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HUMAN PHYSIOLOGICAL STUDIES AT 43 BAR

by

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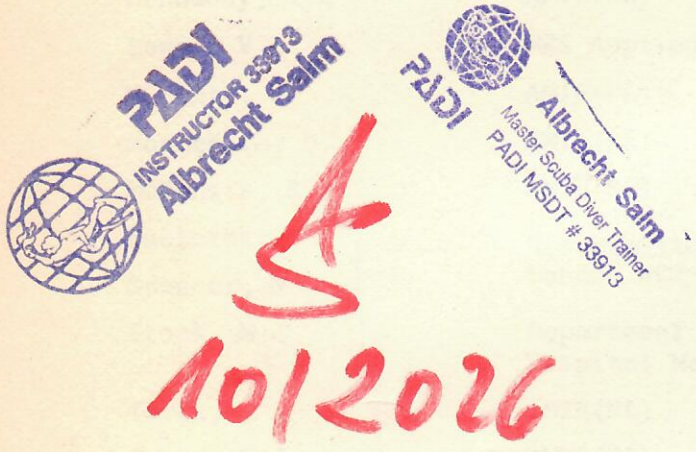
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November 1980

This report gives an account of the investigations carried out during Dives 7 and 8 of the deep dive series which began here in 1975. The research is being performed to throw light on some of the physiological and medical problems of attempting to extend significantly the depth capability of the buoyant submarine escape technique, and also to establish the limits of helium as a diving gas. Some of the work was performed in collaboration with outside investigators to whom we are indebted. Royal Naval Medical Officers provided medical support throughout the series.

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GENERAL INTRODUCTION

During the course of a prolonged and complicated series of experiments it is necessary, from time to time, to attempt an overview of the current situation. Otherwise the research effort tends to fragment and lead to the collection of a vast amount of data in various specialised areas of activity, with little or no appreciation of how the findings inter-relate. With this in mind, the principal findings and lessons learned during the course of the first six dives in the present series will now be given.

Dive 1 employed air as the breathing medium, Dives 2 and 3 used oxy-helium, and all these first three dives were at the low pressure of 3 m and of 9 days' duration. These were valuable and necessary, control dives and served to show that there were no measurable psychological or physiological effects from living in the somewhat cramped conditions of the experimental pressure chambers. Dive 4 consisted of 2 days' control period, breathing oxy-helium at atmospheric pressure, followed by compression at 1 m/minute to a depth of 200 m. The breathing gas consisted of 0.4 bar oxygen, remainder helium. This dive also served to some extent as a control experiment with minimal signs and symptoms characteristic of the high pressure nervous syndrome, and once again there were no physiological or psychological changes of any consequence throughout the 16-day sojourn in the pressure chamber. Dive 5 was to have been an extension of the same compression profile as the previous Dive 4, but reaching 300 m. The 2-day control period at atmospheric pressure in oxy-helium and the 1 m/minute compression with the standard breathing mixture of 0.4 bar oxygen, remainder helium, was completed uneventfully until a depth of about 190 m had been reached. From then on, the effects of HPNS became increasingly evident and compression was halted at 255 m. Compression recommenced approximately one hour later at the previous rate of 1 m/minute and the target depth of 300 m was reached without further need of a halt for recovery, but both divers were clearly suffering quite markedly from the effects of HPNS. Despite the quite severe nausea and vertigo experienced by both subjects, there were no gross or unexpected abnormalities in the heart rate, ECG or EEG, nor were the intentional and postural tremor studies unusually affected. A further one and a half-days were spent at 300 m before both subjects reported feeling well and free from all except trivial symptoms. The severity and duration of the ill-effects caused by compression at the rate of 1 m/minute were unexpected and it was thought that perhaps the 2-day control period spent at atmospheric pressure prior to the commencement of pressurisation, was eliminating the entire dissolved nitrogen gas content of the tissues of the body, thus removing its well-known protective effect against some of the manifestations of HPNS. Accordingly, for Dive 6 the control period in oxy-helium

at atmospheric pressure was abandoned but the pressurisation rate of 1 m/minute, using the standard breathing gas mixture, was retained. Once again, the subjects began to notice the onset of HPNS at a depth of about 190 m. On reaching 225 m it was quite apparent that the two experimental subjects, who were incidentally not the same men as on Dive 5, were becoming increasingly distressed by the compression procedure and consequently compression was halted at this depth for a period of 24 hours in order to ensure a complete return to wellbeing before commencement of the 1 m/minute compression to the target depth of 300 m. This dive confirmed the view gained from previous experience, namely that compression on oxy-helium can be extremely rapid to depths of the order of 180 m but that thereafter the compression rate moves into a very sensitive area. Although adding nitrogen is demonstrably beneficial at dive pressures greater than 180 m, the relatively small partial pressures of nitrogen involved in Dive 6 of this series were clearly having no practical benefit.

Apart from the gross observations mentioned above, a number of carefully controlled investigations were pursued into several physiological systems to ascertain whether there were any signs of breakdown in the normal homeostatic mechanisms. Strong evidence had accumulated to suggest that there is a change in the utilisation of dietary constituents, most particularly with regard to energy exchange. Accordingly, uncontrolled food intake by the subjects was analysed indirectly by the use of standard food composition tables and numerous chemical and physical measurements were made. Several indicative findings were reported but the main conclusion of this area of work can be summarised by a quotation from one of the investigators - "It is obvious from study of the above data and the results discussed elsewhere that in order to analyse more usefully such factors as energy balance, nitrogen balance, mineral balance, and amino acid metabolism in relation to bone necrosis and HPNS, and a host of other biochemical variables, a completely fixed dietary intake is essential so that classical metabolic balance techniques may be used. This procedure is planned for subsequent dives in this series."

In the thermal balance studies, partitional calorimetry techniques as well as direct measurement of skin heat flux reveal the precarious nature of the thermal homeostatic condition in high partial pressures of helium. The reduced effectiveness of the evaporative heat loss mechanism at increased depths was also noted.

In general, the respiratory physiology results agreed with those given in the established literature. For example, the change in maximum voluntary ventilation with gas density harmonised quite well with data obtained from other laboratories and indicated for instance that at 600 m the diver should be able to achieve 42% of his surface value. A measurement unique to this laboratory is the pulmonary tissue volume. There were strong indications that the pulmonary tissue volume

had increased at pressures as low as 200 m. The implications are numerous. Is the pulmonary membrane unique in its response, and is there a significantly increased diffusion pathway? These, and other pertinent questions, were left open to be investigated in subsequent experiments.

There were three separate approaches to the neural problems of these dives. Firstly, there was a neurochemical investigation into the metabolism of dopamine and noradrenaline, measuring urinary outputs of metabolites. It was shown that there was no sustained differential effect of pressure on the metabolism of these transmitter substances and no obvious correlation between the metabolite output and the severity of HPNS experienced during the compression phases of Dives 5 and 6, but it must be borne in mind that a small vital change in a particular mechanism may not significantly affect these measurements of whole body turnover. Secondly, control observations were completed on the knee-jerk reflex during Dive 6, which indicated, in agreement with work from other laboratories, that changes leading to the increased excitability of the mechanically-elicited reflex response are occurring at some higher level than the reflex loop itself. Thirdly, a set of neurological tests, limited in scope by the somewhat cramped conditions and inaccessibility for direct examination, were given. It was concluded that there were no gross neurological changes, of even a temporary nature, at depth. Despite the presence of vertigo and visual disturbances provoked by head or eye movements, particularly marked during the later stages of the compression phase there was no evidence of gross end-organ type vestibular or vestibulo-cerebellar interference. As mentioned previously, the EEG results, and the recordings of intentional and postural tremor, were also remarkably indifferent to the obviously distressing symptoms suffered by the experimental subjects.

A wide selection of psychological and behavioural tests were given, but as might be expected with such small numbers of subjects involved, it is difficult to draw firm conclusions. Not surprisingly sleep quality was poorer in the chamber under all conditions but there was evidence of adaptation and a recovery of sleep quality, even at 300 m. Two further points can be made from the observations at 300 m, namely that decision-making is slowed down at this depth and there is impairment of short-term memory.

Haematological investigations were pursued in Dives 5 and 6. No significant changes were noted in packed cell volume or haemoglobin, and the usual platelet changes seen upon decompression were observed. These findings tend to accord with those previously reported from this laboratory and elsewhere. However, two highly significant further observations were made during the course of Dive 6. A very pronounced rise in the erythrocyte sedimentation rate was noted during the later stages of the decompression which persisted for some weeks afterwards

and a large percentage of erythrocytes, in excess of 10% in all four cases, presented what was termed a "ball race" appearance under the light microscope, and these too persisted for many days after completion of the decompression.

The above paragraphs contain a very condensed summary of a considerable volume of experimental evidence, and hopefully, no major points have been overlooked.

Clearly, before proceeding to any greater depths it was necessary to change the compression profile. Severe symptoms of HPNS were manifesting themselves at depths in excess of about 200 m and it was becoming impossible to distinguish between effects caused by the compression profile and those due to pressure per se. In the next two dives of the series to 420 m it was decided to attempt to separate these effects. It was realised that no symptoms of note appeared at depths less than about 150 m, but it was far from clear whether the relatively rapid compression to depths of this order was precipitating subsequent problems and the decision was made to proceed very slowly to depth both in the early and later stages of the compression phase. In other words, the compression would still remain linear with time but the rate of change of pressure would be slowed down very considerably. It was supposed that if 60 m of depth were accomplished in each 24-hour period then this represented a sufficient departure from the earlier experiments to enable a proper test of the hypothesis.

It was also realised as a result of the earlier dives and from a scrutiny of the literature that no saturation dives had been undertaken using rigidly controlled dietary procedures, and that without such controls it was impossible to make reasonably accurate and meaningful statements on such matters as weight loss, energy balance, mineral exchange to name but a few. It is salutary to note that exactly one hundred years ago P Bert had realised the impossibility of studying metabolic processes in diving without strictly controlled dietary procedures. There are of course numerous measurements which must accompany the strict dietary control, such as the deuterium oxide body water estimations and the skin caliper fat measurements, and these are described in detail later in this report.

A greatly increased volume of data was collected during the course of Dives 7 and 8, as most investigators were now in possession of thoroughly validated techniques applied to very experienced, highly co-operative, experimental subjects in a familiar and standardised chamber environment. The enormous advantage of having a team of investigators and experimental subjects together for an uninterrupted period of three and a half years was amply demonstrated in the conduct of these dives and particularly Dive 8, which yielded a quality and quantity of information that it is impossible to view without a sense of satisfaction being shared by all concerned.

SUMMARY OF EVIDENCE FROM THE FIRST EIGHT DIVES

1. Following three 9-day exposures to 3 m pressure of air or oxy-helium it has been shown that there are no 'caging' effects from living in the somewhat cramped conditions.

2. There is a threshold pressure of 180 ± 20 m for the onset of a variety of characteristic signs and symptoms. The symptoms are described variously as light-headedness, giddiness, clumsiness, 'nervy' feeling. Signs noted are the onset of 'helium tremors', some evidence of nystagmus, and knee-jerk reflex changes (see 14).

3. The effects described in 2 occur whether there is a very fast (6 min) or very slow (2 days) compression to the threshold pressure.

4. If the compression rate is 1 m/min or faster severe ill-effects are experienced by some subjects at depths just greater than the threshold pressure range. These manifest as distressing nausea, vertigo, pallor and a form of drowsiness (sometimes termed micro-sleep). Although the subjects are clearly quite distressed this is not reflected in the neurological and performance tests.

5. There is a threshold pressure of 300 m, or thereabouts, for the onset of occasional involuntary gross twitches of the skeletal muscles. A variety of compression profiles has failed to eliminate or ameliorate this condition.

6. A wide spread of neurological tests supports the view that the hyperbaric oxygen-helium environment causes numerous small disturbances throughout the nervous system, but cerebellum and brain stem are mainly implicated. There are also significant contributions arising from a dysbalance between the responses of the left and right vestibular sensory mechanisms.

7. Pressure arthralgia cannot be completely eliminated by the slow compression used in these dives.

8. Psychological testing revealed no drop in subjective alertness before, during, or after, the 420 m exposures. Sleep quality seemed to deteriorate with increase in pressure but there is a great variability in subject tolerance to the conditions. There is impairment of short-term memory and slowing in speed of decision making. Visual search tasks are also adversely affected at 420 m.

9. The mean weight change of the 10 subjects who went to 21 bar, or deeper, was +0.6 kg, with a mean 24-hour energy intake of 14.14 MJ.

10. Rigorously controlled fixed dietary intake studies on dives at 420 msw revealed that mineral balance, as represented by calcium, magnesium and phosphate, remains undisturbed, but the total nitrogen balance of the body is not maintained,

and a steady loss of nitrogen, mainly as urea, occurs. Relevant to bone metabolism it has been established that the level of hydroxy-proline and collagenase activity are unaffected at depth.

The expected decrease of serum vitamin D content occurred and this is an example of an observation that is potentially very important but requires further experimentation.

Numerous hormonal, enzymatic, and neurochemical measurements have been made but, here again further confirmatory work is needed. All changes seen are reversible, during, or shortly after decompression.

11. The haematological investigations yielded three major new findings. Firstly, a large percentage of the erythrocyte's carbonic anhydrase migrates to the membrane during exposure to 420 m pressure. This change follows the compression profile quite closely and stays constant at constant pressure, but decompression does not reproduce the compression response in reverse, and it takes two or three weeks after the dive for complete return to normal carbonic anhydrase distribution. Secondly, during the decompression, aside from the usual platelet changes, there are marked changes in red cell morphology. These changes can occur in as many as 3-12% of the cells. Once again it takes two or three weeks before the red cell fields regain their normal appearance. Thirdly, the erythrocyte sedimentation rate (ESR) increases greatly during the decompression, and extremely high values have been encountered. These ESR values reach their greatest level at the end of decompression, or shortly afterwards, and take one or two weeks to return to normal. No changes are seen in packed cell volumes, or haemoglobin content or red cell counts, but these measurements are sometimes being made when the red cell morphology has undergone quite marked changes, as noted above, and therefore small changes in such gross measurements as PCV, would probably be masked.

12. The expected changes in distribution of heat exchange by the body were seen, ie marked increase in respiratory and convective heat loss with an equally marked decrease in evaporative and radiation heat loss. A new finding concerned changes in thermoperception at 420 m that took approximately two weeks to return to normal following decompression.

13. The rate of recovery of the fatigued adductor pollicis muscle was unimpaired at all pressures but it was observed that there was a substantial increase in the level of fatigue for a given work load at 420 m.

14. The knee-jerk reflex showed onset of changes at 200 ± 20 m, ie near enough to the threshold value mentioned in 2 above. At 420 m the increases in excitability

were quite marked and shown to be due to a central effect, most probably release of brain stem inhibitory function.

15. Cardiac output falls slightly at 420 m and is accompanied by a tachycardia.

16. Standard 150 W workloads can be completed at 420 m but require not less than 60% of MVV, and do not leave much ventilatory reserve.

17. There was a small increase in pulmonary tissue volume, and there is some evidence that a problem with the movement of the CO_2 across the alveolar-capillary barrier as compared with that of N_2O is beginning to appear at 420 m.

18. There is evidence that a suitable decompression profile can avoid the platelet and ESR changes seen during most saturation decompression procedures.

These summarised findings from the first eight dives can be examined from several standpoints. Firstly, the purely practical position is clear. At 420 m it is possible for men to cope with quite hard sustained physical work (150 W), exacting mental tests, and delicate manipulative tasks, for example venepunctures. This reinforces previous findings at the laboratory during a series of dives in 1970 culminating in a 1500 ft (457 m) exposure and of course many subsequent, and deeper, hyperbaric exposures reported by Comex, USN and Predictive IV. The depth band of 450 $\pm$ 30 m can be attained without any major subjective disturbances, provided care is taken with the compression procedures.

Despite this apparently optimistic finding, it is necessary to establish whether there are changes in homeostasis that are not being detected subjectively but which are nevertheless damaging. Accordingly, an extensive set of observations has been completed to measure the magnitude of any shifts in the principal physiological mechanisms. From these observations two gross statements can be made. Firstly, all changes that occur during the dive revert to normal, either during the decompression, or perhaps as long as three weeks after completing the hyperbaric exposure. Secondly, those changes that do occur at 420 m are not a source of concern, given a suitable compression profile. Nevertheless, there are some haematological changes occurring during the decompression which are certainly not desirable and which, it is believed, can be avoided by adjustment of the decompression profile. There are also changes which, whilst not a source of worry at 420 m, may well become more serious at deeper depths.

The changes which must be regarded seriously are at a very basic level. As stated in 11. above, it has been found that at pressure the enzyme carbonic anhydrase is redistributed within the red cells and attaches itself to the erythrocyte membrane. This must result in a functional change in the membrane, and adds a further complication. The membrane is not just responding to pressure and dissolved gas as a particular structure, but is undergoing structural changes which are themselves dependent upon the dive conditions. Clearly it is most unlikely that the erythrocyte membrane is the only membrane in the body which will be affected in a similar manner and, of course, the role of neural membranes in the reversal of anaesthesia by hydrostatic pressure is well established; but the erythrocyte membrane phenomena, by contrast, may even occur, albeit minimally, at 15 m when breathing air, and this points to a very sensitive response to a physical phenomenon, independent of gas composition, perhaps a colligative property or pressure per se. Indeed there may be, as with the anaesthesia reversal, an effect of increased hydrostatic pressure that interacts with some other physical property of dissolved gas thus giving a far from simple set of responses. This can only be ascertained by further careful human experimentation over a wide range of pressure.

It seems reasonably definite that rapid compression to the threshold level will start minor ill-effects at 150 m in some men, who will be noticeably affected at 200 m, whereas some resistant men will hardly notice any problems until 200 m. Furthermore, once this individual threshold is reached it is necessary to retard the compression rate very considerably, or to give a rest period before proceeding deeper. The latter procedure was successfully employed in the 1500 ft (457 m) dive and during the Predictive IV studies. For the 9th and 10th dives in the current series, this stage compression will be used, with the stages being placed at 180 m, 300 m, 420 m and 540 m. Data for comparison purposes is available at 300 m and 420 m from the first eight dives and this will strengthen the value of any new or modified findings at the deeper depths.

It is not yet possible to reach a set of concepts for guiding future research, except in somewhat vague and very general terms. There are two principal physical factors influencing the physiological mechanisms. Firstly there are the purely mechanical effects of raised pressures of helium, which may cause compression of existing gas nuclei inside the body or produce shearing stresses due to the different compressibilities of adjacent tissues. Then there is the influence of pressure on those biochemical reactions that are associated with volume changes, which would seem not of much physiological significance until the pressure is in

excess of 100 bar. Of more moment at diving pressures would be the biophysical effects, such as shifts in the sol-gel equilibria.

Secondly there are effects due to the use of helium gas as the compressing medium. The respiratory system is faced with a dense gas of altered viscosity and heat exchange is markedly altered. These direct physical effects are accompanied by the physico-chemical consequences of the presence of large concentrations of dissolved gas.

At present the various physical factors involved in breathing hyperbaric oxygen-helium mixtures cannot be directly implicated as causing any of the ill-effects seen. It is always possible to propose any of several views. For example, the arthralgia can be regarded as either due to crushing of gas nuclei, or dissolved gas gradients, or differential compressibility. All these mechanisms can be made to fit the experimental facts. Too little is known about whether sustained dissolved helium gas gradients are attainable, or of sufficient magnitude, or can cause the pain of arthralgia. Also, no satisfactory data are available on the compressibility of different tissue types around joint structures, and whether these various compressibilities might be complicated by being dependent on the absolute pressure; or, again, although undoubtedly gas nuclei are present in tissues, whether they are present in sufficient numbers that crushing them will cause pain, is totally speculative.

Given these basic uncertainties it is necessary to collect more data to clarify the various possibilities. In this search for an understanding of the mechanisms involved the prime consideration is to ensure that the experimental subjects are not adversely affected. It is clear from the carefully controlled measurements made in this present dive series that this is true to depths as great as 420 m and a cautious approach to even greater depths is the next step. Animal experiments are unfortunately not yet directly helpful to the human situation. It is now known that some mammals (sperm whales) can descend to 2250 m depth in about 15 minutes. Experience indicates that this would be lethal for most mammals, including human beings. In contradistinction some varieties of laboratory mammals (rats) are unable to survive for a few days at 300 m, which is quite an uneventful exposure for most mammals. In these circumstances an old philosophical saying is very apt, 'The proper study of mankind is man'.