	0.291		-	-
5		10	0	14	120	1.81	0.227	27.3	-	-	-	-	-	-	-	-	-	-	-	-	-	0	27.3	0.287		-	-
6	3	10	0	11	130	1.42	0.205	26.6	-	-	-	-	-	-	-	-	-	-	-	-	-	0	26.6	0.271		-	-
7		10	0	9	140	1.61	0.189	26.5	-	-	-	-	-	-	-	-	-	-	-	-	-	0	26.5	0.269		-	-
8		1	0	8	150	1.03	0.181	27.2	-	-	-	-	-	-	-	-	-	-	-	-	-	0	27.2	0.285		-	-
9	4	17	0	20	120	2.58	0.278	33.4	10	3	30	-	-	-	-	-	-	3	38	30	68	1.6	31.8	0.386		68.9	3.22
10	5	25	2	30	120	3.87	0.360	43.2	20	3	60	10	10	100	-	-	-	13	164	160	324	7.8	35.4	0.466	Bends	82.6	3.86
11		2	0	25	130	3.23	0.321	41.7	20	3	60	10	10	100	-	-	-	13	164	160	324	7.8	33.9	0.432		76.2	3.56
12	6	8	0	40	120	5.16	0.424	50.9	30	3	90	20	5	100	10	20	200	28	353	390	743	17.9	33.0	0.443		73.1	3.42
13		2	0	35	130	4.52	0.391	50.8	30	3	90	20	5	100	10	20	200	28	353	390	743	17.9	32.9	0.441		72.3	3.38
14	7	9	0	10	140	1.29	0.196	27.4	10	2	20	-	-	-	-	-	-	2	25	20	45	1.1	26.3	0.265		-	-
15		2	0	10	150	1.29	0.196	29.4	10	2	20	-	-	-	-	-	-	2	25	20	45	1.1	28.3	0.309		-	-
16	8	4	0	20	140	2.58	0.278	38.9	20	3	60	10	10	100	-	-	-	13	164	160	324	7.8	31.1	0.371		67.0	3.13
17		2	1*	15	150	1.94	0.233	35.0	20	2	40	10	5	50	-	-	-	7	88	90	178	4.3	30.7	0.362	Itching	64.8	3.03
18		1	0	15	160	1.94	0.233	37.3	20	2	40	10	10	100	-	-	-	12	151	140	291	7.0	30.3	0.353		63.1	2.95
19	9	15	3	25	150	3.23	0.321	48.2	30	3	90	20	5	100	10	15	150	23	289	340	629	15.1	33.1	0.415	Bends	73.4	3.43
20	10	4	0	10	160	1.29	0.196	31.4	10	2	20	-	-	-	-	-	-	2	25	20	45	1.1	30.3	0.353		62.5	2.92
21		6	0	10	170	1.29	0.196	33.3	20	2	40	10	5	50	-	-	-	7	88	90	178	4.3	29.0	0.325		59.2	2.77
22	11	11	2	20	160	2.58	0.278	44.5	30	2	60	20	5	100	10	10	100	17	214	260	474	11.4	33.1	0.415	Bends	73.6	3.44
23		6	0	20	170	2.58	0.278	47.25	30	2	60	20	5	100	10	15	150	22	277	310	587	14.15	33.1	0.415		73.5	3.44
24	12	10	3	25	160	3.23	0.321	51.4	30	2	60	20	10	200	10	15	150	27	340	410	750	18.1	33.3	0.419	Bends	74.5	3.48
25	13	10	0	10	180	1.29	0.196	35.3	20	2	40	10	5	50	-	-	-	7	88	90	178	4.3	31.0	0.369		66.3	3.10
26		1	0	10	190	1.29	0.196	37.2	20	2	40	10	5	50	-	-	-	7	88	90	178	4.3	32.9	0.411		73.0	3.41
27	14	7	0	15	180	1.94	0.233	41.9	30	2	60	20	5	100	10	10	100	17	214	260	474	11.4	30.5	0.358		64.9	3.03
28		1	0	15	190	1.94	0.233	44.3	30	2	60	20	5	100	10	10	100	17	214	260	474	11.4	32.9	0.411		72.8	3.40
29	15	10	0	20	180	2.58	0.278	50.0	30	2	60	20	10	200	10	15	150	27	340	410	750	18.1	31.9	0.389		67.2	3.14
30	16	9	0	10	200	1.29	0.196	39.2	20	2	40	10	10	100	-	-	-	12	151	140	291	7.0	32.2	0.395		70.4	3.29
31	17	10	0	15	200	1.94	0.233	46.6	30	2	60	20	5	100	10	15	150	22	277	310	587	14.1	32.5	0.405		72.1	3.37

TABLE 26

▲ correlation of all except series 8 for $(F_o/SP_o) = 0.413$

MISCELLANEOUS WRECK DIVES - No standard exercise procedure

(Data from Crocker, 1957)

1		4	0	60	70	7.74	0.453	38.0	10	4	40	-	-	-	-	-	-	4	50	40	90	2.2	35.8	0.475			
2		2	0	50	80	6.45	0.484	38.7	20	4	80	10	5	50	-	-	-	9	114	130	244	5.9	32.8	0.408			
3		6	2	40	90	5.16	0.424	38.2	20	3	60	10	5	50	-	-	-	8	101	110	211	5.1	33.1	0.415	Bends		
4		1	0	45	90	5.81	0.454	40.8	20	3	60	10	10	100	-	-	-	13	164	160	324	7.8	33.0	0.413			
5		1	1	60	90	7.74	0.543	48.9	30	4	120	20	5	100	10	20	200	29	365	420	785	18.9	33.0	0.413	Itching		

TABLE 27

previous section, and the correlation according to the approximate analytical method is contained in table 27. These findings show that all cases except one conform to the critical value of (F/SP_o) given by $(F_c/SP_o) = 0.413$.

The case which does not fit (No. 1) is a long exposure (60 mins.). With no exercise routine for an actual job, the absence of any symptoms could well be attributed to the men not working as hard as implied by the ratio of $(b/a) = 4.73$ employed in the analysis. If this dive had been marginal, i.e. $(F/SP_o) = 0.413$, equation 86 would indicate $H_b\Psi(60) = 35.2$ feet, i.e. $\Psi(60) = 0.503$. According to equations VIII, this corresponds to $(a\alpha_1) = 0.282$. According to fig. 42 this implies $(b/a) = 5.00$. This is still closer to the working value of $(b/a) = 4.73$ than the resting value of $(b/a) = 5.29$.

8.55 The staging constant (Λ)

In the preceding analyses of staged dives, the same empirical value of $\Lambda = 0.0241$ feet/min. (equation 85) has been taken for all decompressions. Since all decompressions may be considered to occur under resting conditions $(b/a) = 5.29$ (equation 76) while $D/a^2 = 0.129$ (equation 79) for all conditions, the substitution of these values in the definition of Λ for air (equation 84) gives:-

$$\bar{r} = 1.53\ a$$

This value of $\bar{r}$ would suggest a perfectly reasonable location of the separated gas relative to the capillary for the preceding dives of moderate exposure. It is also in general agreement with the piston of the pneumatic analogue displaying the maximum displacement after the first large decompression employed by conventional methods.

However, $\bar{r}$ must increase appreciably for much greater exposures, or dives in which the initial creation of a large reservoir of separated gas has been avoided by much deeper staging. The steady-state approximation would be valid no longer, so the only method left for analysis of the extreme dives performed by the Okinawans (Appendix I) is that embodied in the pneumatic analogue.

8.56 Okinawan dives

The thirteen Okinawan dives recorded in Appendix I were found to give a satisfactory correlation of bends and no bends cases only if the last chamber (table 16) of the pneumatic analogue was blocked off. For this case the results are given in table 28.

ANALYSIS OF OKINAWAN DIVES BY THE PNEUMATIC ANALOGUE

(Data from Appendix I - fig. 44).

Diver	Dive number (Appendix I)	Maximum volume displacement (ΔV) in c.c.	$\frac{\Delta V}{((b/a)^2 - 1)}$	PRACTICAL RESULTS
Fukumura	22F	108.9	4.40	Bends
Nohara	23N	112.3	4.55	Bends
Fukumura	24F	120.3	4.87	Bends
Fukumura	23F	96.9	3.92	No bends
Uezato	24U	108.3	4.38	No bends
Fukumura	27F	105.2	4.26	No bends
Uezato	23U	130.4	5.28	Bends
Nohara	27N	108.2	4.38	Bends
Fukumura	25F	107.4	4.35	Bends
Fukumura	26F	98.4	3.98	No bends
Nohara	25N	86.7	3.51	No bends
Fukumura	28F	98.5	3.98	No bends
Nohara	26N	102.8	4.16	No bends

TABLE 28 $(b/a) = 5.07$

A critical value of $(\Delta V)/((b/a)^2 - 1) = 4.38$ differentiates between safe and unsafe runs. No such correlation could be obtained using any conventional method of calculation.

8.57 Repetitive dives

The pneumatic analogue described in section 6.6 has been used to analyse the two repetitive dives recorded in fig. 36. With the end chamber blanked off, as required for the correlation in table 28, the results are as follows:-

First dive: $\Delta V = 107.9$ c.c., $(\Delta V)/((b/a)^2 - 1) = 4.37$

Second dive: $\Delta V = 106.0$ c.c., $(\Delta V)/((b/a)^2 - 1) = 4.30$

The fact that both dives proved safe in practice is consistent with the above results in so far as both values of $(\Delta V)/((b/a)^2 - 1)$ are less than the critical value of 4.38 determined for pearl divers in the last section.

8.58 Interpretation of constants for pearl divers

The fact that the end chamber (No. 27 in table 16) had to be blocked off before dives 24U and 27 N could be correlated is indicative of a (b/a) ratio less than that for the resting state. The latter is 5.29 according to equation 76. Hence the above analyses refer to the case where:-

$$b/a = 5.29 \sqrt{(564.8 - 44.8)/564.8} = 5.07$$

since the total volume of the analogue = 564.8 c.c. and of chamber No. 27 is 44.8 c.c. (table 16).

A (b/a) value of 5.07 lies between the value of (b/a) = 4.91 for cruising 'scuba' divers (equation 77) and that for rest when (b/a) = 5.29 (equation 76).

This is consistent with the fact that the pearl divers are towed over the bed of the ocean and only exert themselves when they spy a shell.

The critical value of 4.38 for $(\Delta V)/((b/a)^2 - 1)$ for pearl divers is higher than that of 3.43 for previous analyses based upon 'weak' divers. This would correspond to the pearl divers possessing a susceptibility factor of $F_{\sigma}/SP_o = \frac{4.38}{3.43} \times 0.413 = 0.527$ since equation 68 gibes $F_{\sigma}/SP_o = 0.413$ for weak divers.

The value of 0.527 for pearl divers is almost equal to that for pre-selected Naval divers for whom a value of 0.525 has been determine (equation 67). Thus the pearl diver would appear no less susceptible to decompression sickness than the U.S. Navy diver.

This enhances the potential value of the thermodynamic hypothesis which can correlate both types of diving while conventional theories can offer no explanation for Okinawan-style decompression.

8.6 FUNDAMENTAL INTERPRETATION OF CONSTANTS

8.61 The three groups of constants

The foregoing assessment of the thermodynamic hypothesis would seem most encouraging in view of the fact that the same empirical values of the three groups of constants were used in all sixteen sets of data analysed quantitatively. These may now be summarised as:-

(a) $(b/a) = 4.73$ for hard work,

$(b/a) = 4.91$ for cruising scuba divers, or

$(b/a) = 5.29$ at rest.

(b) $(D/a^2) = 0.129\ \text{min}^{-1}$ for air

(c) $(F_{\sigma}/SP_o) = 0.413$ for air

However, the significance of the preceding correlations in assessing the fundamental nature of the approach is felt to depend upon the values predicted by the above constants for the basic parameters from which the hypothesis has been synthesised.

8.62 Relative exercise levels

While many sets of dives have been included to establish a good correlation for working conditions if (b/a) = 4.73, only one set of resting exposures could be found and for them a value of (b/a) = 5.29 proved satisfactory. To substantiate these relative values a more exacting comparison may be made using Behnke's values (section 1.46) of 25 mins. as the safe working time for no-stage decompression from 100 feet as opposed to 34.5 mins for the same man at rest.

According to equation 73, $\psi(\theta)$ should be the same for both dives since (F/SP_o) and H_b are the same. It can be seen from table 20 that the first term in the expression for $\psi(t)$ (equation XIII) predominates, and that higher roots vary in a manner similar to the first. Hence similar values of $\psi(t)$ in equation XIII would require similar arguments for the first exponential term, i.e. substituting Behnke's relative times:-

$$(25D/a^2)(a\alpha_1)^2_{working} = (34.5D/a^2)(a\alpha_1)^2_{resting}$$

giving:-

$$(a\alpha_1)^2_{working}/(a\alpha_1)^2_{resting} = 34.5/25 = 1.38 \qquad (86)$$

According to table 20,

$$\begin{cases}(a\alpha_1)_{working} = 0.304 \text{ for } (b/a) = 4.73\\ (a\alpha_1)_{resting} = 0.260 \text{ for } (b/a) = 5.29\end{cases}$$

This gives $(a\alpha_1)^2_{working}/(a\alpha_1)^2_{resting} = 1.37$ which is in good agreement with equation 86, confirming relative values of (b/a) = 5.29

for rest compared with (b/a) = 4.73 for work. While the relative values of (b/a) may be correlated successfully, the next stage is to determine whether the absolute values are realistic.

8.63 The dimensionless group (b/a)

It is difficult to compare the ratio (b/a) of inter-capillary distance (2b) to capillary diameter (2a), when one cannot identify the critical tissue type positively. However, it is known that the particular tissue is closely associated with the locomotor system (section 3.11).

Taking muscle, Kety (1951) quotes maximum diffusion distances in fully-vasodilated skeletal muscle given by

{ 15 microns for horse, and
{ 11 microns for dog.

Hence, for fully-vasodilated skeletal muscle in man one would expect:-

$$11 < (b-a) < 15 \text{ microns}$$

The closest state of stimulation in the dives analysed is that for hard work when equation 78 gives:- $b/a = 4.73$

Eliminating b from the above equations:-

$$2.95 < a < 4.01 \text{ microns} \qquad (87)$$

8.64 The capillary diameter

The reason for selecting empirical values for the three basic groups, in preference to deducing such quantities synthetically, becomes apparent when one takes a basic dimension such as the diameter of a capillary. Values quoted in the literature range from 5 microns, used by Kety (1951) on the basis of measured circumferential distance, to 8 microns by Burton (1954).

Even higher values can be found if one searches in the literature for long enough. However, the above range could represent an error of over 150% in the effective capillary area, which is totally unacceptable for any quantitative analysis.

The most realistic appraisal is probably afforded by regarding the capillary as an elastic tube whose dimensions are determined by those of the passing red cells. While this approach would reduce the above range of 5-8μ, it still leaves scope for alternative interpretation. The average diameter of the erythrocyte is quoted by Keele and Neil (1965) as 7.3 microns, while Bazett (1941) gives the equivalent diameter as:-

5.6 microns on a volume basis
6.4 microns on a surface area basis
} average 6.0 microns

It would therefore seem reasonable to reduce the above range of 5-8 microns to 6.0-7.3 microns, or

$$3.0 < a < 3.65 \text{ microns} \qquad (88)$$

This range is in very good agreement with that determined from the b/a ratio derived from diving data, and expressed by equation 87.

8.65 The group (D/a^2)

The empirical value used for the foregoing analyses of the prime transient group is $D/a^2 = 0.129 \text{ min}^{-1}$. Combined with the value from section 8.61 of $b/a = 4.73$ for working conditions, this gives:-

$$\frac{\sqrt{(D/a^2)}}{((b/a)^2 - 1)} = 0.0168$$

which lies within the range 0.0165 - 0.0174 predicted from the $\sqrt{t}$ approximation in equation 75.- also for working conditions.

The most fundamental parameter to be deduced from this group is the diffusion coefficient of nitrogen in cytoplasm (D).

Substituting for (a) according to equation 88, and $D/a^2 = 0.129$ min^{-1} (equation 79),

$$1.16 \times 10^{-6} < D < 1.72 \times 10^{-6} \text{ cm}^2 \text{ min}^{-1}. \qquad (89)$$

Applying Graham's law to the value determined experimentally for acetylene in section 5.48,

For nitrogen, $D = 1.37 \times 10^{-6} \times \sqrt{26/28} = \underline{1.32 \times 10^{-6}}$ cm^2 min^{-1}.

It is regarded as most significant that this value should lie within the range predicted from decompression analyses in equation 89.

8.66 The dimensionless group (F_o/SP_o)

For a weak diver it has been established (equation 68) that $(F_o/SP_o) = 0.413$.

For a predominantly aqueous tissue, as indicated by 'saturation' helium dives (section 8.26), Behnke (1951) gives the solubility of N_2 in tissue as $SP_o = 0.01277$ c.c. N_2/c.c. tissue.

In this case $F_o = 0.413 \times 0.0127 = 0.00525$

This implies that 0.525% volume displacement provides sufficient gas which, if congregated, can give rise to marginal symptoms.

While it is not necessary for proof of the hypothesis, it is interesting to speculate upon the possible size of the "critical bubble". If it is postulated that all gas separated in a cross-section of a fibre must be congregated into one bubble to provoke pain, then the critical bubble radius is given by:

$$\frac{y^2}{(b^2 - a^2)} = 0.00525.$$

Taking b/a = 5.29 (resting) and a = 3.65 microns (red cell radius), the above expression gives y = 1.41 microns.

A diameter of approximately 3 microns would seem reasonable for the bubble causing symptoms in a 'tight' tissue. However, the most significant quantitative appraisal of this value is the additional pressure imparted by surface tension (section 4.6) and its eventual role in predicting 10,500 feet as the minimum altitude at which phase separation is initiated in a man decompressed after living in air at ground level (section 5.68).

In conclusion, there would seem adequate justification for claiming that the values of fundamental parameters derived from dive analyses lie well within the reasonable limits to be anticipated by more direct and conventional methods of determination. It seems most unlikely that every value derived of a fundamental parameter would lie within practical limits if the synthesis of the hypothesis were not realistic.

CHAPTER 9

DISCUSSION

CHAPTER 9

DISCUSSION

9.1 The Controversial Issues

The critical review of the published theories of decompression sickness (section 1.6) led to a list of eleven issues (section 2.3) whose coverage was considered vital in attempting to derive a comprehensive hypothesis Most quantitative approaches tend to avoid discussion of many of these vital issues and so derive 'calculation methods' rather than theories.

The 'thermodynamic' hypothesis, derived in this thesis, has attempted to produce a more comprehensive approach by using more rigorous and fundamental treatments. This has led concepts for the following:-

1. The site of pain-provoking bubbles within the critical tissue and their probable distribution - figs. 7 and 12.

2. The physical mechanism for the formation of a bubble following phase separation (section 4.4).

3. A physical mechanism by which a bubble can provoke pain, and a quantitative description of the process (section 4.1).

While the treatment of these aspects could be incorporated into many existing theories with little modification, the issues in which there is direct contrast with conventional calculation methods may be listed as follows:-

1. The number of tissue types involved.

2. The nature of gas phase initiation upon decompression.

3. The driving force for inert gas elimination following decompression.

4. The transport model.

Since the above list covers almost every major issue, the contents of this thesis cast doubt upon the fundamental basis of all published decompression tables. The validity of these divergencies may now be reviewed for the items disputed.

9.2 The Number of Tissue Types Involved

The number of tissue types postulated as being involved in the manifestation of marginal symptoms of decompression sickness seems to be the least certain aspect in all quantitative theories. No positive evidence is given for the participation of 4-6 tissues of arbitrary half-times (e.g. 5, 10, 20, 40 and 75 mins.) presumed by conventional methods of calculating decompression tables (sections 1.62 and 1.63).

On the other hand, the theoretical approaches of Hempleman, Rashbass and Albano (sections 1.64 - 1.66) can be no more certain that only one tissue type is involved, the only criterion being the relative abilities of the final calculation methods to correlate practical data.

This lack of positive identification stems from the very limited value of the wealth of pathogenic evidence summarised in sections 3.2 and 3.3. The fact that one finds a bubble in a tissue is no justification for claiming that that bubble, or any others in that tissue, could have been responsible for marginal symptoms.

In selecting a single-tissue model for the thermodynamic hypothesis (section 3.24), the argument that no transition points could be detected in the experimental depth-time limits for safe no-stage dives would seem more positive reasoning than simply assuming a convenient number of tissues. However, it

could be argued that conventional calculation methods are really convenient approximations for the case of a continuous spectrum of tissue response times. But, it is difficult to see how a $\sqrt{t}$ effect can arise from multi-tissue participation unless there is a remarkable coincidence in the relative values of time constants and decompression ratios for different tissues. However, these are all arguments based upon calculation methods.

Throughout the literature, the advocates of multi-tissue theories do not seem to have provided any evidence relating the nature or site of symptoms observed to the particular hypothetical tissue whose critical tension limit should have been exceeded.

In physical terms, there would appear to be an even wider variation in the elastic properties of tissues (McDonald, 1960) than in transport characteristics. If the concept of a pressure differential is realistic as a mechanical force deforming nerve endings and giving a rise to pain (section 4.12), then equation II should hold. This expression indicates that bulk modulus should be equally as important as the volume of gas separating in determining the proximity to symptoms. Hence it seems unlikely that more than one tissue type would possess comparable susceptibilities based upon a combination of modulus and response time. Even if this were the case, it would seem most unlikely that they would have half-times for uptake distributed as evenly as the values used for compiling decompression tables. The conventional multi-tissue theories would thus appear to be physiological explanations for convenient mathematical methods rather than approaches synthesised from fundamental parameters.

The emphasis upon the mechanical aspects of tissue would seem well founded in the light of the value of Young's modulus calculated from diving data (section 4.15) and the correlation of susceptibility with age (section 4.16).

9.3 Nucleation

Every published theory of which the writer is aware uses the same mathematical expression(s) to describe the elimination of a gas following decompression as are used to describe its uptake. This implies that no phase change has occurred until the individual critical tension values are exceeded. Only gas in true physical solution can contribute to a driving force for transport - whatever the model.

Hence, for such mathematical forms to be physically consistent, there would have to be a state of supersaturation following decompression, the criterion for symptoms effectively defining a metastable limit. However, the latter concept has been long abandoned in all of some ten or more aspects of suppressed transformation in vitro. The conclusion reached in section 4.2 was that nucleation is a random process and the only effective quantitative treatment must be of a statistical nature. This includes cavitation at liquid-solid boundaries.

The five hundred and eighty decompressions described in section 6.2 would provide strong evidence that nucleation at oil-aqueous phase interfaces is also a random process. Moreover, any threshold decompression for cavitation must be far lower than any limits indicated by the decompression ratios or fixed pressure differentials advocated by published theories of decompression sickness (section 1.6).

Records for solid-liquid interfaces in the literature (section 4), and for liquid-liquid by direct experiment (section 6.2), all indicate that there should be no true metastable limit for any liquid-gel or liquid-liquid boundary likely to occur in vivo. The random nature of nucleation would certainly seem

to be consistent with literature data upon the occurrence of bubbles in vivo - as summarised in section 4.3 and illustrated by table 5.

Hence there would seem to be a very strong case for abandoning the concept of any metastable limit in diving - just as has occurred in the theoretical treatment of all other forms of suppressed transformation. For a random process the worst possible case is therefore that for which there is thermodynamic equilibrium since:-

1. this condition represents maximum separation of the gas phase.
2. zero supersaturation, and hence the minimum driving force for elimination of the separated inert gas via the capillary (section 5.74).

If one accepts the concept of a pressure differential with respect to tissue as a realistic motivating force for pain, then it would seem reasonable that this worst possible case should be the relevant model for calculating decompressions (section 4.54). For this case one must dispense with the concept of limited supersaturation and hence with any theoretical approach which uses the same time functions for both inert gas elimination following decompression and inert gas uptake. This applies irrespective of the postulated mechanism or of the critical parameters selected for predicting symptoms.

The thermodynamic hypothesis would thus appear more consistent with the literature and experimental work upon suppressed transformation than previous theories of which the writer is aware. Justification for this radical divergence from conventional theories, and their quantitative expressions, is afforded by all evidence of phase separation without symptoms - "silent bubbles" This includes X-ray data (section 8.14) and evidence of a phase change at low altitudes (section 5.68). The thermodynamic hypothesis is also far more

compatible with surface decompression, post-decompression sickness and the decreasing tolerance of pilots to successive aerial decompressions (section 8.18) than any theory based upon limited supersaturation.

9.4 The Driving Force for Inert Gas Elimination

In dispensing with the concept of supersaturation for the worst possible case, one is faced with the problem of ascertaining the true driving force for the elimination of inert gas during decompression. The physico-chemical reactor (sections 5.6 and 5.7), shows how a driving force for the inert gas can be provided by an inherent unsaturation arising by virtue of metabolism. This unsaturation has been known for some years for air at ground level, but has probably been dismissed by workers in decompression sickness as insufficient to effect any appreciable transport.

However, the physico-chemical analysis, terminating in equation 48, indicates that the driving force for inert gas elimination should increase with absolute pressure and the mole fraction of inhaled oxygen. Even at conventional staging depths, this becomes an appreciable quantity.

The experimental work described in section 6.3 would represent the strongest practical evidence that the inherent unsaturation exists and that, for the rabbit at least, it varies according to the theoretical predictions of equation 48. However, up to the point of no phase change, this equation indicates a greater driving force for tissue desaturation at greater depth, which is the exact converse of all conventional reasoning based upon supersaturation. In practice this would suggest much deeper staging for a more rapid overall ascent time of a diver (section 5.9).

Very strong practical support for this radical reversal in diving practice is provided by the empirical Okinawan techniques (Appendix I), and the comparative trials of the optimised thermodynamic decompression and standard Naval tables (section 6.8).

Some advocates of conventional theories (U.S. Navy, 1966) have expressed the opinion that the driving force of 195-235 mm. Hg, predicted by equation 48 for a depth of 30 feet, would still be insufficient to account for gas elimination during staging. This might be true for their simple transport model which assumes a linear response for blood tissue exchange. However, for most practical dives such as those described in table 26, gas should separate reasonably close to the capillary (section 8.55) in which case the inherent unsaturation becomes far more effective in motivating inert gas transfer in a diffusion-limited transport system.

The strongest evidence supporting the adequacy of such a driving force is shown by use of the concept in the analyses of practical dives in table 26.

The other aspect of equation 48, i.e. its predictions about the variation of total gas tensions with the mole fraction of oxygen would seem well founded. Support is provided by practical correlation of Δp with x (section 6.4), predictions of pressures for phase changes (section 5.68), and explanations for the effects of increased oxygen in reducing the incidence of symptoms (section 8.15).

9.5 The Transport Model

The changes in decompression techniques suggested by accepting a diffusion-controlling in preference to a perfusion-controlling transport model,

are no where near as radical as those advocated by accepting the inherent unsaturation as the relevant driving force following phase separation. This arises from the similar quantitative results obtained from calculating inert gas uptake by conventional means or by the 3-dimensional approach expounded in sections 5.4 and 5.5.

However, this is a most fundamental issue in which the conclusion that diffusion may make a far more significant contribution to limiting blood-tissue exchange than generally accepted (section 5.2), casts doubt upon the popular method of measuring regional blood flows by isotope clearance techniques In Appendix III it is shown that data popularly quoted as proof of a perfusion-controlling model may be equally well interpreted upon a diffusion-limiting basis. The remarkable parallelism of arguments leads to the necessity of either

1. postulating complex physiological mechanisms invoking shunting between parallel arteriovenous pathways, but using simple quantitative expressions for a perfusion-limited exchange, or
2. performing a far more rigorous quantitative analysis of the simple 3-dimensional histological model, involving far more complex mathematics.

The latter approach has been attempted in section 5.4. The whole problem of perfusion versus diffusion seems to hinge upon the values one is prepared to accept for the diffusion coefficients of cytoplasm and extra-cellular fluid.

If one accepts the values quoted in section 5.3 for diffusion coefficients determined for various solutes by Fenichel and Horowitz, and for inert gases in section 5.4 (using data from 6.3), then diffusion must make a

far larger contribution to uptake control than is generally recognised. From the discussion of this vital issue in section 5.3 the conventional argument expressed by Forster, Kety, Roughton, Thews etc. would appear to have one large error arising from their use of diffusion coefficients determined by methods in which any heterogeneity would completely invalidate any values obtained.

While no one can ever be certain that the model used to determine diffusion coefficients is realistic, there can be little doubt from the uptake results (section 6.34 and fig. 19), that tissue is a heterogeneous diffusion medium for inert gases. Thus there seems to be a sound case for a change of emphasis in the relative contributions of perfusion and diffusion in limiting uptake by tissue. If one accepts this argument then, from the irregular nature of internal tissue geometry, it would seem reasonable for diffusion to be the rate-limiting process in the particular instance of the worst possible case - as envisaged morphologically in section 5.5.

9.6 Other Kinetic Factors

The probability of the worst geometric conditions coinciding with the worst nucleation conditions would seem very small. Hence, despite the very large number of possible micro-tissue regions in which sufficient gas could congregate to give pain, there could still be a reasonable chance of symptoms failing to occur after a potentially unsafe decompression. The thermodynamic hypothesis can thus offer an explanation for one of the major features of decompression sickness, and one which is avoided by most exponents of conventional calculation methods.

Another similar salient feature is the random onset time of symptoms which would seem to be adequately explained in section 8.12, with particular emphasis upon exercise (section 8.13).

However, the almost instantaneous onset of symptoms using conventiona. tables, e.g. U.S. Navy (1964), compared with any following the thermodynamic format indicates that:-

1. the gas phase is well established in the U.S. Navy diver long before he reaches the surface, and has therefore coalesced by the time it is permitted to expand to pain-provoking dimensions during the final 'pull' to the surface.
2. little, if any, gas has separated by the thermodynamic format before the final 'pull' to the surface.- hence longer onset times (see table 18).

The 'thermodynamic' method would seem to achieve more rapid overall decompression by allowing gas to separate in the final stages, thus using the greater driving force associated with greater depth for elimination of gas via the capillary. The reverse would hold for the U.S. Navy format which is effectively a therapeutic treatment for separated gas which has not become manifest in the clinical sense by virtue of the Boyle's law effect.

9.7 Correlation of Practical Data

Qualitatively, the thermodynamic hypothesis has appeared consistent with all the facets of decompression sickness of which the writer is aware. The latter have been reduced to the twenty-three essentially different aspects which are discussed in section 8.1. While parallel arguments can be offered by all theories for most of the topics, it is very difficult to see how conventional theories of limited supersaturation can explain the following points:-

1. the effects of exercise during decompression (item viii-8.13),
2. the threshold altitude for a phase change as indicated by X-rays (item ix-8.14) and the other evidence discussed in section 9.3.
3. the decreased advantage of pre-oxygenation at altitude (item xiv-8.15).
4. the decreasing tolerance of pilots to successive aerial decompressions (item xxi-8.18).
5. surface decompression (item xxiii-8.18).

Quantitatively, the thermodynamic hypothesis would appear to offer better correlation of the occurrence of symptoms than any theory of which the writer is aware. Essentially one expression (equation XXX), whose component terms are defined in section 5.85, has been used to correlate:-

1. The minimum depth for provoking symptoms in 'weak' and pre-selected divers breathing air (section 8.22).
2. The minimum altitude for provoking symptoms in 'weak' and pre-selected pilots breathing air before ascent (section 8.23).
3. The minimum depth for provoking symptoms in divers breathing oxygen-enriched air (section 8.25).
4. The minimum depth for provoking symptoms for divers breathing a mixture of 80% He, 20% O_2 (section 8.26).
5. The threshold altitude for the phase change discussed in section 9.3 (section 8.24).
6. The linear form of the decompression ratio determined experimentally for goats (section 8.27).
7. The $\sqrt{t}$ relationship (section 8.33) and the correlation of the empirical constant with fundamental parameters (section 8.64).

8. No-stage "scuba" dives using air (section 8.41).

9. Various sets of no-stage working dives (sections 8.42 and 8.43).

10. No-stage dives using helium (section 8.44).

11. "Oxygen bends" (section 8.45).

12. Dives with titrated staging (section 8.52).

13. Working dives with and without staging (section 8.53 and 8.54).

14. Okinawan dives (section 8.56).

15. Repetitive dives (section 8.57).

The same critical value of the crucial parameter ($F_c/SP_o = 0.413$) enables theoretical critical pressures to be deduced for each of the aspects of items 1-7 which lie within the various ranges of practical values. The same value of (F_c/SP_o) enables symptoms to be correlated with dive format in all except three out of more than 100 different dives, these differences taking the many forms suggested by items 8-15. However, of the three outstanding cases, in only one did symptoms occur when not predicted by equation XXX, and this was a case of itching.

The other two were less serious in so far as symptoms did not occur although predicted. These could be dismissed on the statistical grounds that each dive was performed by only two men in one case and by three in the other. However, even if one supposes that a "worst possible" site was fully nucleated, it is interesting to note that both exposures were working dives of long duration - 105 mins (table 23) and 60 mins (table 27). Both cases could be readily correlated if these divers had eased their heavy work rate over such extended periods to match that of a cruising "scuba" diver - see sections 8.42 and 8.54.

Hence there would appear to be plausible explanations for the few minor points of discrepancy in an otherwise complete correlation of the occurrence of symptoms with practical dives of widely differing types.

9.8 Fundamental Interpretation

The use of dimensionless groups in analysing dives has proven particularly expedient, and has suggested values for the following basic constants:-

1. A critical bubble diameter of 2.82 microns which seems of reasonable magnitude and implies (section 4.15) a value of Young's modulus for the critical tissue lying within a reasonable range to be anticipated.
2. An intercapillary distance (b) within the range 14.2-17.3 microns for hard work to 15.8-19.2 microns for rest. These values would seem reasonable for a tissue type which is not muscle yet is closely associated with the locomotor system (section 3.11).
3. A diffusion coefficient for cytoplasm, of $1.15 \times 10^{-8} - 1.72 \times 10^{-8}$ cm.^{2} min.$^{-1}$ which is within the range determined by other truly transient methods which do not assume tissue to be a homogeneous diffusion medium (section 5.32).

It would seem most unlikely that theoretically-derived values for three such basic parameters would lie within practical limits if the postulated mechanism and model, and subsequent mathematics, were not realistic. The above

quantitative correlation thus represents the strongest evidence in favour of the fundamental approach employed for synthesising the hypothesis deduced in this thesis.

The more intriguing aspect of this work is the prediction that there is an altogether faster means of decompressing a diver than could be conceived from conventional theories (section 5.9). The comparative trials upon goats for an arbitrary exposure (section 6.8), which showed a saving in decompression time exceeding 30%, would appear to provide "the proof of the pudding".

This would indicate that the analogues described in sections 6.5 and 6.6 must be close to a true simulation of the actual process occurring in the critical tissue during decompression. The thermal analogue would therefore warrant further development for possible use at sea as an automatic indicator of optimal decompression, while the same basic principle might be adapted for simulating the uptake of volatile anaesthetics.

9.9 Conclusions

From the foregoing discussion the following conclusions may be made:-

1. There is a faster means of decompressing a diver than would be predicted from conventional theories and tables.
2. Such reduced decompression times can be attained, with no loss of safety, by employing deeper staging techniques.
3. Such techniques are consistent with the hypothesis described in chapter 7, and summarised quantitatively in section 5.85.
4. The deeper staging advocated by the hypothesis is consistent with the techniques devised empirically by Okinawan pearl divers,

(Appendix I), and with the increased 'inherent unsaturation' which has been observed at greater absolute pressure (section 6.4

5. The thermodynamic hypothesis offers a better quantitative correlation of many types of dives than can be obtained from conventional theories.

6. The thermodynamic hypothesis is more consistent with the many qualitative facets of decompression sickness than conventional theories (section 8.1).

7. There is little justification for the conventional postulation, or implication, that there is a metastable limit to the supersaturation of tissue by gases.

8. Cavitation at a liquid-liquid interface is a random process, any threshold decompression being appreciably less than indicated by the decompression ratios or fixed pressure differentials advocated in conventional theories of decompression sickness.

9. The analysis of diving data is consistent with the concept of considering only the 'worst possible case' from the following points of view:-

   (a) maximum gas phase separation, i.e. thermodynamic equilibrium.

   (b) minimal blood-tissue exchange, i.e. where the space between two adjacent capillaries is occupied by cellular material only.

10. Skeletal muscle cannot be regarded as a homogeneous diffusion medium for inert gases.

11. There is little justification for the conventional practice of assuming that the blood:tissue exchange of a single tissue exhibits a linear response.

12. There could be far greater errors than generally accepted in the popular method of measuring regional blood perfusion rates as the exponential constant × partition coefficient.

13. There would seem to be considerable doubt about the validity of the popular practice of using diffusion coefficients for tissue as those of water or those determined by steady-state methods - particularly when used for calculating transient exchanges.

14. The thermodynamic hypothesis enables values to be determined from dive analysis for fundamental physiological parameters which are within reasonable limits.

Chapter 10

APPENDICES and BIBLIOGRAPHY

Appendix I - Okinawan dives.

Appendix II - Transient diffusion in perfect geometric shapes.

Appendix III - Additional facets of the perfusion vs. diffusion controversy.

Appendix IV - Transient uptake by the linear compartmental model.

Appendix V - Axial diffusion or conduction in a finite hollow cylinder.

Bibliography*

* Since the number of references exceeds 400, titles of articles are omitted to avoid excessive length.

Appendix I

OKINAWAN DIVES

Records

In 1959 the Aeromedical Unit (Adelaide) organised an expedition to the North Queensland coast to record the diving techniques of Okinawans hired upon two-year contracts by the pearling companies. The financial incentive to minimise decompression time has resulted in their developing an empirical diving format over the last century. The feature of diving in the Torres Strait is the long and deep exposures, up to 1 hour at 300 feet, often performed twice in one day by the same man. The divers are towed over the bottom of the ocean while searching for shell, and wear a helmet and full-suit.

The records and results of eleven dives are shown in fig.44 together with the corresponding decompression prescribed by other methods. The writer can claim no credit for any of these records and would like to express his appreciation to the Aeromedical Unit (Adelaide) for access to them. They have since been published (LeMessurier and Hills, 1965) together with the writer's thermodynamic explanation for the success of the Okinawan's decompression technique.

Features

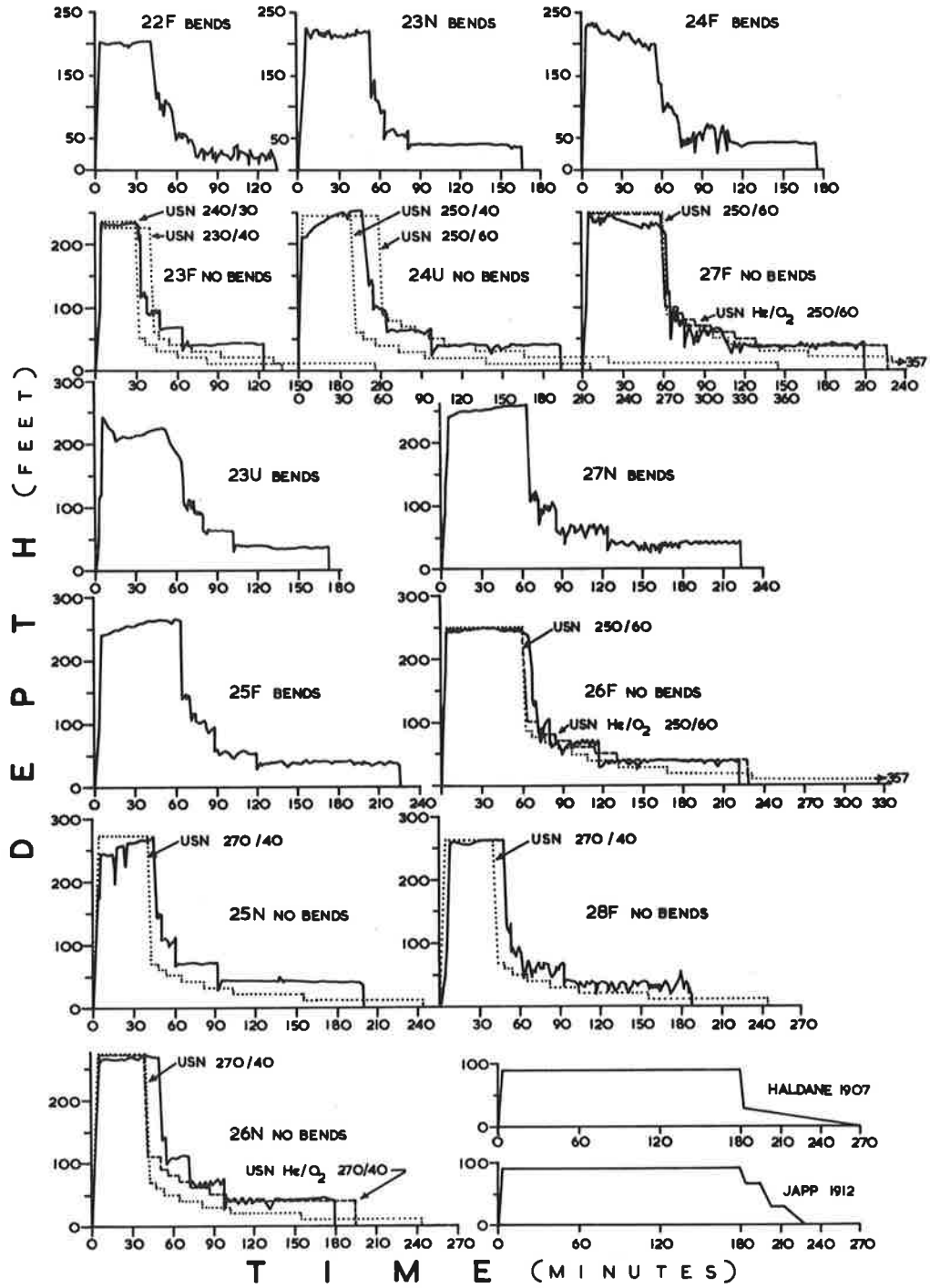
The Okinawan dives differ greatly from all Naval tables and defy correlation by any conventional theory. However their technique has been shown to permit more rapid surfacing from long

and deep dives, although Naval tables are faster for short exposures. The qualitative features of the Okinawan-type of decompression are:-

1. Direct surfacing from 30 - 40 feet.
2. Deeper staging throughout the decompression than any advocated by conventional tables or theory.

A quantitative analysis is performed in section 8.67.

It should be emphasized that the methods used by indentured Okinawans are entirely different to those introduced by the Royal Australian Navy and Department of Primary Industries for use by native 'islanders' diving for pearl shell in the same waters.



GRAPHS 1-14. A COMPARISON OF RECORDED OKINAWAN AND OTHER DIVING PROFILES.

Fig. 44

APPENDIX II

TRANSIENT DIFFUSION IN PERFECT GEOMETRIC SHAPES

THE INFINITE HOLLOW CYLINDER

Transient radial diffusion equation

Applying Fick's law to the conservation of a solute at a point given by the radial coordinate (r), the tension (p) of that solute may be expressed as:-

$$\frac{1}{r} \cdot \frac{\partial}{\partial r}\left[r \frac{\partial p}{\partial r} \right] = \frac{1}{D} \cdot \frac{\partial p}{\partial t} \qquad (201)$$

where D is the diffusion coefficient.

Tension distribution

Let the infinite hollow cylinder have an internal radius (a) and external radius (b), and zero initial tension throughout, i.e. $p = 0$ for $t = 0$. Carslaw and Jaeger (1959a) have derived a general solution for the tension in the cylinder $a \leq r \leq b$ as:-

$$p = \frac{-ak_3(k'_1 - bk'_2 \cdot \log(r/b)) + bk'_3 (k_1 + ak_2 \cdot \log(r/a))}{ak_2 \cdot k'_1 + bk_1 \cdot k'_2 + abk_2 k'_2 \log (b/a)}$$

$$- \pi \sum_{n=1}^{\infty} \frac{\exp(-D\alpha_n^2 t)}{F(\alpha_n)} (k'_1 \cdot \alpha_n J_1(b\alpha_n) - k'_2 J_o(b\alpha_n))\, C_o(r,\alpha_n)$$

$$\left[k_3(k'_1 \alpha_n J_1(b\alpha_n) - k'_2 J_o(b\alpha_n)) - k'_3(k_1 \alpha_n J_1(a\alpha_n) + k_2 J_o(a\alpha_n)) \right] \qquad (202)$$

where $F(\alpha_n) = ((k'_1)^2 \alpha_n^2 + (k'_2)^2)(k_1 \alpha_n J(a\alpha_n) + k_2 J_o(a\alpha_n))^2$

$$- (k_1^2 \alpha_n^2 + k_2^2)\, (k'_1 \alpha_n J_1(b\alpha_n) - k'_2 J_o(b\alpha_n))^2 \qquad (203)$$

and $C_o(r,\alpha_n) = J_o(r\alpha_n)(k_1\alpha_n Y_1(a\alpha_n) + k_2 Y_o(a\alpha_n))$

$$- Y_o(r\alpha_n)(k_1\alpha_n J_1(a\alpha_n) + k_2 J_o(a\alpha_n)) \qquad (204)$$

for which $\pm\alpha_n$ are the roots, all real and simple, of:-

$$(k_1\alpha J_1(a\alpha) + k_2 J_o(a\alpha))(k_1'\alpha Y_1(b\alpha) - k_2' Y_o(b\alpha)) =$$

$$(k_1\alpha Y_1(a\alpha) + k_2 Y_o(a\alpha))(k_1'\alpha J_1(b\alpha) - k_2' J_o(b\alpha)). \qquad (205)$$

k_1, k_2, k_3, k_1', k_2' and k_3' are defined by the general boundary conditions:-

$$k_1(\partial p/\partial r) - k_2 p = k_3 \text{ for } r = a \qquad (206)$$

and $$k_1'(\partial p/\partial r) + k_2' p = k_3' \text{ for } r = b \qquad (207)$$

k_1, k_2, k_1' and k_2' are constants which may be positive or zero provided k_1 and k_2 or k_1' and k_2' do not both vanish.

Model for decompression sickness

The model for the worst possible case (fig. 8) has two boundary conditions:-

1. No mass transfer across the boundary r = b since such points would be supplied equally by two capillaries, i.e. $(\partial p/\partial r) = 0$ at r = b.

   This satisfies equation 207 if $k_1' = 1$, $k_2' = 0$ and $k_3' = 0$.

2. No concentration gradient across the capillary. Such a step in blood tension, defined by p = 0 for t < 0 to $p = P_A$ for $t \geq 0$ and $r \leq a$, means that equation 206 is satisfied if $k_1 = 0$, $k_2 = 1$ and $k_3 = -P_A$.

Thus equation 202 becomes:-

$$p = P_A \left(1 - \pi \sum_{n=1}^{n=\infty} \frac{a_n^2 (J_1(ba_n))^2 C_o(r, a_n) \exp(-a_n^2 Dt)}{F(a_n)}\right) \quad (208)$$

Similarly, equation 203 gives:-

$$F(a_n) = a_n^2 \left((J_o(aa_n))^2 - (J_1(ba_n))^2\right)$$

equation 204 gives:-

$$C_o(r, a_n) = J_o(ra_n) Y_o(aa_n) - Y_o(ra_n) J_o(aa_n)$$

Thus the overall solution becomes:-

$$p = P_A \left[1 - \pi \sum_{n=1}^{n=\infty} \frac{(J_o(ra_n) Y_o(aa_n) - Y_o(ra_n) J_o(aa_n)) \exp(-a_n^2 Dt)}{\left((J_o(aa_n)/J_1(ba_n))^2 - 1\right)}\right] \quad (209)$$

where $\pm a_n$ are the roots, all real and simple, of equation 205, which now becomes:-

$$J_o(a\alpha) . Y_1(b\alpha) = Y_o(a\alpha) . J_1(b\alpha) \quad (210)$$

Bessel and Neumann functions are defined according to Watson (1944).

Total uptake

The total gas (G), expressed as volume (S.T.P.), entering extravascular tissue may be obtained by applying Fick's law to the capillary wall:-

$$\frac{dG}{dt} = -2\pi a D . S . \left(\frac{\partial p}{\partial r}\right)_{r=a} \quad (211)$$

where S is the solubility of the inert gas in cytoplasm - expressed as vol. gas (S.T.P.)/vol. tissue x pressure.

Applying equation 211 to equation 209, we have:-

$$\frac{dG}{dt} = 2\pi^2 a P_A S.D \sum_{n=1}^{n=\infty} \frac{\alpha_n (J_1(a\alpha_n) - Y_1(a\alpha_n) J_o(a\alpha_n)) \exp(-\alpha_n^2 Dt)}{\left((J_o(a\alpha_n)/J_1(b\alpha_n))^2 - 1\right)}$$

Integration, assuming G = 0 for t = 0, gives

$$G = 2\pi^2 a P_A S \sum_{n=1}^{n=\infty} \frac{(J_1(a\alpha_n) Y_o(a\alpha_n) - Y_1(a\alpha_n) J_o(a\alpha_n))(1 - \exp(-\alpha_n^2 Dt))}{\alpha_n \left((J_o(a\alpha_n)/J_1(a\alpha_n))^2 - 1\right)}$$

For $t = \infty$, $G = G_\infty = \pi(b^2 - a^2) S P_A$

Thus $$\frac{G}{G_\infty} = \frac{G}{\pi(b^2 - a^2) S P_A} = 1 - \frac{2\pi}{((b/a)^2 - 1)} \cdot$$

$$\sum_{n=1}^{n=\infty} \frac{(J_1(a\alpha_n) Y_o(a\alpha_n) - Y_1(a\alpha_n) J_o(a\alpha_n)) \exp(-\alpha_n^2 Dt)}{(a\alpha_n) \left((J_o(a\alpha_n)/J_1(b\alpha_n))^2 - 1\right)}$$

But $J_o(x).Y_1(x) - Y_o(x)J_1(x) = 2/\pi x$

Hence

$$\frac{G}{G_\infty} = \frac{G}{\pi(b^2 - a^2) S P_a} = 1 - \frac{4}{((b/a)^2 - 1)} \sum_{n=1}^{\infty} \frac{\exp(-\alpha_n^2 Dt)}{(a\alpha_n)^2 \left((J_o(a\alpha_n)/J_1(b\alpha_n))^2 - 1\right)} \qquad (212)$$

Approximations

Until the diffusing gas reaches the 'back wall' (r = b), the boundary condition given by equation 207 may be waived. The solution to equation 201 for such values of (t) is then the same as that of an infinite region bounded internally by the surface r = a. Carslaw and Jaeger (1959b), give:-

$$\frac{p}{P_A} = 1 + \frac{2}{\pi} \int_0^\infty \frac{\exp(-Du^2t)\left(J_o(ur)Y_o(ua) - Y_o(ur)J_o(ua)\right)}{\left((J_o(au))^2 + (Y_o(au))^2\right)} \left(\frac{\partial u}{u}\right)$$

Application of equation 211 gives the gas uptake as:-

$$G = \frac{8}{\pi} DP_A S \int_0^t \int_0^\infty \frac{\exp(-Du^2t)\,\partial u.\partial t}{u\left((J_o(au))^2 + (Y_o(au))^2\right)} \qquad (213)$$

Carslaw and Jaeger (1959b) give a plot of the dimensionless groups

$$\frac{dG}{dt} \Big/ 2\pi P_A DS \text{ vs. } Dt/a^2$$

Graphical integration gives a plot of the dimensionless quantities $\frac{G}{2\pi a^2 P_A S_T}$ vs. $\frac{Dt}{a^2}$

Further approximations

For smaller values of t,

$$\frac{dG}{dt} = 2\pi P_A DS\left[\left(\frac{Dt}{a^2}\right)^{\frac{1}{2}} + \frac{1}{2} - \frac{1}{4}\left(\frac{Dt}{a^2}\right)^{\frac{1}{2}} + \frac{1}{8}\left(\frac{Dt}{a^2}\right) + \right] \qquad (214)$$

Ultimate approximation

For smaller values of t such that $\frac{a}{\sqrt{(Dt)}} >> \frac{1}{2}$

i.e. $t << 4a^2/D$, other terms become negligible relative to the first, and

$$\left(\frac{dG}{dt}\right) = 2\pi SaP_A \sqrt{\frac{D}{t}} \qquad (215)$$

for which integration gives $G = 4\pi a P_A S\sqrt{(Dt)}$ (216)

Jaeger (1956) gives plots of (p/P_A) vs. $\log_{10}(r/a)$ for various values of (Dt/a^2).

These range from $r/a = 0.1$ to 100 and (Dt/a^2) from 10^{-3} to 10^3.

INFINITE SOLID CYLINDER

Tension distribution

Let us consider a solid cylinder of radius (b), i.e. $0 \leq r \leq b$, initially at zero tension, i.e. $p = 0$ for $t < 0$. For a step in external tension, defined by $p = 0$ for $t < 0$ to $p = P_A$ for $t \geq 0$ at $r = b$, Goldstein (1932) gives the solution to equation 201 for such boundary conditions as:-

$$p = P_A \left(1 - 2 \sum_{n=1}^{n=\infty} \frac{J_o(ra_n)\exp(-a_n^2 Dt)}{(ba_n)J_1(ba_n)}\right) \quad (217)$$

where $\pm a_n$ are the roots of:-

$$J_o(ba) = 0 \quad (218)$$

Total uptake

Application of equation 211 to equation 217 for gas traversing the capillary membrane gives:-

$$\frac{dG}{dt} = 4\pi P_A DS \sum_{n=1}^{n=\infty} \exp(-a_n^2 Dt) = 2\pi a DS \left(\frac{\partial p}{\partial r}\right)_{r=b}$$

Integration gives:-

$$\frac{G}{G_\infty} = \frac{G}{\pi b^2 P_A S} = 1 - 4 \sum_{n=1}^{n=\infty} \frac{\exp(-a_n^2 Dt)}{(ba_n)^2} \qquad (219)$$

Approximations

From Goldstein's approximation for equation 217,

$$\frac{p}{P_A} = \left(\frac{b}{r}\right)^{\frac{1}{2}} \operatorname{erfc}\left(\frac{b-r}{2\sqrt{(Dt)}}\right) + \frac{(b-r)(Dtb)^{\frac{1}{2}}}{4ar^{3/2}} \operatorname{ierfc}\left(\frac{b-r}{2\sqrt{(Dt)}}\right)$$

$$+ \frac{(9b^2-7r^2-2br)Dt}{32b^{3/2}.ra^{5/2}} \operatorname{i^2erfc}\left(\frac{b-r}{2\sqrt{(Dt)}}\right)$$

For small values of t, all but the first term may be neglected when $p = P_A \left(\frac{b}{r}\right)^{\frac{1}{2}} \operatorname{erfc} \frac{b-r}{2\sqrt{(Dt)}}$

$$\left(\frac{\partial p}{\partial r}\right)_{r=b} = \frac{P_A}{\sqrt{(\pi Dt)}} - \frac{P_A}{2b} \approx \frac{P_A}{\sqrt{(\pi Dt)}} \quad \text{if} \quad t << \frac{4b^2}{\pi d}$$

Applying Fick's law to the surface, $(dG/dt) = 2bSP_A\sqrt{(\pi D/t)}$

Integrating, $G = 4bP_A S\sqrt{(\pi Dt)}$ (220)

SOLID SPHERE

Radial diffusion equation

$$\left(\frac{\partial^2 p}{\partial r^2}\right) + \frac{2}{r}\left(\frac{\partial p}{\partial r}\right) = \frac{1}{D} \cdot \left(\frac{\partial p}{\partial t}\right) \qquad (221)$$

Tension distribution

Let us consider a solid sphere of radius (b), i.e. $0 \leqslant r \leqslant b$, initially at zero tension, i.e. $p = 0$ for $t < 0$.

For a step in external tension, defined by $p = 0$ for $t < 0$ to $p = P_A$ for $t \geq 0$ and $r \geq b$, Carslaw and Jaeger (1959c) give the solution to the above expression as:-

$$p = P_A \left[1 - \frac{b}{r} \sum_{n=1}^{n=\infty} \left[\operatorname{erfc} \left(\frac{(2n+1)b - r}{2\sqrt{(Dt)}} \right) - \operatorname{erfc} \left(\frac{(2n+1)b + r}{2\sqrt{(Dt)}} \right) \right] \right] \quad (222)$$

from which the application of Fick's law at the surface ($r = b$) gives:-

$$\frac{dG}{dt} = 4\pi b D S . P_A \sum_{n=0}^{\infty} \left(\operatorname{erfc} \left[\frac{nb}{\sqrt{(Dt)}} \right] - \operatorname{erfc} \left[\frac{(n+1)b}{\sqrt{(Dt)}} \right] \right)$$

$$- 4b^2 P_A S \sqrt{\frac{\pi D}{t}} \sum_{n=0}^{\infty} \left(e^{-\frac{n^2 b^2}{Dt}} + e^{-\frac{(n+1)^2 b^2}{Dt}} \right)$$

where G is the total gas entering the sphere.

Carslaw and Jaeger (1959d) give $\frac{\bar{p}}{P_A} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{\exp(-Dn^2\pi^2 t/b^2)}{n^2}$

Thus $$\frac{G}{G_\infty} = \frac{3G}{4\pi b^3 P_A S} = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{\exp(-n^2\pi^2 Dt/b^2)}{n^2} \quad (223)$$

THE INFINITE PARALLEL-FACED SLAB

Linear diffusion equation

In one dimension (z), Fick's law becomes:-

$$\left(\frac{\partial^2 p}{\partial z^2} \right) = \frac{1}{D} \cdot \left(\frac{\partial p}{\partial t} \right) \quad (224)$$

Tension distribution

Let us consider a flat parallel-faced slab of thickness (2b), i.e. $-b \leq z \leq b$, initially at zero tension, i.e. $p = 0$ for $t < 0$.

For a step in external tension, defined by $p = 0$ for $t < 0$ to $p = P_A$ for $t \geqslant 0$ and $b \leqslant z \leqslant -b$, Gray (1924) gives many solutions to equation 224, the simplest being

$$\frac{2p}{P_A} = \text{erf}\left(\frac{b-z}{2\sqrt{(Dt)}}\right) + \text{erf}\left(\frac{b+z}{2\sqrt{(Dt)}}\right) \qquad (225)$$

Expanding the error functions as series, and applying Fick's law to the faces:-

$$\frac{G}{G_\infty} = \frac{G}{2bP_AS} = 1 - \frac{8}{\pi^2}\sum_{n=1}^{\infty}\frac{\exp(-(2n-1)^2\pi^2Dt/4b^2)}{(2n-1)^2} \qquad (226)$$

N.B. The first 3 terms give the basis of the Rashbass equation (section 1.65).

DEFINITIONS

1. Bessel and Neumann functions are used according to the definitions of Watson (1944).

2. Error functions defined as:-

$$\text{erf}(z) = \frac{2}{\sqrt{\pi}}\int_0^z e^{-u^2}\,du = 1-\text{erfc}(z); \quad i^n\text{erfc}(z) = \int_z^\infty i^{n-1}\text{erfc}(u)\,du.$$

for $n = 1, 2$, etc.

Appendix III

ADDITIONAL FACETS OF THE PERFUSION vs. DIFFUSION CONTROVERSY

Introduction

It is not intended to prove in this thesis that diffusion is the process limiting the uptake of inert gases by tissue. However the writer does dispute the popular concept of assuming that blood:tissue exchange is entirely circulation-controlled, and would hope to show that the resistances to uptake afforded by diffusion are far more significant than the calculations of Forster (1964) would suggest.

This statement is based upon the fact that such authors have used values for diffusion coefficients determined by methods whereby the solute could by-pass cells. Moreover they presume that each tissue has homogeneous diffusion properties.

The arguments disputing these assumptions have been expressed in section 5.2, the heterogeneous nature of skeletal muscle being emphasized by the very large difference in the diffusion coefficients for cellular and extracellular material found for:-

(1) inert solutes of varying dipole moment by Fenichel and Horowitz - see section 5.3, and

(2) inert gases - see sections 5.48 and 6.3.

While such data would support diffusion making a far more significant contribution to limiting blood:tissue than normally acredited, there is much other evidence quoted by the proponents of perfusion. Before reaching any decision it would seem desirable

to see if such evidence were not equally compatible with a diffusion-controlling model.

In the literature upon decompression sickness the work most frequently quoted in support of a circulation-limited uptake, and the subsequent use of simple expontial functions (equation 19), is that of Jones (1951).

Simultaneous wash-out of inert gases

Jones' chief argument in favour of exchange being controlled by the circulation is the similarity of time constants for different gases simultaneously eliminated from the body by an 'oxygen wash-out'. He measured nitrogen together with one of the following:- helium, krypton or radioactive xenon.

However, in his comparison of values, Jones' method of enumerating exponential terms would seem to be purely arbitrary, there being no apparent reason why k_1 should be assigned the largest value, k_2 the second largest, etc. On the other hand there would seem to be at least three reasons for adopting the reverse order, i.e. k_1 is the smallest, k_2 the next smallest, etc. These are:-

1. The process of extracting linear components from the overall semi-log plot must start with the smallest, and work to successively higher values. With a little experience at the technique, the writer completely fails to see how Jones can leave blanks in his table for values smaller than the largest quoted for a particular run. It would seem impossible to extract a component of large time

constant (k_j in equation 6) without knowing precise values for all 'slower' components.

2. From experience it is impossible to isolate the very fast components such as in figs. 17 and 19. It is therefore difficult to see how Jones could say which was the first component according to his method of enumeration. For small values of time a $\sqrt{t}$ relationship would seem most realistic for total elimination as for diving (see section 1.64). On the other hand, the reverse order to that of Jones avoids any ambiguity however the values are interpreted.

3. If diffusion is rate-contributing, the solutions to all bulk diffusion equations (fig 3) **are series** in which the first time constant (k_1) is the smallest.

A comparison of Jones' values for different gases is made by both methods of enumeration in table 30.

ANALYSIS OF INERT GAS ELIMINATION FROM MAN

(Data from Jones, 1951)

Gas	Jones' method of enumeration					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	0.087	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	-	-

TABLE 30

Nitrogen Values given by Behnke (1951) are:-

**0.0054 min^{-1}

*0.019 min^{-1}

+0.085 min^{-1}

++Average values quoted by Jones.

According to a circulation-limiting system, each time constant (k) is equal to (s.B), where B is the blood perfusion rate and s is the blood:tissue partition coefficient. Hence, if perfusion is rate-limiting the ratio of corresponding k values for Kr/N_2 or N_2/He should lie within the range 1 - 1.5 depending upon lipid content since $s_{Kr} > s_{N_2} > s_{He}$

On the other hand, if diffusion were rate-limiting similar k values should be inversely proportional to diffusion coefficients and solubilities. Thus one would anticipate the ratio of k values for N_2/He or Kr/N_2 to be within the range 3.5 - 6 depending upon the lipid content of the particular tissue.

It can thus be seen from table 30 that Jones' method of enumeration would indicate blood perfusion as the rate-limiting process while the reverse order would suggest diffusion. While the writer feels that the latter order of enumeration is more realistic for the reasons listed above, it would seem fair to claim that Jones' data does not exclude diffusion from being rate-limiting.

Elimination with exercise

The real problem is one of identifying time constants, or combinations thereof, with a particular tissue type. Towards this end Jones (1951) has measured nitrogen washout for various exercise levels. It would seem most significant that none of the time constants vary by a factor greater than 2 when the subject changes from rest to pedalling a bicycle. The blood flow in muscle should increase at least 10 - 20 times, in which case at least one of the time constants should be reduced by a similar factor if circulation were rate-controlling.

However the proponents of a perfusion-limited uptake explain this apparent anomaly by postulating parallel arterio-venous pathways.

The general tendency for time constants to increase with the extent of physical activity may be attributed to either increased circulation in the case of the perfusion model or to the geometric changes associated with increased vasodilatation for the diffusion model. This is just one of many facets of the controversy which can be interpreted equally well by both models and so offers no scope for comparison. Hence the ensuing discussion will be restricted to the few sets of data which appear to afford some scope for differentiation.

Arterio-venous measurements

Diffusion and blood perfusion are mass transfer resistances in series. Hence 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 but the venous tension may be regarded as the best attainable approximation. Should it approach closer to the arterial than the average tissue tension then this would be a good indication that diffusion was rate-limiting - otherwise it must be perfusion controlling.

Unfortunately no set of results could be found in which arterial venous and average tissue tensions had all been measured directly with increasing time. Most tissue tensions have been estimated by arterio-venous difference, using an integrated form of equation 18. However, after estimating s, there are still two unknowns - B and p_T in the mass balance equation, often with no convenient alternative means of measuring B. Thus Kety and Schmidt (1945) assume $p_T = p_V$ in deriving values for B in brain for interpretation of their data upon inhaled N_2O. Taking values for cerebral blood flow determined by a less acceptable method they obtain values of s which seem reasonable.

However, in addition to calculating cerebral blood flow (B) by the mass balance equation (18), they quote simultaneously derived values of the time constant (k) for the exponential decay of $(p_A - p_V)$. To be consistent with a perfusion-controlling mechanism, B must equal (k/s) (equation 19).

Comparison of cerebral blood flows determined by different methods

(data from Kety and Schmidt, 1945).

k	s	B - Cerebral Blood Flow (c.c./gm. tissue. min.)		
		(I) k/s (perfusion controlling)	(II) by mass balance	(III) 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

TABLE 31.

The considerable deviation of values in determination (I), from those in (III), would imply that the graph of Kety and Schmidt in which they display a theoretical curve for mean tissue tension almost coincident with the venous curve creates an impression unduly favoring perfusion as the rate-limiting process.

From columns I and III, the indication that true blood flow may be significantly greater than the rate constant, modified by solubility considerations, is another point suggesting that diffusion cannot be ignored as not rate-contributing.

Kety and Schmidt claim the agreement between columns II and III as their main evidence in favour of perfusion as the rate-limiting step since, in deriving values of B, they assume that $p_T = p_V$ after

10 mins. Although corrected in a later paper by Kety (1960), they make no adjustment for the arterio-venous difference which must occur on account of blood residence time.

Modified methods employing the same basic principle of estimating mean tissue tension by arterio-venous difference have been described by many later workers including Lassen and Munck (1954), Lambertsen (1960) and Sokoloff (1960) using ^{85}Kr. Incorporating these modifications, Lassen and Klee (1965) derive a mean brain tension whose deviation from that of venous blood exceeds the A-V difference after 2-3 mins of krypton inhalation. Moreover, their measurements of Kr^{85} elimination, immediately succeeding those for 10 mins of uptake, confirm that equilibrium between the measured venous blood and tissue could not have been obtained in this period.

However Lassen and Klee explain this apparent discrepancy from a perfusion-limited model by the familiar postulation of parallel arterio-venous pathways, claiming that samples of jugular blood represent the product of mixed venous returns.

The same argument may be used to interpret the wide discrepancy between venous values and mean tissue tensions determined by direct analysis of excised tissue.

Direct tissue analysis

Campbell and Hill (1933), who cut out the organs of goats electrocuted before decompression from 3, 4, and 5 atmospheres gauge pressure of air, obtained the following half saturation times for nitrogen:-

brain -- 4 hrs
liver -- 3 hrs
bone marrow -- 4 hrs

These times are several orders greater than the periods required for arterial and venous tensions to come within 5% of each other, e.g.

about 10 mins. by Kety and Schmidt (1945) for N_2O in brain,
about 5 mins. by Ingvar and Lassen (1962) for Kr in cerebral cortex,
about 14 mins. by Lassen and Munck (1954) for Kr in brain,
about 6 mins. by Pittinger et al (1956) for xenon in brain,
about 5 mins. by Pittinger et al (1956) for CCl_4 in brain.

While it would seem quite plausible to explain the A-V tensions by parallel A-V pathways, it is difficult to account for results of Campbell and Hill on a circulation-controlling model. On this basis Jones (1951) admits that their half-times would seem far too long for such well-perfused organs as brain and liver.

Direct analysis of segments of excised organs, described by Johnson et al (1952) has confirmed the heterogeneous assimilation of deuterated water by heart and liver. Such differences were much reduced in the case of skeletal muscle.

The controversy between perfusion and diffusion as the rate-limiting process is thus transposed to one of diffusion versus parallel arterio-venous pathways.

Parallel arterio-venous pathways

While it would seem perfectly reasonable to postulate parallel arterio-venous pathways in whole organs, the real question arises when considering one tissue type only, e.g. skeletal muscle. In this case the parallel pathways would need to be direct A-V shunts, although Barlow et al (1959 and 1961) invoke connective tissue as a source of heterogeneous perfusion.

In summarising the morphological evidence, Barcroft (1963) states that "most anatomists will deny the existence of A-V anastomoses in skeletal muscle". However a few authors claim to have seen blood short-circuiting, notably Zweifach (1949).

Dieter (1954) found that small plastic spheres (20 microns dia.) failed to traverse skeletal muscle from arterial to venous sides. This would indicate that if direct A-V shunts exist then their diameter, and hence their blood-carrying capacity, must be very limited.

Flow characteristics

The means of increasing blood flow in skeletal muscle include decreased stimulation of the sympathetic vasoconstrictor nerves or greater stimulation via the hypothalamic vasodilator pathway. Since the latter process has no appreciable effect upon the rates of blood-tissue exchange of various substances (Hyman et al, 1959), it has been claimed (Pappenheimer, 1940) that the additional flow is shunted direct to the venous side, by-passing the capillaries. Thus it would not have the opportunity of equilibrating with extravascular tissue

according to the conventional approach of such uptake or elimination being perfusion controlled.

However the diffusion-limiting theory is equally compatible with the flow and exchange characteristics if one postulates that the vasodilator nervous system controls the overall blood flow by means of the muscular walls of arterioles and other "resistance vessels" as termed by Mellander (1960). Increased flow per capillary should not influence a diffusion-limited exchange. On the other hand, if vasoconstrictor nerves determine vascularity by means of the "sphincters", then their stimulation should change the geometry of the tissue and so decrease exchange by diffusion.

Both diffusion and perfusion models would thus appear to offer explanations for simultaneous flow and control observations, although the writer could not comment upon their relative merits without going into the vast literature in much more detail.

Uptake versus flow

A most relevant experiment has been performed by Renkin (1958) using ^{42}K and urea for uniform stimulation of the vasoconstrictor nervous system. His curves of uptake vs. blood flow include the following features:-

1. For low perfusion rates (0.5 ml./100 ml. min), they are linear, i.e. circulation-limited uptake.
2. For high perfusion rates (10 ml./100 ml. min), the uptake is within 10% of the asymptote, i.e. largely diffusion-limited.

If a similar curve applied to man, it would seem reasonable to suppose that both perfusion and diffusion represent comparable resistances for normal blood flow rates in skeletal muscle of 4-7 ml./100 ml. min. - as quoted by Guyton (1963b). With blood flow increasing 10 - 15 times with muscular activity, the uptake should be largely diffusion controlled. Similar results were obtained by Renkin and Rosell (1962) using radio-active rubidium in a dog's gracilis muscle. It is unfortunate that both isotopes used by Renkin have been cations, since it leaves the results open to possible alternative explanation. The writer feels that Renkin's experiments should be repeated using an inert gas such as ^{85}Kr. Tentative arrangements have been made to collaborate with a physiologist experienced in these matters in undertaking the work.

Other comparisons

From the many other facets of this subject, two which offer some scope for differentiating between the parallel arguments which can be advanced for perfusion or diffusion as rate-limiting include:-

1. It is difficult to derive a $\sqrt{t}$ relationship, for small values of time (t), from any perfusion-controlling model.
2. Clearance of ^{24}Na from skeletal muscle has been found to be four times faster (Hyman et al, 1959) when the isotope has been introduced intra-arterially compared with intramuscular injection. This is consistent with a diffusion-limiting model in so far as any solute just acquired from blood should be concentrated close to the

capillary and therefore more rapidly returned to the blood than if it were evenly dispersed.

Conclusion

The writer considers that the work of Jones (1951) can be equally well interpreted upon a diffusion as on a perfusion-controlling model. The same may be said of the much-quoted work of Kety and Schmidt (1945). The other points discussed would indicate that neither process may be ignored and that the relative resistances derived in section 5.4 according to the model advanced in fig. 5 would seem realistic.

The whole question would seem to rise or fall upon the values one takes for the diffusion coefficients of cellular and extra-cellular material. If the values for cytoplasm are really of the order determined by true transient methods by Harris and Burn (1949), Fenichel and Horowitz (1963), Dick (1959) and the writer (section 5.4), then diffusional resistances are appreciably greater than indicated by Forster (1964). Hence there would be no justification for the popular practice of ignoring them in calculating decompression tables or determining regional blood perfusion rates by clearance methods.

For the particular geometry of the worst possible case (fig. 7), the diffusion coefficients would be such as to permit circulation to be ignored, i.e. the bulk diffusion model advocated in fig. 8 for diving only.

APPENDIX IV

TRANSIENT UPTAKE BY THE LINEAR COMPARTMENTAL MODEL

In the equivalent linear model shown in fig. 5, let the resistances to mass transfer be:-

Ω_i from external to extracellular fluid.

Ω_1 from extracellular fluid to the 1st root compartment.

Ω_2 from extracellular fluid to the 2nd root compartment.

while the gas capacities per unit tension are:-

C_1 for the 1st root compartment

C_2 for the 2nd root compartment

C_i for the compartment including extracellular and the higher roots of cellular material.

The rates of transfer to the compartments, $q_1(t)$, $q_2(t)$, $q(t)$ are given by:-

$$q_1(t) = \Omega_1(p_i(t)-p_1(t)) \tag{401}$$

$$q_2(t) = \Omega_2(p_i(t)-p_2(t)) \tag{402}$$

$$q(t) = \Omega_i(p_A(t)-p_i(t)) \tag{403}$$

The transient mass balances for each compartment give:-

$$q_1(t) = C_1(\partial p_1(t)/\partial t) \tag{404}$$

$$q_2(t) = C_2(\partial p_2(t)/\partial t) \tag{405}$$

$$q(t) - q_1(t) - q_2(t) = C_i(\partial p_i(t)/\partial t) \tag{406}$$

Eliminating $q_1(t)$ from equations 401 and 404,

$$(\partial p_1(t)/\partial t) = (\Omega_1/C_1)(p_i(t)-p_1(t)) = k_1(p_i(t)-p_1(t)) \tag{407}$$

Eliminating $q_2(t)$ from equations 402 and 405,

$$(\partial p_2(t)/\partial t) = (\Omega_2/C_2)(p_i(t)-p_2(t)) = k_2(p_i(t)-p_2(t)) \qquad (408)$$

Eliminating $q(t)$ from equations 403 and 406,

$$(q_1(t)+q_2(t))/C_i+(\partial p_i(t)/\partial t)=(\Omega_i/C_i)(p_A(t)-p_i(t))=k_i(p_A(t)-p_i(t))$$

Substituting for $q_1(t)$ and $q_2(t)$ in the above expression according to equations 407 and 408,

$$k_i(p_A(t)-p_i(t)) = (\partial p_i(t)/\partial t) + \beta_1(\partial p_1(t)/\partial t) + \beta_2(\partial p_2(t)/\partial t) \qquad (409)$$

since $\beta_1 = \frac{C_1}{C_i}$ and $\beta_2 = \frac{C_2}{C_i}$

Taking Laplace transforms:-

equation 407 becomes: $$sP_1(s) = k_1(P_i(s)-P_1(s)) \qquad (410)$$

equation 408 becomes: $$sP_2(s) = k_2(P_i(s)-P_2(s)) \qquad (411)$$

equation 409 becomes: $$k_i(P_A(s)-P_i(s))=sP_i(s) + \beta_1 sP_1(s) + \beta_2 sP_2(s) \qquad (412)$$

where s is the Laplace operator, and $P_1(s) = \mathcal{L}p_1(t)$

$$P_2(s) = \mathcal{L}p_2(t)$$
$$P_A(s) = \mathcal{L}p_A(t)$$
$$P_i(s) = \mathcal{L}p_i(t),$$

and $p_1(0) = p_2(0) = p_A(0) = p_i(0) = 0$.

Eliminating $P_1(s)$ and $P_2(s)$ from equations 410-412,

$$P_i(s)(s+k_i) = k_i P_A(s)-s\beta_1 k_1 P_i(s)/(s+k_1)-s\beta_2 k_2 P_i(s)/(s+k_2)$$

For a unit step in external or arterial tension from $p_A(t) = 0$ for $t \leq 0$ to $P_A(t) = 1$ for $t > 0$, $P_A(s) = 1/s$, when

$$sP_i(s) = \frac{k_i(s+k_1)(s+k_2)}{s^3+s^2(k_1+k_2+k_i+\beta_1 k_1+\beta_2 k_2)+s(k_i k_1+k_i k_2+k_1 k_2(1+\beta_1+\beta_2))+k_1 k_2 k_3} \quad (413)$$

If it is known experimentally that q, and hence $p_i(t)$, are the sum of a number of exponential terms, i.e.

$$p_i(t) = A_1(1-\exp(-\lambda_1 t)) + A_2(1-\exp(-\lambda_2 t)) + A_3(1-\exp(-\lambda_3 t))$$

$$\text{where} \quad A_1 + A_2 + A_3 = 1.$$

Taking Laplace transforms:-

$$sP_i(s) = \int_0^\infty e^{-st} p_i(t)dt = \left[\frac{A_1\lambda_1}{(s+\lambda_1)} + \frac{A_2\lambda_2}{(s+\lambda_2)} + \frac{A_3\lambda_3}{(s+\lambda_3)} \right] \quad (414)$$

Hence the experimental and theoretical responses have identical time constants if the denominators of equations 413 and 414 are identical, while the intercepts are also identical if the numerators are likewise. For the analysis of data in figs. 17 and 19, one is only concerned with time constants, i.e. identical characteristic equations for $P_i(s)$ in equations 413 and 414, when

$$s^3+s^2(k_1+k_2+k_i+\beta_1 k_1+\beta_2 k_2) + s(k_i k_1+k_i k_2+k_1 k_2(1+\beta_1+\beta_2)) + k_1 k_2 k_i$$

$$\equiv s^3+s^2(\lambda_1+\lambda_2+\lambda_3) + s(\lambda_1\lambda_2+\lambda_2\lambda_3+\lambda_3\lambda_1) + \lambda_1\lambda_2\lambda_3.$$

which holds if:-

$$k_1+k_2+k_i+\beta_1 k_1+\beta_2 k_2 = \lambda_1+\lambda_2+\lambda_3 \quad (415)$$

$$k_i k_1+k_i k_2+k_1 k_2(1+\beta_1+\beta_2) = \lambda_1\lambda_2+\lambda_2\lambda_3+\lambda_3\lambda_1 \quad (416)$$

and $k_1 k_2 k_i = \lambda_1\lambda_2\lambda_3$ (417)

Substituting half-saturation times for time constants, i.e. $k_1 = 0.693/T_1$, $k_2 = 0.693/T_2$, $k_i = 0.693/T_i$, $\lambda_1 = 0.693/\theta_1$, $\lambda_2 = 0.693/\theta_2$ and $\lambda_3 = 0.693/\theta_3$, equation 417 gives:-

$$T_1 T_2 T_i = \theta_1 \theta_2 \theta_3 \qquad (418)$$

equation 416 gives:-

$$\frac{T_2+T_1+T_i(1+\beta_1+\beta_2)}{T_1 T_2 T_i} = \frac{\lambda_1+\lambda_2+\lambda_3}{\lambda_1 \lambda_2 \lambda_3}$$

Eliminating denominators according to equation 418,

$$T_2+T_1+T_i(1+\beta_1+\beta_2) = \lambda_1+\lambda_2+\lambda_3 \qquad (419)$$

Substitution of half-times in equation 415, with similar elimination of denominators according to equation 418, gives:-

$$T_1T_2+T_1T_i(1+\beta_2)+T_2T_i(1+\beta_1) = \theta_1\theta_2+\theta_2\theta_3+\theta_3\theta_1 \qquad (420)$$

Equations 418-420 thus account for the perturbation terms arising by virtue of interaction between compartments.

APPENDIX V

AXIAL DIFFUSION OR CONDUCTION IN A FINITE HOLLOW CYLINDER

Introduction

Axial transfer has been ignored in the cases of radial diffusion into tissue (section 5.5) and radial conduction in the thermal analogue (section 6.5). In both cases expressions derived for an infinite hollow cylinder have been used to interpret data obtained from annular models of finite length. Moreover, no reference could be found from which it was possible to determine the errors involved as functions of the geometric parameters of the various systems.

Diffusion equation

A transient heat balance at any point in any isotropic medium gives the distribution of temperature (Θ) as:-

$$\nabla^2(\Theta) = \frac{1}{D} \left(\frac{\partial \Theta}{\partial t}\right) \qquad (501)$$

This may be expressed in cylindrical co-ordinates (r, ϕ, z) as:-

$$\frac{1}{r} \cdot \frac{\partial}{\partial r} \left(r \cdot \frac{\partial \Theta}{\partial r}\right) + \frac{1}{r^2} \left(\frac{\partial^2 \Theta}{\partial \phi^2}\right) + \left(\frac{\partial^2 \Theta}{\partial z^2}\right) = \frac{1}{D} \left(\frac{\partial \Theta}{\partial t}\right) \qquad (502)$$

For an annulus there is axial symmetry, such that

$\frac{\partial^2 \Theta}{\partial \phi^2} = 0$, when equation 502 becomes:-

$$\frac{1}{r} \cdot \frac{\partial}{\partial r} \left(r \cdot \frac{\partial \Theta}{\partial r}\right) = \frac{1}{D} \left(\frac{\partial \Theta}{\partial t}\right) - \left(\frac{\partial^2 \Theta}{\partial z^2}\right) \qquad (503)$$

Before attempting to solve these equations it is necessary to define the boundary conditions of the system.

The System

For an annulus of internal radius (a), external radius (b) and length (L), the boundaries may be expressed mathematically as:-

$$\begin{cases} a \leqslant r \leqslant b \\ o \leqslant z \leqslant L \end{cases}$$

If the convention is continued of taking the initial tension or temperature as the datum, then $\theta = 0$ for $t < 0$.

Transient conditions

For both the tissue model and thermal analogue, the ends start at the same tension or temperature as the outer boundary, the greatest discrepancies occurring when $\theta = 0$ for $t \geqslant 0$ for both $r \geqslant b$ and $0 > z > L$.

For such conditions the isotherms must be concave with respect to the axis for rising temperature throughout the annulus, or

$$\frac{\partial^2\theta}{\partial z^2} < 0 \quad \text{for} \quad \frac{\partial\theta}{\partial t} > 0.$$

This means that

$$\left(\frac{\partial^2\theta}{\partial z^2}\right) \text{ and } \left(\frac{\partial\theta}{\partial t}\right)$$

are of opposite sign such that ignoring either term in equation 503 will cause an error in estimating θ of the same sign. Thus the maximum error in neglecting axial conduction, i.e. putting $(\partial^2\theta/\partial z^2) = 0$ should occur when $(\partial\theta/\partial t) = 0$. This means that the error introduced by neglecting end effects is greatest under steady-state conditions.

$$\text{i.e.} \quad \epsilon_{tr} < \epsilon_{ss}$$

where ϵ_{tr} and ϵ_{ss} are the relevant errors calculated by steady-state and transient methods respectively.

Steady-state conditions

The most conservative assessment of the model would thus refer to steady-state conditions, when equation 503 reduces to:-

$$\frac{1}{r} \cdot \frac{\partial}{\partial r} \left(r \cdot \frac{\partial \Theta}{\partial r} \right) - \frac{\partial^2 \Theta}{\partial z^2} = 0 \qquad (504)$$

Steady-state boundary conditions may be defined as:-

$$\begin{cases} \Theta = 0 \text{ for } r \geq b \text{ and } 0 \geq z \geq L \\ \Theta = \Theta_1 \text{ for } r \leq a. \end{cases}$$

Neglect of end effects

Neglecting axial flow, $\partial^2\Theta/\partial z^2 = 0$ when equation 504 reduces to:-

$$\frac{1}{r} \cdot \frac{\partial}{\partial r} \left(r \cdot \frac{\partial \Theta}{\partial r} \right) = 0 \qquad (505)$$

from which simple integration gives the radial temperature distribution as:-

$$\Theta = \Theta_1 \log (r/b)/\log(a/b) \qquad (506)$$

No error can occur at $r = a$, or $r = b$ since these are defined boundary conditions, but would probably occur in the region of the mean temperature $(\Theta_1/2)$, which should be situated at $r = \sqrt{(ab)}$ according to equation 506.

Hence, for the purposes of comparing end effects, a discrepancy (ϵ) will be defined as the percentage deviation of the temperature, at the geometric mean radius and $z = L/2$, from that of the equivalent position in the corresponding hollow cylinder of infinite length.

$$\text{i.e.} \quad \epsilon = 100 \left(\frac{\frac{1}{2}\Theta - \Theta'}{\frac{1}{2}\Theta_1} \right) \doteq 100(1-2\Theta'/\Theta_1) \qquad (507)$$

where Θ' is the true temperature at $r = \sqrt{(ab)}$, $z = L/2$.

Exact solution for the finite cylinder

The following solution for equation (504) is given by Carslaw and Jaeger (1959e) for the boundary conditions as specified above:-

$$\Theta = \frac{2}{L} \cdot \sum_{n=1}^{n=\infty} \left(\frac{F_0[(n\pi\ r/L);(n\pi\ b/L)]}{F_1[(n\pi\ a/L);(n\pi\ b/L)]} \cdot \sin(n\pi\ z/L) \cdot \int_0^L f(z') \frac{n\pi z'}{L} \cdot dz' \right) \qquad (508)$$

where $F_0(x;y) = I_0(x) \cdot K_0(y) - K_0(x) \cdot I_0(y)$

and $F_1(x;y) = I_1(x) \cdot K_0(y) + K_1(x) \cdot I_0(y)$

where the Bessel functions I_0, I_1, K_0, K_1 are defined in accordance with standard notation (Jahnke et al, 1960).

Introducing a suitable stepwise function to accommodate dual temperature conditions at $z = 0$ and $z = L$, equation 508 becomes:-

$$\Theta = C. \sum_{n=0}^{n=\infty} \left(\frac{F_0[(2n+1)\pi\ r/L];[(2n+1)\pi\ b/L]}{F_1[(2n+1)\pi\ a/L];[(2n+1)\pi\ b/L]} \cdot \frac{\sin[(2n+1)\ z/L]}{(2n+1)} \right) \qquad (509)$$

where the constant (C) may be eliminated by imposing the boundary conditions $\Theta = \Theta_1$ for $r = a$. Hence by determining Θ' for $r = \sqrt{(ab)}$ and $z = L/2$, equation 509 gives

$$\epsilon = 100 \left[1 - 2. \frac{\sum_{n=0}^{n=\infty} \left(\frac{F_0[(2n+1)\pi\sqrt{ab}/L];[(2n+1)\pi b/L]}{F_1[(2n+1)\pi\ a/L];[(2n+1)\pi\ b/L]} \cdot \frac{\sin[(2n+1)\pi/2]}{(2n+1)} \right)}{\sum_{n=0}^{n=\infty} \left(\frac{F_0[(2n+1)\pi\ a/L];[(2n+1)\pi\ b/L]}{F_1[(2n+1)\pi\ a/L];[(2n+1)\pi\ b/L]} \cdot \frac{\sin[(2n+1)\pi/2]}{(2n+1)} \right)} \right] \% \qquad (510)$$

However solutions of this equation for $(\pi a/L) = 0.05$ give negative values of ϵ for $(\pi\ b/L)$ in the range 0.11 to 0.19. This is illustrated in fig. 45.

Now it is impossible for ϵ to be negative since this would imply the flow of heat axially in a direction contrary to the temperature gradient.

Upon checking the Carslaw and Jaeger equation (508), the term $F_1[(n\ \pi\ a/L);(n\ \pi\ b/L)]$ would not seem to correspond to zero amplitude at $z = 0$ and $z = L$, for each term contributing to the Fourier series. The true solution would therefore need to replace the above term by $F_o[(n\ \pi\ a/L);(n\pi\ b/L)]$, giving a general expression for Θ as:-

$$\Theta = C'.\ \sum_{n=0}^{n=\infty}\left(\frac{F_o\left[\left[(2n+1)\pi\ r/L\right];\left[(2n+1)\pi\ b/L\right]\right]\sin\left[(2n+1)\pi\ z/L\right]}{F_o\left[\left[(2n+1)\pi\ a/L\right];\left[(2n+1)\pi\ b/L\right]\right]\quad(2n+1)}\right) \qquad (511)$$

The writer approached Professor Jaeger who replied (Jaeger, 1965) stating that there was a printing error in his book and F_1 should read F_o.

Imposing the boundary conditions $\Theta = \Theta_1$ in the revised equation (511) for $r = a$ and $z = L/2$,

$$\Theta_1 = C' \sum_{n=0}^{n=\infty} \frac{\sin\left[(2n+1)\pi/2\right]}{(2n+1)} = \frac{\pi}{4} \cdot C'$$

Thus with $C' = \frac{4}{\pi} \cdot \Theta_1$, and determining Θ' for $r = \sqrt{(ab)}$ and $z = L/2$, equation (507) gives:-

$$\epsilon = 100.\left[1 - \frac{8}{\pi} \cdot \Sigma(0 \text{ to } \infty)\right] \qquad (512)$$

where

$$\Sigma\left[0 \text{ to } \infty\right] = \sum_{n=0}^{n=\infty}\left(\frac{F_o\left[\left[(2n+1)\pi\sqrt{(ab)}/L\right];\left[(2n+1)\pi\ b/L\right]\right]\sin\left[(2n+1)\pi/2\right]}{F_o\left[\left[(2n+1)\pi\ a/L\right];\left[(2n+1)\pi\ b/L\right].\right](2n+1)}\right)$$

Determination of ϵ from this equation for π a/L = 0.05 and π b/L in the range 0 - 0.32 gave no negative values as illustrated in fig.45. Equation (512) may thus be taken as the correct solution to equation 504.

Practical values

For the thermal analogue (section 6.5),

a = 0.5 ins.

2b = 5.29 ins.

L = 10 ins.

i.e. πa/L = 0.157 and πb/L = 1.66 when equation 512 gives ϵ < 0.10%.

Since the transient error should be no greater, there would seem to be negligible error introduced into the thermal analogue by neglecting end effects.

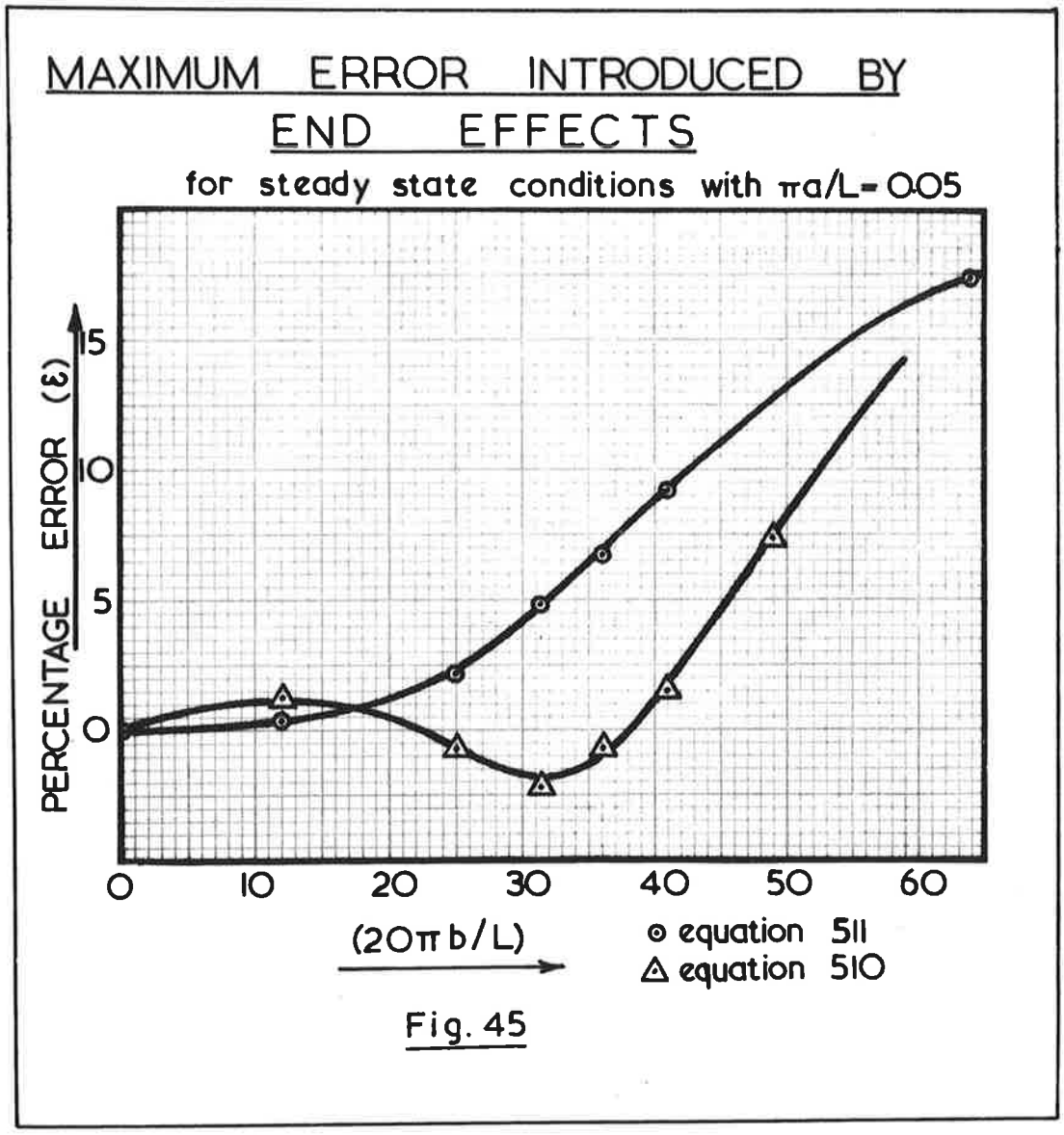

MAXIMUM ERROR INTRODUCED BY
END EFFECTS
for steady state conditions with πa/L = 0.05
PERCENTAGE ERROR (ε)
15
10
5
0
0
10
20
30
40
50
60
(20π b/L)
⊙ equation 511
△ equation 510

Fig. 45

BIBLIOGRAPHY

Abbot, B.C. and Lowy, J. (1958), J. Physiol., 141, 385.

Abelson, P.H. and Durjee, W.R. (1949), Biol. Bull., 96, 205.

Adam, N.K. (1930), "The Physics and Chemistry of Surfaces", 1st ed., p.3, pub. Oxford.

Aksnes, E.G. and Rahn, H. (1957), J. Appl. Physiol., 10, 174.

Albano, G. (1960), Premier Colloque International de Médecine Sub-acquatique, Cannes.

Albano, G. (1962), Med. del Sport, 2, 57.

Albritton, E.C. (1952), "Standard Values in Blood", p.120, pub. Phil..

Allan, J.H. (1945), J. Aviat. Med., 16, 235.

Altman, P.L. and Dittmer, D.S. (1964), "Biology Data Book", p. 402-3, pub. Fed. Amer. Soc. Exp. Biol..

Anderson, J.S. and Saddington, K. (1949), J. Chem. Soc., suppl. 2, S381.

Anthony, R.A., Clarke, R.W., Liberman, A., Nims, L.F., Tepperman, J. and Wesley, S.M. (1943a), U.S. NRC, C.A.M. rep. 143.

Anthony, R.A., Clarke, R.W., Liberman, A., Nims, L.F., Tepperman, J. and Wesley, S.M. (1943b), U.S. NRC, C.A.M. rep. 136.

Armstrong, H.G. (1939), "Principles and Practice of Aviation Medicine", p.496, pub. Williams and Wilkins (Balt.).

Arnold, J.H. (1930), J. Amer. Chem. Soc., 52, 3937.

Asmussen, E. and Nielsen, M. (1952), Acta Physiol. Scand., 27, 217.

Barcroft, H. (1963), "Handbook of Physiology", Sect II, vol. 2, ch.40, pub. Amer. Physiol. Soc..

Barlow, T.E., Haigh, A.L. and Walder, D.N. (1959), J. Physiol., 149, 18.

Barlow, T.E., Haigh, A.L. and Walder, D.N. (1961), Clin. Sci., 20, 367.

Bateman, J.B. (1951), "Decompression Sickness", ch. 9 (pt. I), ed. Fulton, J.F., pub. Saunders (Phil.).

Bateman, J.B. and Lang, J. (1945), Canad. J. Res., E23, 22.

Bazett, H.C. (1941), "Physiology in Modern Medicine", 8th ed., p.299, ed. Bard, P., pub. Mosby.

Bean, J.W. (1945), Physiol. Rev., 25, 1.

Becker, R., and Doering, W. (1935), Ann. Physik, 24, 719.

Behnke, A.R., Thomson, R.M. and Shaw, L.A. (1935a), Amer. J. Physiol., 114, 137.

Behnke, A.R., Thomson, R.M. and Motley, E.P. (1935b), Amer. J. Physiol., 112, 554.

Behnke, A.R., Shaw, L.A., Messer, A.C. Thomson, R.M. and Motley, E.P. (1936), Amer. J. Physiol., 114, 526.

Behnke, A.R. (1937), Nav. Med. Bull. (Wash.), 35, 219.

Behnke, A.R. and Shaw, L.A. (1937), Nav. Med. Bull. (Wash.), 35, 61.

Behnke, A.R. and Willmon, T.L. (1939), Nav. Med. Bull. (Wash.), 37, 629.

Behnke, A.R., Feen, B.G, and Willmon, T.L. (1940), U.S. NRC C.A.M. rep.3.

Behnke, A.R. and Willmon, T.L. (1941a), Amer. J. Physiol., 131, 627.

Behnke, A.R. and Willmon, T.L. (1941b), Amer. J. Physiol., 131, 619.

Behnke, A.R. (1942a), Med. Clin. N. Amer., 26, 1213.

Behnke, A.R. (1942b), Milit. Surg., 90, 9.

Behnke, A.R., Feen, B.G. and Welham, W.C. (1942), J.A.M.A., 118, 495.

Behnke, A.R. (1945), Medicine (Balt.), 24, 381.

Behnke, A.R. (1951), "Decompression Sickness", ch. 3, ed. Fulton, J.F., pub. Saunders (Phil.).

Behnke, A.R., Osserman, E.F. and Welham, W.W. (1953), A.M.A. Arch. Int. M., 91, 585.

Berg, W.E., Baumberger, J.P., Crescitelli, F., Rapaport, S. and Greeley, P.O. (1943), U.S. NRC C.A.M. rep. 173.

Berg, W.E., Harris, M., Whitaker, D.M. and Twitty, V.C. (1945), J. Gen. Physiol., 28, 253.

Bert, P. (1878), "Barometric Pressure-Researches in Experimental Physiology", ed. Hitchcock, M.A. and Hitchcock, F.A. (1943), pub. Columbus.

Berthelot, M. (1850), Ann. Chim (Phys.), 30, 232.

Blake, F.G. (1949), Harvard U. Acoust. Res. Lab. Tech. Memo. 12.

Blankenhorn, M.A., Ferris, E.B., Romano, J., Ryder, H.W., Engel, G.L., Webb, J.P., Safer, L.A. and Stevens C.D. (1942), U.S. NRC, C.A.M. rep. 6.

Blankenhorn, M.A. and Ferris, E.B. (1944), Trans. Ass. Am. Phys., 58, 86.

Blinks, L.R., Twitty, V.C. and Whitaker, D.M. (1951), "Decompression Sickness", ch. 5 (pt.II), ed. Fulton, J.F., pub. Saunders (Phil.)

Blum, J.J. (1960), Amer. J. Physiol., 198, 991.

Bogert, B.P. (1951), J. Maths. and Physics, 30, 102.

Boothby, W.M., Lovelace, W.R. and Benson, O.O. (1940), J. Aero. Soc. Amer., 7, 1.

Bornstein, A. (1910), Berl. klin. Wschr., 47, 1275.

Bornstein, A. and Plate, E. (1911), Fortschr. Röntgenstr., 18, 197.

Boycott, A.E., Damant, G.C.C. and Haldane, J.S. (1908a), J. Hyg. Camb., 8, 342.

Boycott, A.E. and Damant, G.C.C. (1908b), J. Hyg. Camb., 8, 445.

Boyle, R (1670), Phil. Trans., 5, 2011.

Bozler, E. (1957), "Tissue Elasticity", ed. Remington, J.W., pub. Amer. Physiol. Soc..

Bridge, E.V., Henry, F.M., Cook, S.F., Williams, O.L., Lyons, W.R. and Lawrence, J.A. (1944), J. Aviat. Med., 15, 316.

Briggs, L. (1952), J. Appl. Physics, 23, 931.

Burton, A.C. (1954), Physiol. Rev., 34, 619.

Campbell, J.A. (1924), J. Physiol., 59, 1.

Campbell, J.A. (1929), J. Physiol., 68, 81.

Campbell, J.A. and Hill, L. (1931), J. Physiol., 71, 309.

Campbell, J.A. and Hill, L. (1933), Quart. J. Exp. Physiol., 23, 197 and 219.

Cander, L. and Forster, R.E. (1959), J. Appl. Physiol., 14, 541.

Carslaw, H.S. and Jaeger, J.C. (1959a), "Conduction of Heat in Solids", p.332-4, pub. Oxford.

Carslaw, H.S. and Jaeger, J.C. (1959b), ibid., p. 336-8.

Carslaw, H.S. and Jaeger, J.C. (1959c), ibid., p. 348.

Carslaw, H.S. and Jaeger, J.C. (1959d), ibid., p. 234.

Carslaw, H.S. and Jaeger, J.C. (1959e), ibid., p. 220.

Catchpole, H.R. and Gersh, I., (1946), J. Cell. Comp. Physiol., 27, 15 and 27.

Catsaras, M. (1890), refer Gray (1951).

Chase, W.H. (1934), Surg. Gynec. Obstet., 59, 569.

Chidsey, C.A. Fritts, H.W., Hardewig, A., Richards, D.W. and Cournand, A. (1959), J. Appl. Physiol., 14, 63.

Chinard, F.P., Enns, T. and Nolan, M.F. (1962), J. Appl. Physiol., 17, 179.

Clare, N.D. (1925), Trans. Roy. Soc. Can., 19, 32.

Clarke, R.W., Hamm, F.D. and Nims, L.F. (1945), U.S. NRC, C.A.M. rep. 472.

Conn, H.L. and Robertson, J.S. (1955), Amer. J. Physiol., 181, 319.

Cook, S.F. (1944a), U.S. NRC C.A.M. rep. 295.

Cook, S.F., Williams, O.L., Lyons, W.R. and Lawrence, J.H. (1944b), U.S. NRC, C.A.M. rep. 245.

Cook, S.F., Williams, O.L., Lyons, W.R. and Lawrence, J.H., (1944c), War Med., 6, 182.

Cook, S.F. (1951), "Decompression Sickness", ch. 8 (pt.II), ed. Fulton, J.F., pub. Saunders (Phil.).

de Coppet, L. (1911), Ann. Chim. Phys., 10, 457.

Coryllos, P.N. and Birnbaum, G.L. (1932), Amer. J. Med. Sci., 183, 326.

Coulson, J.M. and Richardson, J.F. (1957), "Chemical Engineering", vol. 1, p.52, pub. Pergammon.

Crank, J. (1956), "Mathematics of Diffusion", p.326, pub. Oxford.

Crellin, R.Q., Crocker, W.E. and Hollis, H. (1954), R.N. rep. RNP 54/791, U.P.S. 141.

Crocker, W.E., Davidson, W.M. and Goodenough, F.C. (1951), R.N. rep. R.N.P. 509628, U.P.S. 118.

Crocker, W.E. and Taylor, H.J. (1952), pt. B, R.N. rep. R.N.P. 52/705, U.P.S. 131.

Crocker, W.E. (1957), R.N. rep. R.N.P. 58/902, U.P.S. 171.

Crocker, W.E. and Hempleman, H.V. (1957), R.N. rep. RNP 57/887, U.P.S. 163.

Crump, S.F. (1949), David Taylor Model Basin. rep. 575.

Daly, de B. (1941), R.A.F. FPRC rep. 238.

Danielli, J.F. (1935), J. Cell. Comp. Physiol., 7, 393.

Darling, R.C., Cournand, A. and Richards, D.W. (1944), J. Clin. Invest., 23, 55.

Davidson, W.M. and Taylor, H.J. (1952), R.N. rep. RNP 52/705, U.P.S. 130.

Davidson, W.M., Sutton, B.M. and Taylor, H.J. (1950), R.N. rep. R.N.P. 50/582, U.P.S. 110.

Davies, J.T. and Rideal, E.K. (1963), "Interfacial Phenomena", 2nd ed., p.33, pub. Acad. Press.

Davies, P.W. and Bronk, D.W. (1957), Fed. Proc. Amer. Physiol. Soc., 16, 689.

Davson, H. (1964a), "A Textbook of General Physiology", 3rd ed., p.185, pub. Churchill (Lond.).

Davson, H. (1964b), ibid., p.329-331.

Davson, H. (1964c), ibid., p.413-5.

Dawson, J.A. (1929), Biol. Bull., 56, 80.

Dean, R.B. (1944), J. Appl. Physics, 15, 446.

Degner, E.A., Ikels, K.G. and Allen, T.H. (1965), Aerospace Med., 36, 418.

Dick, D.A.T. (1959), Exp. Cell. Res., 17, 5.

Dieter, E. (1954), Pflugers Arch, ges Physiol., 258, 470.

Dixon, H.H. (1914a), Proc. Roy. Soc. Dublin, NS 14, 229.

Dixon, H.H. (1914b), "Transpiration and the Ascent of Sap in Trees", pub. Macmillan (Lond.).

Dobson, E.L. and Warner, G.F. (1957), Amer. J. Physiol., 189, 269.

Dobson, E.L. and Warner, G.F. (1960), "Methods in Medical Research", 8, 248, ed. Bruner, H.D., pub. Year Book Publishers (Chic.).

Donald, K.W. (1954), J. Appl. Physiol., 7, 639.

Duffner, G.J., Van der Aue, O.E. and Behnke, A.R. (1946), U.S.N. Exp. Div. Unit, proj. X-443, rep 3.

Duffner, G.J., Snyder, J.F. and Smith, L.L. (1959), U.S.N. Exp. Div. Unit, proj. NS186, rep 3-59.

Dwyer, J.V. (1956), U.S.N. Exp. Div. Unit, proj. NS185-005, subtask 5.

Eggleton, P., Elsden, S.R., Fegler, J. and Hebb, C.O. (1945), J. Physiol., 104, 129.

Eisenberg, P. (1961), "Handbook of Fluid Dynamics", sect. 12, ed. Streeter, V.L., pub. McGraw-Hill.

Engel, G.L., Romano, J., Webb, J.P., Ferris, E.B., Ryder, H.W. and Blankenhorn, M.A. (1944), U.S. NRC, C.A.M. rep. 263.

Epstein, P.S. and Plesset, M.S. (1950), J. Chem. Phys., 18, 1505.

Evans, N.T.S. and Naylor, P.F.D. (1964), Phys. Med. Biol., 9, 43.

Evelyn, K. (1941), Canada NRC, Proc. 9th Meet. Aviat. Med. Res., App. A.

Eyring, H. (1936), J. Phys. Chem., 4, 238.

Fahri, L.E. (1963), "Handbook of Physiology", Sect. 3, vol. 1, ch.34, pub. Amer. Physiol. Soc..

Farncombe, F.J. (1925), Trans. Roy. Soc. Canada, 19, 32.

Fenichel, I.R. and Horowitz, S.B. (1963), Acta Physiol. Scand., 60, suppl. 221.

Ferris, E.B., Molle, W.E. and Ryder, H.W. (1942), U.S. NRC, C.A.M. rep. 60.

Ferris, E.B., Webb, J.P., Ryder, H.W., Engel, G.L., Romano, J. and Blankenhorn, M.A. (1943a), U.S. NRC, C.A.M. rep. 121.

Ferris, E.B., Webb, J.P., Ryder, H.W., Engel, G.L., Romano, J. and Blankenhorn, M.A. (1943b), U.S. NRC, C.A.M. rep. 132.

Ferris, E.B., Webb, J.P., Engel, G.L. and Brown, E.W. (1944), U.S. NRC, C.A.M. rep. 363.

Ferris, E.B. and Engel, G.L. (1951), "Decompression Sickness", ch.2, pub. Saunders (Phil.).

Forster, R.E. (1963), "Handbook of Physiology", sect. 3, vol. 2, ch.33, pub. Amer. Physiol. Soc.

Forster, R.E. (1964), "The Uptake and Distribution of Anesthetic Agents," ed. Papper, E.M. and Kitz, R.J., pub. McGraw-Hill.

Fox, F.E. and Herzfeld, K.E. (1954), J. Acous. Soc. Amer., 26, 984.

Fraser, A.M. (1942), Canada NRC, Comm. Aviat. Med. Res., 15th Meet., App. J.

Fraser, A.M. (1943), Canada NRC, Comm. Aviat. Med. Res., R.C.A.F. Training Sch. Unit 2.

Frenkel, J. (1939), J. Chem. Physics, 7, 208.

Fryer, D.I. (1962), "Physiological Requirements for Protection against Atmospheric Pressure Changes", issued R.A.F. Inst. Aviat. Med. (Farnborough).

Fürth, R. (1941), Proc. Camb. Phil. Soc., 37, 252.

Galloway, W. (1954), J. Acous. Soc. Amer., 26, 849.

Geigy (1954), "Scientific Tables", 6th ed., ed. Dien, K., pub. Geigy Pharmaceuticals (Sydney).

Gellhorn, A., Merrell, M. and Rankin, R.M. (1944), Amer. J. Physiol. 142, 407.

Gersh, I. (1944), Hawkinson, G.E. and Rathbun, E.N. (1944), J. Cell. Comp. Physiol., 24, 35.

Gersh, I., Hawkinson, G.E. and Jenney, E.H. (1945a), J. Cell. Comp. Physiol., 26, 63.

Gersh, I. (1945b), J. Cell. Comp. Physiol., 26, 101.

Gersh, I. and Still, M. (1945c), J. Exp. Med., 81, 219.

Gersh, I. and Catchpole, H.R. (1946a), J. Cell. Comp. Physiol., 28, 253.

Gersh, I. (1946b), J. Cell. Comp. Physiol., 28, 271.

Gersh, I. and Catchpole, H.R. (1951), "Decompression Sickness", ch.6, ed. Fulton, J.F., pub. Saunders (Phil.).

Gessell, R. (1923), Amer. J. Physiol., 66, 5.

Glasstone, S. (1954), "A Textbook of Physical Chemistry", 2nd ed., p.485, pub. Macmillan (Lond.).

Goldstein, S. (1932), Proc. Lond. Math. Soc., 34, 51.

Goodman, M.W. (1961), U.S.N. Med. Res. Lab. 20, No. 22, rep. 368.

Goodman, M.W. and Workman, R.D. (1966), U.S.N. Buships proj. SF 0110605, task 11513-2, rep. 5-65.

Gouze, F.J. (1944), Nav. Med. Bull. (Wash.), 42, 578.

Gray, J.S. (1942), U.S. NRC, C.A.M. rep. 123.

Gray, J.S. (1943a), U.S. NRC, C.A.M. rep. 168.

Gray, J.S. (1943b), U.S. NRC, C.A.M. rep. 169.

Gray, J.S. (1944a), refer Cook (1951).

Gray, J.S. (1944b), U.S. NRC, C.A.M. rep. 260.

Gray, J.S. (1944c), U.S. NRC, C.A.M. rep. 258.

Gray, J.S. Masland, R.L. and Mahady, S.C.F. (1945), U.S. AAF, Sch. Aviat. Med., proj. 409, rep. 1.

Gray, J.S. (1951), "Decompression Sickness", ch. 7, ed. Fulton, J.F pub. Saunders (Phil.).

Gray, M.C. (1924), Proc. Roy. Soc. Edin., 45, 230.

Guyton, A.C. (1963a), Circ. Res., 12, 399.

Guyton, A.C. (1963b), "Medical Physiology", p.52, pub. Saunders (Phil.).

Haggard, H.W. (1924), J. Biol. Chem., 59, 737.

Haldane, J.S. and Priestley, J.G. (1935a), "Respiration", 2nd ed., p.337, pub. Oxford.

Haldane, J.S. and Priestley, J.G. (1935b), ibid., p.339.

Hallock, P. and Benson, I.C. (1937), J. Clin. Invest., 16, 595.

Harkins, B. and Brown, F.E. (1919), J. Amer. Chem. Soc., 41, 449.

Haring, M.M. and Van den Bosche, E.G. (1929), J. Phys. Chem., 33, 161.

Harris, M., Berg, W.E., Whitaker, D.M. Twitty, V.C. and Blinks, L.R. (1945a), J. Gen. Physiol., 28, 225.

Harris, M., Berg, W.E., Whitaker, D.M. Twitty, V.C. and Blinks, L.R. (1945b), J. Gen. Physiol., 28, 241.

Harris, M., Berg, W.E., Whitaker, D.M. and Twitty, V.C. (1945c), J. Gen. Physiol., 28, 253.

Harris, E.J. and Burn, G.P. (1949), Trans. Farad. Soc., 45, 508.

Harvey, E.N., Barnes, D.K., McElroy, W.D., Whiteley, A.H., Pease, D.C. and Cooper, K.W. (1944a), J. Cell. Comp. Physiol., 24, 1.

Harvey, E.N., Whiteley, A.H., McElroy, W.D., Pease, D.C. and Barnes, D.K. (1944b), J. Cell. Comp. Physiol., 24, 23.

Harvey, E.N. Mc.Elroy, W.D., Whiteley, A.H., Warren, G.H. and Pease, D.C. (1944c), J. Cell. Comp. Physiol., 24, 117.

Harvey, E.N. (1945), Bull. N.Y. Acad. Med., 21, 505.

Harvey, E.N. Mc. Elroy, W.D. and Whiteley, A.H. (1947), J. Appl. Physics, 18, 162.

Harvey, E.N. (1951a), "Decompression Sickness", ch. 4, ed. Fulton, J.S., pub. Saunders (Phil.).

Harvey, E.M. (1951b), "Decompression Sickness", ch. 5, (pt.I), ed. Fulton, J.F., pub. Saunders (Phil.).

Hawkins, J.A., Shilling, C.W. and Hansen, R.A. (1935), Nav. Med. Bull., 33, 327.

Haymaker, W. (1957), "Handbuch der Speziellen Pathologischen Anatomie und Histologie", vol.1, p.1600, pub. Springer-Verlag (Berlin).

Heller, R., Mager, W. and von Schrotter, H. (1900), "Luftdruckerkrankungen", pub. Hölder (Vienna).

Hempleman, H.V. (1952), R.N. rep. RNP. 52/705, U.P.S. 131.

Hempleman, H.V. (1957), R.N. rep. RNP. 57/896, U.P.S. 168.

Hempleman, H.V. (1960), R.N. rep. RNP. 62/1019, U.P.S. 195.

Hempleman, H.V. (1961), R.N. rep. RNP. 62/1020, U.P.S. 202.

Hempleman, H.V. (1962), Proc. 2nd World Congress Underwater Activities (Lond.), p.60.

Henry, F.M. (1943a), U.S. NRC, C.A.M. rep. 176.

Henry, F.M., Jones, H.B., Mohney, J.B. and Tobias, A.A. (1943b), U.S. NRC, C.A.M. rep. 264.

Henry, F.M., Cook, S.F., Strajman, E. and Lund, D.W. (1944), U.S. NRC, C.A.M. rep. 384.

Henry, F.M., Cook, S.F., Lawrence, J.H. and Lund, D.W. (1945a), U.S. NRC, C.A.M. rep. 446.

Henry, F.M. (1945b), U.S. NRC, C.A.M. rep. 460.

Henry, F.M. (1945c), Amer. J. Physiol., 145, 279.

Henry, F.M. (1946), J. Aviat. Med., 17, 28.

Henry, F.M. and Ivy, A.C. (1951), "Decompression Sickness", ch.10, ed. Fulton, J.F., pub. Saunders (Phil.).

Hill, L. and Greenwood, M. (1905), Proc. Roy. Soc., B, 77, 442.

Hill, L. and Greenwood, M. (1910), J. Physiol., 39, 23.

Hill, L. (1912), "Caisson Sickness and the Physiology of Work in Compressed Air", pub. Arnold (Lond.).

Hill, A.V. (1928), Proc. Roy. Soc., B, 104, 39.

Hills, B.A. (1962), J.O.C.C.A., 45, 251.

Hills, B.A. (1965), Australian patent application 48304.

Hitchcock, F.A. (1951), "Decompression Sickness", ch. 12, ed. Fulton, J.F., pub. Saunders (Phil.).

Hodes, R. and Larrabee, M.G. (1946), Amer. J. Physiol., 147, 603.

Hoff, C.A. (1948), "A Bibliographical Sourcebook of Compressed Air, Diving and Submarine Medicine", pub. U.S. Govt. Print. Off. (Wash.).

Holmgren, A., Jonsson, B. and Sjostrand, T. (1960), Acta Physiol. Scand., 49, 343.

Hoppe-Seyler, F. (1857), Arch. Anat. Physiol., 24, 63.

Horstmann, E. (1960), "Structure and Function of the Cerebral Cortex", ed. Tower, D.B. and Schadé, J.P., pub. Elsevier (Amsterdam).

Houston, C.S. (1946), U.S.N. proj. X-270, rep. 2.

Hyman, C., Rosell, S., Rosen, A., Sonnenschein, R.R. and Unvas, B. (1959), Acta Physiol. Scand., 46, 358.

Ikels, K.G. (1964), U.S.A.F. Aerospace Med. Div., rep. SAM-TDR-64-28.

Ingvar, D.G. and Lassen, N.A. (1962), Acta Physiol. Scand., 54, 325.

Inman, V.T. and Saunders, J.B. (1944), J. Nerv. Ment. Dis., 99, 660.

International Commission on Radiology (1955), Brit. J. Radiol., suppl.6.

International Critical Tables, 3, 259.

Jaeger, J.C. (1956), J. Math. Physics, 34, 316.

Jahnke, E., Emde, F. and Lösch, F. (1960), "Tables of Higher Functions", 6th ed., pub. McGraw-Hill.

Japp, H. (1909), Trans. Amer. Soc. Civil Eng., 65, 1.

Jenērus, R., Lundin, G. and Thomson, D. (1963), Acta Physiol. Scand., 59, 390.

Johansson, B., Linder, E. and Seeman, T. (1964), Acta Physiol. Scand., 62, 263.

Johnson, J.A., Cavert, H.M. and Lifson, N. (1952), Amer. J. Physiol., 121, 687.

Johnson, S. (1964), Circ. Res., 15, suppl. 1.

Jones, H.B., Tobias, C., Loomis, W.F., Mohney, J.B., Sears, W.N., Larkin, J.C., Hamilton, J.G. and Lawrence, J.H. (1942), U.S. NRC, C.A.M. rep. 81.

Jones, H.B. (1945a), U.S. NRC, C.A.M. rep. 491.

Jones, H.B., Myers, E.H. and Berg, W.E. (1945b), U.S. NRC, C.A.M. rep. 429.

Jones, H.B. (1951), "Decompression Sickness", ch.9 (pt.II), ed. Fulton, J.F., pub. Saunders (Phil.).

Karpovich, P.V. (1943), U.S. NRC, C.A.M. rep. 217.

Keays, F.L. (1909), Cornell Univ. Med. Coll., 2, 1.

Kedem, O. and Essig, A. (1965), J. Gen. Physiol., 48, 1047.

Keele, C.A. and Neil, E. (1965), "Samson Wright's Applied Physiology", 11th ed., pub. Oxford.

Kenrick, F.B., Gilbert, C.S. and Wismer, K.L. (1924a), J. Phys. Chem., 28, 1297.

Kenrick, F.B., Wismer, K.L. and Wyatt, K.S. (1924b), J. Phys. Chem., 28, 1308.

Kety, S.S. and Schmidt, C.F. (1945), Amer. J. Physiol., 143, 53.

Kety, S.S. (1951), Pharm. Rev., 3, 1.

Kety, S.S. (1960), "Methods in Medical Research", vol.8, p.228, ed. Bruner, H.D., pub. Year Book Publishers (Chic.).

Kety, S.S. (1963), "Selective Vulnerability of the Brain in Hypoxaemia", p.21, ed. Schade, J.P. and Mc.Menemy, W.H., pub. Blackwell (Oxford).

Keys, A. and Brozec, J. (1953), Physiol. Rev., 33, 245.

Kopac, M.J. (1940), Proc. Cold Spr. Harb. Symp., 8, 154.

Krogh, A. (1918a), J. Physiol., 52, 391.

Krogh, A. (1918b), J. Physiol., 52, 457.

Lambertsen, C.J., Kough, R.H., Cooper, D.Y., Emmel, G.H., Loeschke, H.H. and Schmidt, C.F. (1953), J. Physiol., 5, 471.

Lambertsen, C.J. and Owen, S.G. (1960), "Methods in Medical Research", vol.8, p.262, ed. Bruner, H.D., pub. Amer. Physiol. Soc..

Landis, E. and Pappenheimer, J.R. (1963), "Handbook of Physiology", Sect.II, vol.2, ch.29, pub. Amer. Physiol. Soc..

Lassen, N.A. and Munck, O. (1954), Acta Physiol. Scand., 33, 30.

Lassen, N.A. and Klee, A. (1965), Circ. Res., 16, 26.

Lategola, M.T. (1964), J. Appl. Physiol., 19, 322.

Lawrence, J.H. and Hamilton, J.G. (1945), U.S. OSRD-NRDC, Contract OEM cmr-196, rep. 25.

Lawton, R.W. (1954), Circ. Res., 2, 344.

LeMessurier, D.H. and Baxter, R. (1964), Med. J. Austral., 1, 188.

LeMessurier, D.H. and Hills, B.A. (1965), Hvralradets Skrifter, 48, 54.

Lennard-Jones, J. (1937), Physica, 4, 491.

Levy, E. (1922), U.S. Bureau of Mines, Tech. Paper 285, pub. Govt. Print. Off. (Wash.).

Lewis, G.N. and Randall, M. (1923), "Thermodynamics and Free Energy of Chemical Substances", pub. McGraw-Hill.

Leyden, E. (1879), Arch. Psychiat. Nervenkr., 9, 316.

Lieberman, L. (1957), J. Appl. Physics, 28, 2.

Lierse, W. (1961), Z. Zellforch., 54, 199.

Lilienthal, J.L., Riley, R.L., Proemmel, D.D. and Franke, R.E. (1946), Amer. J. Physiol., 147, 199.

Littleton, A. (1855), refer Hoff (1948).

Low, B.B. (1955), "Strength of Materials", 2nd ed., p.165, pub. Longman (Lond.).

Lund, D.W., Lawrence, J.H. and Lawrence, L.B. (1945), U.S. NRC, C.A.M. rep. 404.

Lundin, G. (1953), Acta Physiol. Scand., 30, suppl. 107.

Macfarlane, W.V. (1965), "Studies in Physiology", p.191-9, ed. Curtis, D.R. and Mc.Intyre, A.K., pub. Springer-Verlag (Berlin).

Mc.Cabe, W.L. and Smith, J.C. (1956), "Unit Operations in Chemical Engineering", pub. McGraw-Hill.

McCance, R.A. and Widdowson, E.M. (1951a), Proc. Roy. Soc., B, 138, 115.

Mc.Cance, R.A. and Widdowson, E.M. (1951b), Brit. Med. Bull., 7, 297

Mc.Donald, D.A. (1960), "Blood Flow in Arteries", pub. Arnold (Lond.

Mc.Elroy, W.D., Whiteley, A.H., Warren, G.H. and Harvey, E.N. (1944a J. Cell. Comp. Physiol., 24, 133.

Mc.Elroy, W.D., Whiteley, A.H., Cooper, K.W., Pease, D.C., Warren, G.H. and Harvey, E.N. (1944b), J. Cell. Comp. Physiol., 24, 273.

Mc.Masters, P.D. and Parsons, R.J. (1939)., J. Exp. Med., 69, 247.

Manery, J.F. and Hastings, A.B. (1939), J. Biol. Chem., 127, 657.

Mapleson, W.W. (1963), J. Appl. Physiol., 18, 197.

Marotta, S.F., Marbarger, J.P., Anderson, N., Hansen, J., and Kadetz, W. (1961), Aerospace Med., 32, 289.

Masland, R.L. (1943), U.S. NRC, C.A.M. rep. 179.

Maximow, A.A. and Bloom, W. (1948a), "A Textbook of Histology", 5th ed., p.63-73, pub. Saunders (Phil.).

Maximow, A.A. and Bloom, W. (1948b), ibid., p.191-201.

Maximow, A.A. and Bloom, W. (1948c), ibid., p.257-269.

Mayerson, H.S. (1963), "Handbook of Physiology", sect.II, vol.2, ch.30, pub. Amer. Physiol. Soc..

Mellander, S. (1960), Acta Physiol. Scand., 50, suppl. 176.

Meyer, J. (1911), Z. Electrochem., 17, 743.

Miers, H. (1927), J. Inst. Met., 37, 331.

Miers, H.A. and Isaac, F. (1906), J. Chem. Soc., 89, 413.

Miers, H.A. and Isaac, F. (1907), Proc. Roy. Soc., A, 79, 322.

Miers, H.A. and Isaac, F. (1908), J. Chem. Soc., 93, 927.

Miles, S. (1960), R.N. rep. R.N.P. 60/995, U.P.S. 184.

Miles, S. (1962), "Underwater Medicine", pub. Staples (Lond.).

Molumphy, G.G. (1950), U.S.N. Exp. Div. Unit, proj. NS 186-201, sub-task 4, rep. 7-50.

Montgomery, H. (1957), Fed. Proc. Amer. Physiol. Soc., 16, 697.

Morales, M.F. and Smith, R.E. (1944), Bull. Math. Biophys., 6, 141.

Morales, M.F. and Smith, R.E. (1945a), ibid., 7, 47.

Morales, M.F. and Smith, R.E. (1945b), ibid., 7, 99.

Morales, M.F. and Smith, R.E. (1948), ibid., 10, 191.

Motley, H.L., Chinn, H.I. and Odell, F.A. (1945), J. Aviat. Med., 16, 210.

Moulten, C.R. (1920), J. Biol. Chem., 43, 67.

Muller-Girard, O. (1955), Proc. A.S.M.E. Semi-ann. Meet., pap. 54-SA-29.

Newman, F.H. and Searl, V.H.L. (1957), "The General Properties of Matter", 5th ed., p.431, pub. Arnold (Lond.).

Nims, L.F. (1951), "Decompression Sickness", ch.8 (pt.I), ed. Fulton, J.F., pub. Saunders (Phil.).

Noltingk, B.E. and Neppiras, E.A. (1950), Proc. Roy. Soc., B, 63, 674 and 1032.

Osserman, E.F., Pitts, G.C., Welham, W.C. and Behnke, A.R. (1950), J. Appl. Physiol., 2, 633.

Ostwald, W. (1911), Z. Physic. Chem., 22, 148.

Pappenheimer, J.R. (1940), J. Physiol., 99, 182.

Pease, D.C. and Blinks, L.R. (1947), J. Phys. Coll. Chem., 51, 556.

Pellegrini, L. (1962), Proc. 2nd World Congr. Underwater Activities (Lond.), p.133.

Perl, W., Rackow, H., Salanitre, E., Wolf, G.L. and Epstein, R.M. (1965), J. Appl. Physiol., 20, 621.

Perry, J. (1950), "Chemical Engineer's Handbook," 3rd ed., pub. McGraw-Hill.

Persoff, D.A. (1960), J. Physiol., 152, 354.

Peters, J.P. and Van Slyke, D.D. (1932), "Quantitative Clinical Chemistry", pub. Williams and Wilkins (Balt.).

Piccard, J. (1941), Proc. Mayo Clin., 16, 700.

Piper, J. (1963a), "Handbook of Physiology", sect.III, vol.2, p.1209, pub. Amer. Physiol. Soc..

Piper, J. (1963b), Amer. J. Physiol., 205, 1005.

Pittinger, C.B., Featherstone, R.M., Stickley, E., Levy, L. and Cullen, S.C. (1956), Anesthesiology, 17, 523.

Plate, E. (1912), Dtsch. Med. Wschr., 38, 1768.

Pol, B. and Watelle, J.J. (1854) refer Gray (1951).

Pound, G.M. (1952), Ind. Eng. Chem., 44, 1278.

Preckshot, G.W. and Brown, G.G. (1952), Ind. Eng. Chem., 44, 1314.

Probstein, R.F. (1955), Proc. Conf. on Nucleation, Air Force Cambridge Res. Cent., Geophysical Res. Direct., 37, 1.

Rackow, H., Salanitre, E., Epstein, R.M., Wolf, G.L. and Perl, W. (1965), J. Appl. Physiol., 20, 611.

Rahn, H. (1961), Harvey Lect., ser.55, pub. Acad. Press (N.Y.).

Rashbass, C. (1954), R.N. rep. RNP 54/789, U.P.S. 139.

Rashbass, C. (1955), R.N. rep. RNP 55/847, U.P.S. 151.

Rathbun, E.N. and Pace, N. (1945), J. Biol. Chem., 158, 667.

Reed, L.L., Yamaguchi, F., Anderson, W.E. and Mendel, L.B. (1930), J. Biol. Chem., 87, 147.

Renkin, E.M. (1958), Proc. 5th Conf. on Microcirculatory Physiology, pub. Univ. Illinois Press.

Renkin, E.M. (1959), Amer. J. Physiol., 197, 1205.

Renkin, E.M. and Rosell, S. (1962), Acta Physiol. Scand., 54, 223.

Rennie, D.W., Reeves, R.B. and Pappenheimer, J.R. (1958), Amer. J. Physiol., 195, 120.

Reynolds, O. (1878), Mem. Manch. Lit. Phil. Soc., 17, 159.

Riley, R.L. and Cournand, A. (1951), J. Appl. Physiol., 4, 77.

Robertson, J.S. (1963), "Handbook of Physiology", sect.III, vol.1, ch.19, pub. Amer. Physiol. Soc..

Robinson, T.W. (1943), U.S. AAF-ATSC, ENG-49-696-IE.

Romano, J., Engel, G.L., Webb, J.P., Ferris, E.B., Ryder, H.W. and Blankenhorn, M.A. (1943), War Med., 4, 475.

Ross, E.T. (1938), Pacif. Chem. Met. Inds., 2, 9.

Roth, E. (1959), U.S. Sch. Aviat. Med. (Brooks A.F. Base), rep. 58-152.

Roughton, F.J.W. (1952), Proc. Roy. Soc., B, 140, 203.

Roughton, F.J.W. (1953), "Handbook of Physiology", sect.III, vol.1, ch.31, pub. Amer. Physiol. Soc..

Ryder, H.W., Stevens, C.D., Webb, J.P. and Blankenhorn, M.A. (1945), U.S. NRC, C.A.M. rep. 412.

Sapirstein, L. (1958), Proc. 5th Conf. on Microcirculatory Physiology and Pathology, p.47, pub. Univ. Illinois Press.

Saunders, J.B. and Inman, V.T. (1943), unpublished results quoted by Nims (1951).

Schafer, E.S. (1929), "The Essentials of Histology", p.37, pub. Longmans (Lond.).

Schneider, M. (1963), "Selecting Vulnerability of the Brain in Hypoxaemia", p.7, ed. Schade, J.P. and Mc.Menemy, W.H., pub. Blackwell (Oxford).

Schölander, P.F. (1960), Science, 131, 585.

von Schrotter, H. (1906), "Handbuch der Sauerstofftherapie", ed. Michaelis, M., pub. Hirschwald (Berlin).

Schultze, F. (1879), Virchows Arch., 79, 124.

Sharples, C.W. (1894), J. Nerv. Ment. Dis., 21, 636.

Shaw, L.A., Behnke, A.R., Messer, A.C., Thomson, R.M. and Motley, E.P. (1935), Amer. J. Physiol., 112, 545.

Sheldon, C.H., Pudenz, R.H., Restarski, J.S. and Craig, W.M. (1944). J. Neurosurg., 1, 67.

Shilling, C.W., Hawkins, J.A., Polak, I.B. and Hansen, R.A. (1935), U.S. Nav. Med. Bull., 33, 434.

Sjöstrand, T. (1935), Skand. Arch. Physiol., 71 (suppl.).

Smith, J.J. (1942), U.S. War Dept., rep. EXP-M-54-653-34D.

Smith, R.E. and Morales, M.F. (1944), Bull. Math. Biophys., 6, 125 and 133.

Smoluchowski, R. (1952), Ind. Eng. Chem., 44, 1321.

Snell, E.H. (1896), "Compressed Air Illness", pub. H.K. Lewis (Lond.).

Sokoloff, L. (1960), "Methods in Medical Research", vol. 8, p.253, ed. Bruner, H.D., pub. Amer. Physiol. Soc..

Stadie, W.C., Riggs, B.C. and Haugaard, N. (1944), Amer. J. Med. Sci., 207, 84.

Staverman, A.J. (1948), Trans. Farad. Soc., 48, 176.

Stevens, C.D., Ryder, H.W., Ferris, E.B., Engel, G.L., Webb, J.P., Senior, F. and Friedlander, J.K. (1943), U.S. NRC, C.A.M. rep. 237.

Stevens, C.D., Inatome, M., Ryder, H.W., Ferris, E.B. and Blankenhorn, M.A. (1945), U.S. NRC, C.A.M. rep. 456.

Stevens, C.D., Ryder, H.W., Ferris, E.B. and Inatome, M. (1947), J. Aviat. Med., 18, 111.

Stewart, C.B., Warwick, O.H., Thompson, J.W., Bateman, G.L., Milne, D.J. and Gray, D.E. (1943), Canada NRC, Assoc. Comm. Aviat. Res., rep. FPMS-D-2, No.1. (App.I).

Stoever, H.J. (1941), "Applied Heat Transmission", pub. McGraw-Hill.

Strasberg, M. (1956), "Undissolved Air Cavities as Cavitation Nuclei", Symposium on Cavitation in Hydrodynamics (Lond.).

Swann, H.G. and Rosenthal, T.B. (1944), U.S. AAF. Sch. Aviat. Med., rep. 32.

Tait, R.W.F. and Hills, B.A. (1964), Ind. Eng. Chem., 56, 29.

Temperley, H.N.V. and Chambers, L.L.G. (1946), Proc. Physics Soc., 58, 420.

Teorell, T. (1937), Arch. Int. Pharmacodyn, 57, 205 and 226.

Thaler, G.J. and Brown, R.G. (1960), "Analysis and Design of Feedback Control Systems", 2nd ed., ch.2, pub. McGraw-Hill.

Thews, G. (1960), Pflugers Arch. ges. Physiol., 271, 227.

Thews, G. (1963), "Selective Vulnerability of the Brain in Hypoxaemia", p.27, ed. Schadē, J.P. and Mc.Menemy, W.H., pub. Blackwell (Oxford).

Thomas, S. and Williams, O.L. (1944), U.S. NRC, C.A.M. rep. 395.

Thorburn, G.D., Kopald, H.H., Herd, J.A., Hollenberg, M., O'Morchoe C.C. and Barger, A.C. (1963), Circ. Res., 13, 290.

Thorne, I.J. (1941), J.A.M.A., 117, 585.

Ting, H.H. and Mc.Cabe, W.L. (1934), Ind. Eng. Chem., 26, 120.

Tobias, C.A. (1951), "Decompression Sickness", ch.11, ed. Fulton, J.F., pub. Saunders (Phil.).

Tobias, C.A., Loomis, W.F., Henry, F.C., Lyons, W.R., Jones, H.B., Sears, W.N., Cook, S.F., Mohney, J.B., Hamilton, J.G. and Lawrence, J.H. (1943), U.S. NRC, C.A.M. rep. 144.

Tomlinson, C. (1867), Phil. Mag., 34, 136 and 229.

Tomlinson, C. (1873), Phil. Mag., 34, 276.

Tureen, L.L. and Devine, J.B. (1936), J. Mo. Med. Ass., 33, 141.

Twynam, G.E. (1888), Brit. Med. J., 1, 190.

U.S. Navy (1922), U.S. Pat. 1404422.

U.S. Navy (1943), Diving Manual, Bureau of Ships, pub. Govt. Print. Off. (Wash.).

U.S. Navy (1954), ibid..

U.S. Navy (1964), ibid..

Van der Aue, O.E. (1951), unpublished results quoted by Duffner et al. (1959).

Van der Aue, O.E., Gwilliam, H.D., Kellar, R.J. and Barron, G. (1936), unpublished results quoted by Behnke (1951).

Van Liew, H. (1962), J. Appl. Physiol., 17, 359.

Van Rensselaer, H. (1891), Med. Res., 40, 141 and 178.

Vernon, H.M. (1907), Proc. Roy. Soc., B, 79, 366.

Vincent, R.S. (1941), Proc. Physics Soc., 53, 126.

Volmer, M. (1939), "Kinetic der Phasenbildung", pub. Theodor Steinkopf.

Wagner, C.E. (1944), U.S. NMRI, proj. X-284, rep. 4.

Walsh, M.N. (1941), Proc. Mayo Clin., 16, 220.

Watson, G.N. (1944), "Theory of Bessel Functions", 2nd ed., pub. Cambridge Univ. Press.

Webb, J.P., Ryder, H.W., Engel, G.L., Romano, J., Blankenhorn, M.A. and Ferris, E.B. (1943), U.S. NRC, C.A.M. rep. 134.

Webb, J.P., Engel, G.L., Stevens, C.D. and Ferris, E.B. (1944a), U.S. NRC, C.A.M. rep. 385.

Webb, J.P., Ferris, E.B., Ryder, H.W., Engel, G.L., Romano, J., Stevens, C.D. and Blankenhorn, M.A. (1944b), U.S. NRC, C.A.M. rep. 305.

Welham, W., Blanch, J.J. and Behnke, A.R. (1944), U.S. NRC, C.A.M. rep. 282.

Whitaker, D.M., Blinks, L.R., Twitty, V.C., Dean, R.B., Berg, W.E. and Harris, M. (1942), U.S. NRC, C.A.M. rep. 84.

Whitaker, D.M., Blinks, L.R., Berg, W.E., Twitty, V.C. and Harris, M. (1945), J. Gen. Physiol., 28, 213.

White, J.C., Field, M.E. and Drinker, C.K. (1933), Amer. J. Physiol., 103, 34.

Whiteley, A.H., Mc.Elroy, W.D., Warren, G.H. and Harvey, E.N. (1944), J. Cell. Comp. Physiol., 24, 257.

Whiteley, A.H. and Mc.Elroy, W.D. (1946), Amer. J. Physiol., 146, 229.

Whitman, W.G. (1923), Chem. and Met. Eng., 29, 147.

Widdowson, E.M., Mc.Cance, R.A. and Spray, C.M. (1951), Clin. Sci., 10, 113.

Wiedeman, M.P. (1963), "Handbook of Physiology", sect.II, vol.2, p.902, pub. Amer. Physiol. Soc..

Wiggers, C.J. (1944), "Physiology in Health and Disease", 4th ed., ch.58, pub. Lea and Febiger (Phil.).

Willard, G. (1953), J. Acous. Soc. Amer., 25, 669.

Willmon, T.L. and Behnke, A.R. (1941), Amer. J. Physiol., 131, 633.

Wismer, K. (1922), Trans. Roy. Soc. Canada, 16, 217.

Workman, R.D. (1964), U.S.N. Exp. Div. Unit, Proj. F-011-06-01, task 3361, rep. 2-64.

Yarborough, O.D. and Behnke, A.R. (1939), J. Ind. Hyg. Tox., 21, 213

Young, S. (1911), J. Amer. Chem. Soc., 33, 148.

Young, S. (1913), J. Amer. Chem. Soc., 35, 1067.

Zografidi, S. (1907), Rev. Med., 27, 159.

Zuntz, N. (1897), Fortschr. Med., 15, 632.

Zweifach, B. (1949), Trans. 3rd Conf. on Factors Regulating Blood Pressure (N.Y.), p.13.