

THE TWENTY-THIRD UNDERSEA MEDICAL SOCIETY WORKSHOP

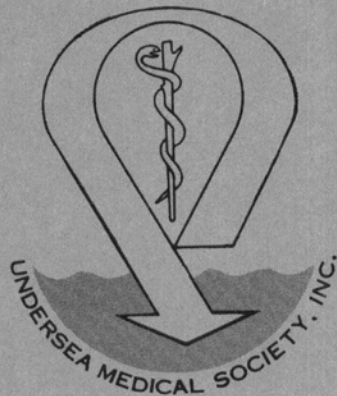
TECHNIQUES FOR DIVING DEEPER THAN 1,500 FEET

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WILMINGTON, NORTH CAROLINA, U.S.A.

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Editor

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The Twenty-third Undersea Medical Society Workshop



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9650 Rockville Pike  
Bethesda, Maryland 20014





Workshop: Techniques for Diving Deeper Than 1,500 Feet  
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### Chairman's Introduction

Just five years ago, twenty-four people met in a remote California lodge, Sea Ranch, to discuss the 'Strategy for future diving to depths greater than 1000 feet'. We discussed a number of questions; is there a barrier beyond which divers will not be able to go ?; could the use of anaesthetic additives, including nitrogen, enable men to go deeper?; what are the specific problems introduced by working in the sea at great depths?; how may an adequate therapy for decompression sickness at great depths be established? These, and many other questions, were debated and a number of general conclusions were reached. These were summarised in the report of the meeting and still make interesting reading today.

About 18 months ago Val Hempleman suggested to me that it was time that these conclusions be re-examined and, if necessary, updated. He suggested a further meeting in the style of that at Sea Ranch (which became known to those planning it as 'Son of Sea Ranch'). With the active support of the officers of the U.M.S. and many others, the necessary funds were raised and the meeting became a practical possibility.

The importance of workshops is that they can provide a more varied format than is common at most scientific meetings. A wide breadth of issues can be raised. The participants are all familiar with the field and are capable of discussing not only their own contributions but can take a broad view of the subject, both in their formal presentations and in the discussion. I am very pleased that we have been able (as at Sea Ranch) to find some common ground; collective wisdom which we have agreed and which forms the conclusions of this meeting. One theme that emerged

clearly was the continuing need, particularly in the commercial sector, for free divers operating at depth. It was made clear that without such a capability, the winning of undersea resources, so necessary at the present time, cannot be accomplished. Another was the superiority of the dives in which the breathing mixture contained added nitrogen when compared with the straight heliox dives. This distinction was not as clear at previous meetings and has now raised considerable optimism about our capacity to dive even deeper. However, a word of caution is appropriate. The underlying mechanisms which govern the effects of high pressures and dissolved gases are for the most part little understood. It is essential that we establish a strong scientific foundation by a considerable research effort in order to place our achievements in deep diving on a secure basis.

During our discussions there emerged a number of general conclusions. It is this guidance which, I believe, is the end product of our workshop and may enable the ideas raised to influence not only the twenty or so present but the wider constituency of those concerned with diving to very great depths.

BRIAN SMITH  
Chairman, Wilmington, N.C., March 1980.

Editors' Note:

The material in this report has been compiled from the participants' verbal and written material presented at the meeting together with additional information collated afterwards. It has been edited to conform with the workshop format and the final wording is the responsibility of the Chairman and Editors.

We would like to thank Ms Cathleen Coppola for tape recording the 15 hours of the meeting and Miss Brenda Dobson for both the typing and the final layout of the camera ready copy.



Summary of General Conclusions1. Diving Limits

There is a continuing need for deep diving which at the present time cannot be met by remote or one atmosphere systems. From the evidence presented of recent dives it was concluded that open sea deep water work to 460 m was entirely practical and that the future extension of working dives to 650 m appears to present no physiological problem.

2. Oxy-helium diving

The balance of evidence presented at the meeting indicated that diving below 450 m on heliox is not a practical possibility and may, indeed, become hazardous at marginally deeper depths. The use of TRIMIX in diving to depths ranging from 150 m to 650 m appears to be beneficial.

3. High Pressure Neurological Syndrome (HPNS) and its amelioration

HPNS is the major problem in deep sea diving and it is now recognised to be more complex than had previously been thought. The pharmacological techniques for ameliorating HPNS have now proved to be of practical value. New and significant evidence was presented that the addition of nitrogen to oxy-helium breathing mixtures (TRIMIX) is beneficial and opens up the possibility of diving to depths significantly greater than those yet attained. The early problems with euphoria associated with this technique seem to have been overcome. Despite this success, it was felt that a wider pharmacological approach to the problem using more selective drugs may prove even more advantageous.

4. Chronic Hazards and Additional Problems

The new techniques in very deep diving appear to be safe and reliable. Apart from bone necrosis, no permanent effects of exposure to depths have been recognised at the moment. Additional

problems include temperature control, respiration, diver monitoring and decompression. The solutions involve difficult technology as well as physiological investigations. For example, there does not appear to be any adequate breathing apparatus for open water diving below 460 m. Research in these areas is important for both current and future diving practice.

#### 5. Diver Selection

As men push to new limits, selection of individuals is likely to become particularly important. Effective selection procedures have yet to be fully devised but evidence was presented that this is a practical possibility.

#### 6. Basic Research

Despite the recent practical success in deep diving, the principles underlying the majority of the physiological effects that are encountered are not yet understood. In view of the difficulties in pursuing research with man below 300 m, due both to the small number of dives and to the physical problems involved, there is no doubt that much of our understanding must come from studies with animals.

Only an understanding of the basic mechanisms involved in man's response to high pressure gases can ensure that a deep diving programme can be pursued in safety.

Naval Requirements for Underwater ActivityJ. Vorosmarti

The U.S. naval requirement for underwater activity can be stated very simply: it is to perform the various naval diving missions at any depth up to 1000 ft., which at the present time is the limit of the Navy's manned diving systems. For work at greater depths, unmanned or manned 1 ATA systems are to be used to accomplish these missions.

These diving missions include ship repair and maintenance, ship salvage, retrieval of equipment, searches and surveys, special warfare operations, explosive ordnance disposal and submarine rescue. One can deduce from this list that most of Navy diving is done in relatively shallow water. This is borne out by analysis of diving records: 99% of Navy dives are done at depths shallower than 200 ft.

Using 200 m (660 ft.) as the depth where "deep diving" begins, I will discuss what are considered to be the major problems in supporting a diver to ensure that he can do useful work in the range of 200-300 m.

The first of these is the protection of the diver from the cold environment, both in the water and in a personnel transfer capsule. The physiologic and engineering data needed to provide the optimum protection are not available, although good progress is being made in this area.

The other area of major importance is the provision of underwater breathing apparatus which does not increase the respiratory burden already faced by the diver because of the flow restrictions imposed in his lungs by the increased gas density. There is probably a connection between the respiratory limitations and/or changes in respiratory control and the dramatic and sometimes fatal sudden loss of consciousness in divers at these depths. This also requires a solution.



Other problems requiring study but which are not directly related to putting a diver at depth and having him do his job are the long term effects of diving (genetic changes, changes in immunologic response, chronic CNS changes, etc.) and the care of the injured or sick diver under pressure.

Although the U.S. Navy's requirement for diving is 1000 ft., the biomedical research program has been tasked to investigate the physiological problems associated with diving to 1500 ft.

The problems mentioned above, of course, are of greater magnitude at deeper depths. In addition, deeper than 1000 ft. the High Pressure Nervous Syndrome becomes a major problem if useful work is expected of the divers. I did not list it as a problem shallower than 1000 ft. even though some of the manifestations of HPNS appear at lesser depths because not all divers are affected and the problems associated with it are minor, except if rapid compression is required in an emergency. Deeper than 1000 ft. all divers will be affected and interference with accomplishing required tasks is obvious. Some means must be found to overcome this syndrome (drugs, different gas mixtures, selection of personnel) if diving to 1500 ft. becomes a Navy requirement.

In summary, the Navy's requirement is to accomplish any diving task to a depth of 1000 ft. In addition, the research program in support of this requirement has been tasked to investigate the biomedical problems of extending the Navy diving capability to 1500 ft.

Commercial Requirements and CapabilitiesD.H. Elliott

The primary objective of commercial diving is no different from that of naval diving. It is to enable man to work efficiently at the maximum safe depth and then, when his task is complete, to return to the surface with no consequential ill effects. Any differences in the requirements between naval and commercial diving are mainly associated with the nature of the divers' tasks.

Deep diving for commercial reasons is performed almost exclusively on behalf of the offshore oil and gas industry. Economic considerations are encouraging the exploration rigs into deeper and more inhospitable waters. The exploration phase should be completed without intervention by divers. As is well known, considerable sums of money are now being spent on developing alternatives to divers in the later stages of offshore field development: construction, production and maintenance. No doubt the next decade will bring a new generation of diverless systems: improved remote-controlled vehicles and other robots, one atmosphere sea-bed habitats with greater operating potential and, of course, the grandchildren of "Jim" and mutants of "Wasp". In spite of these efforts, which are welcomed in the interests of human safety, it remains certain that man will continue to be required at depth. There are some tasks in the construction phase which are best suited to human hands co-ordinated by the human brain. Equally certain in underwater engineering is the prediction that the diverless alternative may fail or may not be able to cope with some unforeseen situation and then human intervention will be needed in a hurry.

The requirement will undoubtedly exist for man to attain the maximum safe depth and at that depth to be capable of useful physical work. The primary problem is not really physiological but ethical. What is safe? No dive is without risk. Risk analysis may be able to estimate some figures for the various hazards to which the diver is exposed in his employment but, in the end, a decision has to be made

on what risks are to be acceptable. Not only should man be able to perform his underwater task effectively but at all times he should have sufficient mental and physical reserves to have a good chance of survival in an underwater emergency.

We are aware of the many problems to be solved so, if the objective is a commercial dive to some extreme depth then, from a commercial point of view, I would list the following problems, some of which are equally unsolved at shallower depths. The order in which they are presented is no indication of their relative importance:-

#### Selection Criteria

There are some large differences between individuals in their ability to perform work on arrival at saturation depth or at excursion depth after the compression phase. What selection tests have reliable predictive value in picking out those who will be able to perform efficiently and safely? What criteria other than HPNS susceptibility need to be considered? Will a chamber test dive to the maximum depth be essential for each candidate?

#### Compression Rates

While rapid compression techniques may be required, for instance, for a dry intervention dive by a doctor in an emergency, a deep commercial dive could postpone its water excursions until the recovery phase at depth is complete. I would therefore be concerned about compression studies primarily in so far as they relate to performance in the ultimate steady-state.

#### Breathing apparatus

Dysfunction of the respiratory system, rather than HPNS, may prove to be the limiting factor in deep diving for work in the water. Breathing apparatus should not compound respiratory difficulties and more studies are needed to define the physiological criteria for breathing apparatus design. UBA must then be designed and tested to such standards as well as meeting safety requirements such as bale-out bottles of sufficient duration and at a respirable temperature.



### Diver Heating and Thermal Protection

Protection of the diver's body against heat loss in the water together with heating his inspiratory gas needs to be studied further since current systems appear to be near the limits of effectiveness and reliability. Thresholds for recalling the diver back into the bell must be defined.

In the diving bell, passive and active systems for maintaining thermal balance of the divers need to be developed further, with special emphasis on 72-hour survival in the lost and isolated bell.

In the deck chamber, techniques for ensuring post-excursion restoration of correct thermal balance of the diver need to be studied. If successful these could reduce any demand for in-water thermal monitoring of the diver rather than of his equipment.

### Work Efficiency in the Water

In addition to the influence of specific factors such as compression rate, UBA design and function, and thermal balance upon mental and physical performance in the water, the interplay between these factors and others such as  $P_{O_2}$  levels,  $CO_2$  retention, etc. need to be studied in man at depth as relevant not only to work efficiency but also to safety, for instance the prevention of unexplained loss of consciousness in the water.

### Diver Monitoring

A number of persons may consider that diving safety would be improved just by a greater degree of on-line physiological monitoring of the diver in the water. This would be in addition to conventional communications and occasional TV surveillance. A number of us believe that the first priority should be improved verbal communications with the diver. Any proposal related to in-water physiological monitoring must be scrutinised carefully in order to exclude anything that might further encumber the diver or that might provide unreliable or ambiguous information. The only acceptable objective is on-line monitoring that has an established predictive value in preventing

accidents. "Black boxes" for retrospective analysis may have a place in diving safety but have little or no immediate relevance to the particular dive.

If on-line physiological monitoring is achieved then some additional work will be needed to interpret and display all relevant information to the diving supervisor in such a way that his decision-making is enhanced rather than impaired.

#### Environmental Control

A review of deck chamber environmental control is needed with special attention to CO<sub>2</sub> scrubbing, elimination of trace contaminants and the control of micro-organisms.

#### Decompression

Some additional work may be needed to confirm the acceptability of saturation excursion tables.

#### The Ill or Injured Diver at Depth

This problem is medical and is primarily logistic: how to bring to the diver at depth the specialist care that he needs. Some further research may be needed, for instance, on the effectiveness of ventilators at depth and of analgesic agents.

#### Post-Dive Effects

The causes and significance of various post-dive manifestations such as red-cell abnormalities, pulmonary symptoms, and excessive weight loss need investigation notwithstanding the general observation that these are probably transients. The study of non-transient long-term effects such as osteonecrosis and the possibility of CNS damage needs to be continued.

It is the deep-sea engineers' intention to eliminate the diver from the underwater scene. Nevertheless the need for oil companies to have contingency plans for emergency intervention will, I believe justify deep diving for some time to come.

## Future Manned Undersea Activity

T. E. Berghage

Current statistics reveal that 99% of the diving by the U.S. Navy is to depths of 200 feet or less. It appears that the advancements in diving technology are leading the operational needs of the Navy by about 60 to 70 years. Private industry is doing much better at capitalizing on the advancing technology; the profit motive appears to be a very effective stimulus for the utilization of new concepts. The average depth of a commercial saturation dive in the North Sea has been to about 500 to 600 feet. This is approximately 23 years behind the capability already demonstrated experimentally. The deepest commercial open-sea dive, made by the French to a depth of 1574 feet, is only about 5 years behind the diving physiology frontier. How close one stays to the pressure frontier, or how much one pushes the diving technology is probably dependent upon the economic incentives involved.

As we look at our present capability and speculate about the future manned undersea activity of the United States, we must turn to the diving research program for answers. In this country the U.S. Navy is the only organization that has maintained a consistent diving physiology research program. This is partially due to the high cost of such research and partially due to the Navy's continuing operational commitment to submarine rescue and salvage. We can categorize the Navy's current and future diving programs into five time/depth groupings (Figure 1):

1. The depth range currently found in the vast majority of Navy diving;
2. The Navy's existing operational diving capability, which is not yet fully utilized;
3. The Navy could extend its diving capability to 2500 feet within the next 10 years.
4. The best estimates currently available suggest that within 50 years we could be diving to depths of 5000 fsw (feet of sea water):
5. The extent of our diving capability 100 years from now is pure speculation.

The French have already made successful manned chamber exposures to pressures equivalent to a depth of 2000 feet of sea water (fsw). The U.S. Navy Experimental Diving Unit has made five hyperbaric chamber exposures to pressures greater than that found at 1000 fsw; the deepest was to an equivalent depth of 1600 fsw. It appears that the development of a diving capability to 2500 fsw within the next 10 years is not an unreasonable expectation.

An essential element in extending our diving capability is the research capability provided by experimental hyperbaric facilities. Only 3 times during the last 100 years has the U.S. Navy had a hyperbaric research chamber capability that exceeded the then-existing diving capability. Research programs are supposed to anticipate change and to lead the way in developing needed technology. Hyperbaric research should be paving the way for man's advance into the sea. Yet, in actuality, for only 22 out of the past 66 years has the Navy's hyperbaric chamber capability been greater than the existing diving capability.

At the present time the U.S. Navy Experimental Diving Unit has a depth capability of 2250 fsw. This is a mere 250 fsw deeper than the existing record chamber dive (2001 fsw). The Naval Medical Research Institute in Bethesda, Maryland, is constructing a hyperbaric research facility that will have a depth capability of 3367 fsw. This complex should be operational by 1980 and should keep the U.S. Navy ahead of the advancing hydrostatic frontier until about 1990. With a lead time of some 7 to 10 years required for the construction of such a research complex, it is not too early for the United States to start planning the next one if it hopes to keep pace with the rest of the world.

The depth of diving in the intermediate future was removed from the arena of pure speculation by an experimental chamber exposure at the University of Pennsylvania. The experiments conducted during the dive indicated that man can breathe gases as dense as those that will

be encountered at 5000 fsw. There are, however, a host of additional problems associated with diving to this depth, but we have no indication at this time that these problems are insurmountable. The times between the major breakthroughs in our knowledge about hyperbaric physiology are decreasing in a linear fashion. If this trend continues, we should have another significant advance in the early 1980's, and it will probably be the control of the high pressure nervous syndrome (HPNS). The alterations in function of the central nervous system that are associated with fast compression and deep depths seem to be the present limiting factor for man's further advance into the sea. If a breakthrough takes place as conjectured, it may well open to exploration depths of 5000 feet.

It is impossible to specify the depth at which we will be operating in the more distant future, say 100 years from now. One hundred years ago this year Paul Bert wrote his book on barometric pressure, and if we had told Paul Bert that humans would be exposed to environmental pressures of almost 900 pounds per square inch, I am not sure he would have believed us. As time passes and technology improves, it may be reasonable to use hydrogen as the major component of our breathing medium. Eventually, the need for an inert gas in the breathing medium may be eliminated altogether by the breathing of a saline solution saturated with oxygen.

The impression is given of a rapidly expanding diving technology that could have us walking on the ocean floor within a matter of years. However, this notion is a long way from actual fact - our capability to work on the sea floor is still in its infancy. To put our present capability in proper perspective we must refer to Figure 2, which presents the proportion of the sea floor associated with various depths. The deepest open-sea dive to date has been to a depth of 1574 fsw. Diving to this depth provides access to about 7% of the ocean floor. Even if we had hardware to dive to a depth equivalent to the greatest hydrostatic pressure to which man has been experimentally exposed (2001 fsw), we would have access to only about 10% of the ocean floor.

Man has made significant progress in his ability to work in the sea, but there is still a vast underwater frontier waiting for exploration. Eventually, man will reach a depth (a hydrostatic pressure) beyond which he cannot descend. This depth is unknown at the present time and will be a question of scientific interest well into the future. Large animals have been exposed to hydrostatic pressures equivalent to a depth of 8000 fsw and safely returned to the surface environment. Whether man will be able to attain these depths is still open to question. The subtle molecular changes and the alterations of excitable tissues that are associated with elevated pressures suggest that at some depth man will have to give way to machines. For underwater work beyond this pressure barrier man will have to resort to the use of armored suits, submersibles with manipulators, and remotely controlled robots.

All of these alternatives are under investigation and hold great promise for the future. The future role of manned deep diving depends upon the ocean floor environment (bottom composition and visibility conditions) and our ability to engineer around these environmental constraints, the cost of life support systems, and finally, the limits of human physiology.

Figure 1:

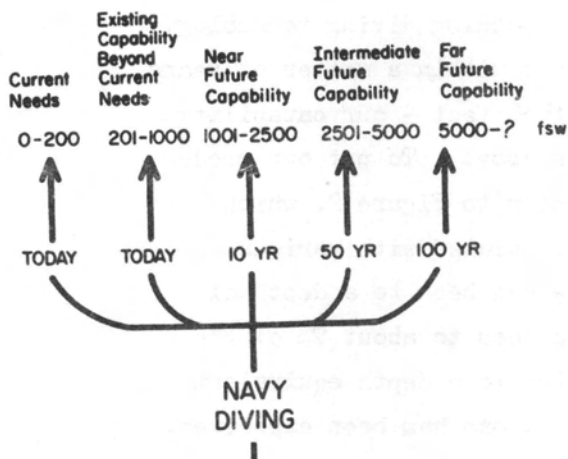
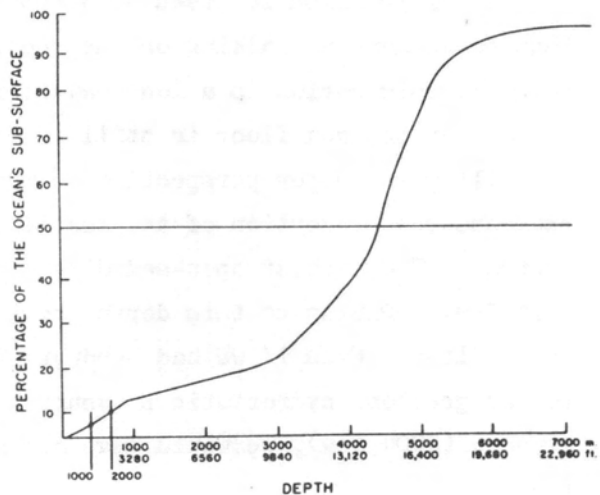


Figure 2:





Prediction of Physiological Limits to Deep Diving  
and  
Extension of Physiological Tolerance

C. J. Lambertsen

The Diver

Physiological limits do exist for diving at all depths. Some limits can be postponed by modification of diving method. Some can be masked. Some can be eliminated by engineering. Most persist and must emerge with the increasing pressures and durations of deep diving. Diving is not simply passive exposure to gas pressure in a chamber or simply breathing underwater. Therefore prediction of limitations must be concerned not only with the absence of convulsions or unconsciousness but also with the quality of thought and the capacity for useful physical action. The progress and limits in direct manned undersea work are indicated in Figure 1.

The working diver is unique in the spectrum of exposure to extreme physiological stress. The athlete functions to physical exhaustion, but in an ideal and harmless environment. The astronaut is essentially unstressed, regardless of distance from earth, protected by engineering from harmful environment or even need for severe exertion. The mountaineer suffers the cold and hypoxia of Everest, but after weeks of progressive adaptation prior to executing his final ascent. Even the whale is not exposed to the complex severities of human diving. It does not have to ventilate its lungs, it has no narcotic, decompression, temperature or strenuous exercise stress. Its exposures are acute, and the requirement for detailed performance is limited. For the human diver each of many forces or effects increases with the greater pressures of deep diving, and some increase with duration. Of all these examples he is the only one who becomes "physiologically" trapped by his environment and unable to leave it at will. It requires longer to decompress from exposure to a helium pressure of 1000 feet of sea water than to return to earth from lunar landing.

Fundamental Mechanisms Affected

It is a large error to simplify the prediction of extreme pressure effects in diving by assuming that a specific site or structure is the primary limiting target. Even with equivalent effects upon the chemistry or membrane characteristics of many different cells, the measurable consequences can be expected to vary greatly. In great physiological systems, such as the entirety of our neurological assets, the more complex functions (with more components and steps in chemical and electrical activity), can be expected to fail at lower pressures than will the simpler functions.

It is clear that to learn the limits of (deep) diving requires two related forms of investigation and analysis. Fundamental mechanisms must be examined in any appropriate tissue or animal to pressures well beyond those conceivably reachable by man. And man himself must be systematically examined, step by step, in minute physiologic detail under conditions beyond those to be encountered in practical operations.

#### Primary Stresses of Undersea Activity

A classical philosophy out of basic pharmacology and applied engineering, and applied Pennsylvania's "Predictive Studies" is that response to a drug or physical stress is usually proportional to the drug dose or to the severity of the stress. The quantitative "dose-response" curve can often be used to describe basic cellular reactions or overall human physiologic competence.

Temperature control, hypothermia and hyperthermia are the background against which nearly every other stress of undersea activity expresses itself.

Depth (Feet)	Thermal Comfort Ranges*			
	Low Limit		High Limit	
	°C	°F	°C	°F
400	28.5	83.3	31.5	88.7
700	29.0	84.2	31.5	88.7
900	30.0	86.0	32.0	89.6
1200	32.5	90.5	33.5	91.4

\*From Predictive Studies III (1)

Deep body temperature is a controlled component of the design of the internal environment of the mammalian organism, affecting such basic factors as hydrogen ion activity, calcium ionization, and the kinetics of numerous enzymatic reactions. Its control is not to be interfered with in diving. The real requirement is to eliminate temperature abnormality at all depths rather than

to provide physiologic countermeasures in the presence of uncontrolled or abnormal body temperature.

Physicochemical Effects are important. Helium and neon produce no prominent depression of mental or sensory function at 1200 feet of sea water (1). Since all indications are that inert gases should induce "dose-effect" patterns of functional change, it is probable that helium or neon will not induce disruptive effects on central nervous system function comparable in degree to those of nitrogen until ambient pressures much in excess of 3000 feet of sea water are experienced.

Extreme increase in hydrostatic pressure, even without accompanying solution of gases in tissues, can produce spastic immobilization, paralysis, convulsions, cardiac arrest and death in experimental animals (2,3,4,5).

In man, "moderate" increase in hydrostatic pressure (e.g. 0 to 500 feet of sea water) produces no clearly detectable effect. Higher pressures (e.g. 700 to 2000 feet of sea water), especially when rapidly attained, induce increasing degrees of derangement, including temporary incapacitation (6,7,8). In the absence of evident effect of helium itself, it is generally presumed that the derangement is due to hydrostatic pressure.

#### Limitations

Determination of limitations imposed by hydrostatic pressure has involved (a) study of rate and degree of compression in man to approximately 62 ata (11) and (b) extension of hydrostatic pressure exposures to over 200 ata in animals and isolated tissues (12,9,10).

Prediction of limitations to increased hydrostatic pressure requires the same philosophical reasoning as for narcosis and/or oxygen toxicity. This is that each must be considered to exert effects on more than a single biophysical or chemical mechanism, at many sites and therefore on many functions (12).

On gross and purely practical grounds it is evident from experiment in man that between 0 and 1200 feet of sea water no acute or lasting general handicaps develop when compression is slow, or when a waiting period follows rapid compression (1,11,8). Moreover, adaptation to rapid compression to this pressure appears complete. Following slow compression to 1200 and 1600 feet of sea water general functions remain close to normal in spite of prolonged persistence of some electroencephalographic effects of compression (1, 13,8). At helium pressures between 1600 and 2000 feet of sea water serious limitations of activity appear to persist for prolonged periods without full adaptation, even when compression is slow (14, 11). Rapid compression on He-O<sub>2</sub> to these pressures comparable to

those used in animal studies, could be expected to produce either convulsions or other severe incapacitation.

In the range of still higher pressures not yet explored in humans, it is not possible to predict which of many affected functions have reached their tolerable limits and which have only begun to be affected.

#### Extension of Tolerance

Addition of narcotic substances (gases or other drugs) has been shown to prominently modify effects of very high hydrostatic pressure on isolated tissues (16) and in intact aquatic or terrestrial animals (5,15,12). Conversely, compression can at least partially overcome effects of depressant gases or drugs (5,2). These classical findings in animals have been applied to undersea physiology. The addition of nitrogen to helium breathed by man at high pressure increases tolerance to the effects of hydrostatic compression (22).

Since determination of the scope and quantitative degree of effects produced by hydrostatic pressure alone and with helium has been accomplished only in part, the specific influences of concurrent exposure to other inert gases cannot be defined (8). As pointed out in the previous conference in this series, any site of neurotransmission is a potential site where pressure or anaesthetic may alter several functions (17).

#### Inert Gas Exchange

There is as yet no indication that rate of uptake of inert gas during compression should be limiting for ultimate diving depth. Even if the concept of osmotic forces related to local differential inert gas concentration (18) is eventually determined to have importance, its effects will most probably continue to be over-shadowed by the more drastic influences of hydrostatic pressure. An exception, though not strictly limiting, is the arthralgia of compression which has been conceived as possibly related to osmotic influences of inert gas uptake.

#### Oxygen Toxicity and Oxygenation

Oxygen toxicity must be paired with hydrostatic pressure in any ranking of factors affecting predictions of ultimate diving capability. It presents limits to oxygenation as well as to attainable rates of inert gas exchange and effectiveness in therapy.

At extreme pressures, beyond those yet reached by man, it has been considered on theoretical and indirect empirical grounds that large mammals are incapacitated through limitation of intrapulmonary diffusion of oxygen (19). This is not grossly evident in monkeys exposed even to 200 atmospheres and has not been found in man breathing dense gases to 1200 feet, even in severe exercise (1).

#### Decompression and Counterdiffusion

Extension of limits for excursion diving from saturation depends upon improvement in oxygen tolerance, as does increase in safety of decompression from each other form of diving, and improved therapeutic success in all forms of decompression sickness. The problems of isobaric gas counterdiffusion also have to be considered (23).

While substantial gains in extending oxygen tolerance are being made by programmed alternation of high and normal  $P_{O_2}$ , prediction of further influence upon diving depends in part both upon methods of oxygen use and upon resolution of the scope of acute and chronic effects of hyperoxia.

#### Density of Respired and Ambient Gas

The linear increase in gas density which occurs with increasing pressure induces non-linear decrements in two forms of interchange between internal and external environments. It progressively modifies thermal exchange and ventilatory exchange, toward potential failure of each function.

#### Thermal exchange

The compression of gas (helium) molecules increases heat capacity of the respired and ambient atmosphere, leading to excessive heat transfer between lungs and atmosphere or skin and atmosphere. The result may be intolerable or incapacitating hypothermia or hyperthermia. Since this aspect of deep undersea activity involves physical exchange processes not adaptable to physiological modification, the limitations upon temperature regulation imposed by increased gas density can be predicted to remain unless minimized by engineered systems for adjusting the temperature of ambient and respired gas.

#### Pulmonary Ventilation, Respiratory Control and Exercise Tolerance

Increased respiratory gas density increases respiratory resistance and work of breathing, with inevitable decrements in (a) alveolar ventilation and (b) capability for sustained respiratory muscular effort. At any gas density each is related to the magnitude of pulmonary ventilation and hence to the degree and the duration of physical work being performed.



In the absence of prominent effects of hydrostatic pressure, acute exposure to increased gas density diminishes pulmonary ventilatory capacity in rest and in exercise (1,20) (Figure 2). Predictive Studies III indicated that density effects upon respiratory function (pulmonary ventilation, and respiratory reactivity) at rest and in mild exercise should be tolerable even at gas density equivalent to helium breathing at 5000 feet of sea water (1). There is as yet no reason to revise this prediction for gas density alone.

However, increase in gas density during compression in a helium atmosphere is inevitably accompanied both by increase in hydrostatic pressure and increase in any effect which may be produced by solution of helium in critical tissues. The interaction of such effects with the better defined influences of increased gas density induces subjective respiratory distress not importantly associated with increased gas density at lower pressures (21,14). Even moderate exertion appears impractical during prolonged exposure to helium at pressures of 1800 feet of sea water (14). Since vigorous underwater work has clearly been shown in Predictive Studies to be practical in helium excursions to 1600 feet of sea water (8) (Fig. 1), a zone of sharply increasing decrement between 1600 - 1800 - 2000 feet of sea water breathing helium-oxygen can be predicted. The subjective limitations encountered should be expected to be tolerable at rest, and to be magnified by increasing severity or duration of work.

#### Compensation and Adaptation

Part of the large advance, which has included sustained open sea diving operations at approximately 1200 feet of sea water and demonstration of capacity for hard work underwater to 1600 feet (8), has resulted from determination of the diver, from physiological adjustments of compensation, and from adaptation to the stresses considered in this analysis. Such adaptations will require time, and the time course cannot be expected to be the same for all functions and for all degrees of failure. At the limits of compensation and adaptation acute decrement can then be followed by progressive deterioration and failure of specific functions. This is the ultimate and potentially irreversible limitation to deeper or longer exposure.

#### Deterioration

In several situations exposure to physical or toxic stress will predictably impose true limitations upon extension of diving depth. A considered example is an increase in pressure and respired gas density to such a degree that respiratory work, even at rest, is severe. Continued excessive exertion by respira-



tory muscles, even without considering the probable overlay of hydrostatic effects upon neuromuscular function, will necessarily result in progressive respiratory muscle fatigue, decompensation of respiratory muscles and failure of ventilatory function (1). Sleep would predictably further diminish respiratory reactivity and accelerate the failure of ventilation (21). Since decompression from prolonged exposure to high pressure cannot be rapid, escape or withdrawal from the respiratory decompensation can only be slow.

The example is cited here again to indicate that limits of several forms for compression can indeed ultimately be expected (Fig. 3), even if all factors but helium density and associated hydrostatic pressure are controllable. These limits must be expected to be more stringent in open sea operations than in laboratory chambers.

### CONCLUSIONS

#### Temperature (Hypothermia, Hyperthermia)

Major limitation. Tolerable environmental and respiratory temperature range narrows drastically as pressure increases. No physiological solution, but severe physiological interactions. Should be solvable only by engineering and discipline.

#### Narcosis and other Physicochemical Effects of Inert Gas

Narcosis not limiting. Other effects not defined.

#### Compression and Hydrostatic Pressure Effects

Probably major limitation at great depth. However, even extreme compression rates to moderate depths induce no limiting hydrostatic influences. Prominent adaptation occurs in rapid compression to intermediate depths (1200 - 1600 fsw).

Even slow compression to extreme depths of 1600 to 2000 fsw leads to detectable, sustained effects of pressure. They may not be limiting but need detailed study.

Muscular function - whale can swim at 5000 feet, human muscle should be functional.

Cardiac function - probably not limited to 5000 feet, but uncertain.

### Inert Gas Exchange

Decompression advances in shallow and moderate depths depend upon advanced studies for extension of oxygen tolerance.

Rate of tissue inert gas elimination will remain a physical barrier.

A new bubbledisease, isobaric inert gas counterdiffusion, is important in deep tissues as well as in superficial structures. It is mutually exacerbating with decompression sickness.

### Oxygen Tolerance

Remains the key to improved decompression and therapy. Provides a major area both for improved practical and scientific understanding.

### Gas Density (Respiratory, ambient)

Human lungs are probably not limiting at rest or mild work to depths of 2000 - 5000 feet. Prominent decrease in respiratory reactivity expected to limit alveolar ventilation and work tolerance at depths between 1600-2000 feet. Expect gross interaction with effects of hydrostatic pressure deeper than 1200 - 1600 feet.

### Alveolar/Arterial Gas Exchange

Most likely will not be limiting at pressures to at least 3000 feet.

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Figure 1.

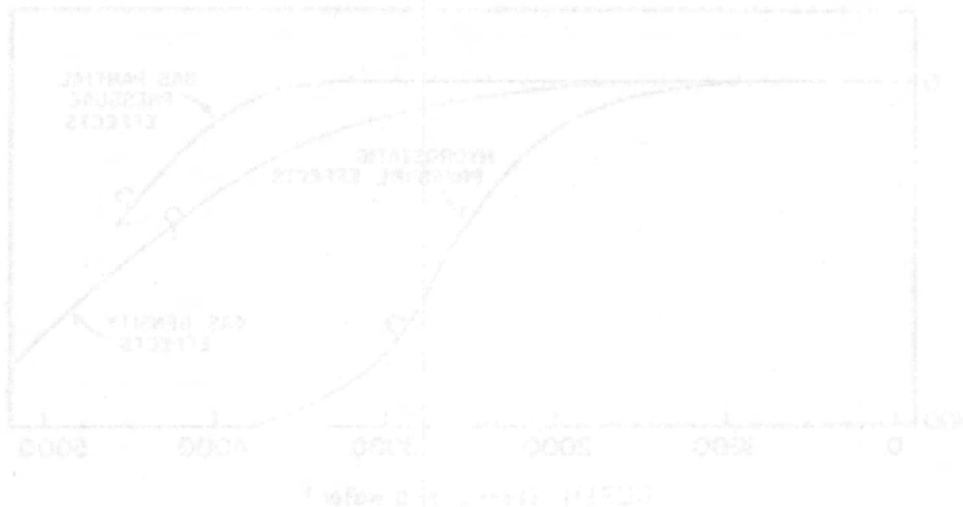
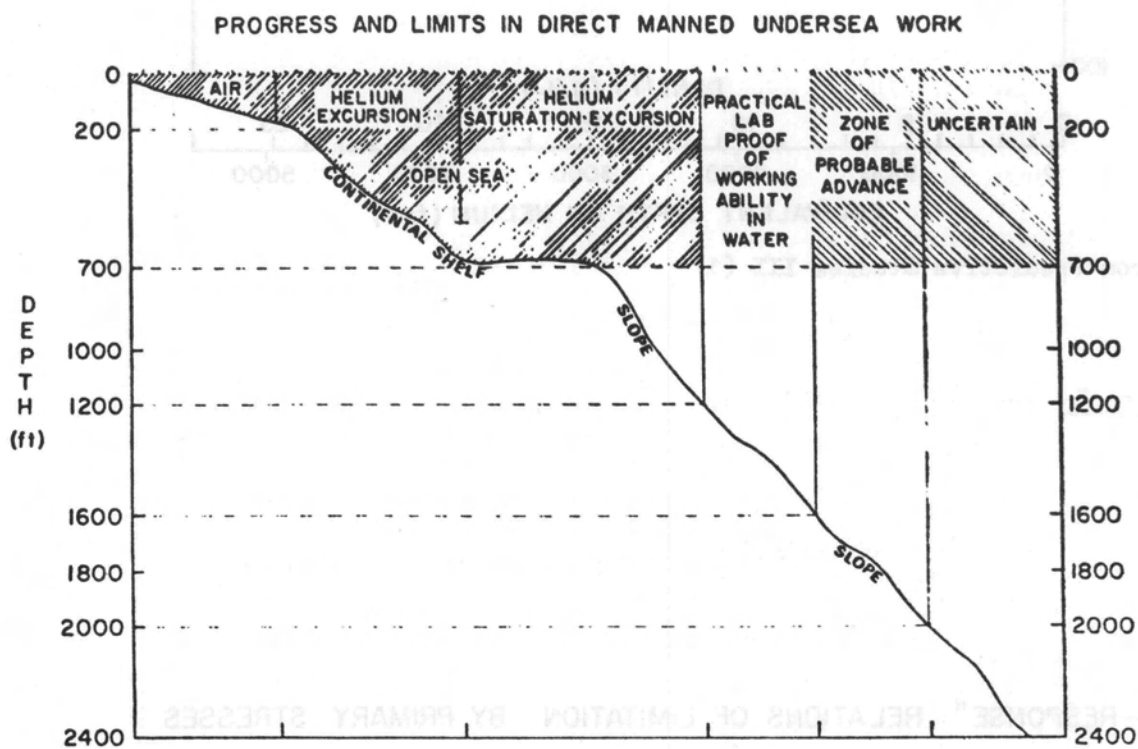
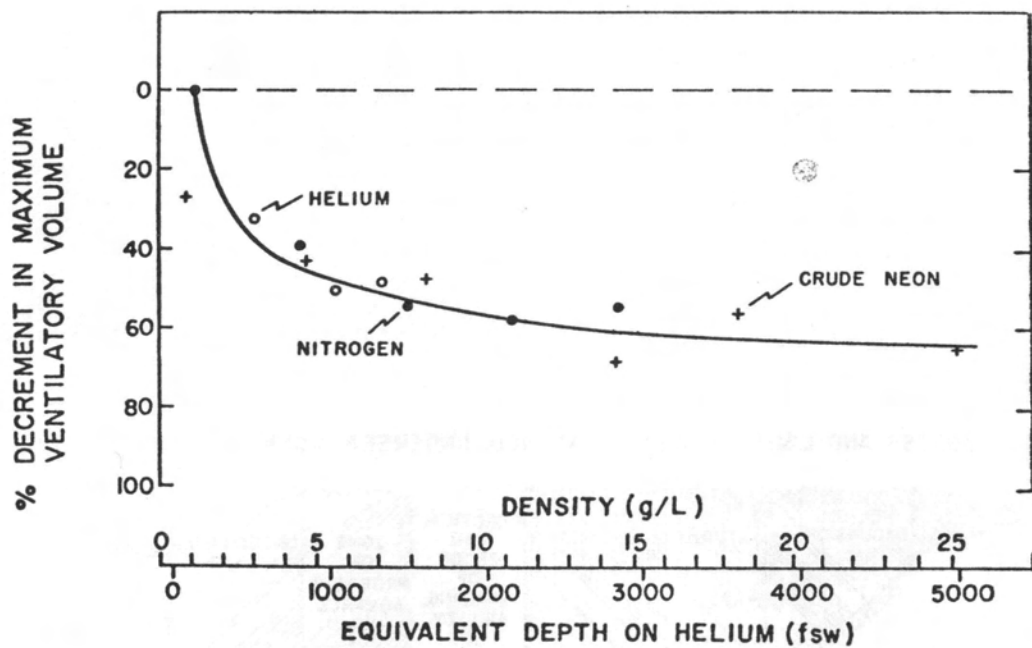


Figure 2

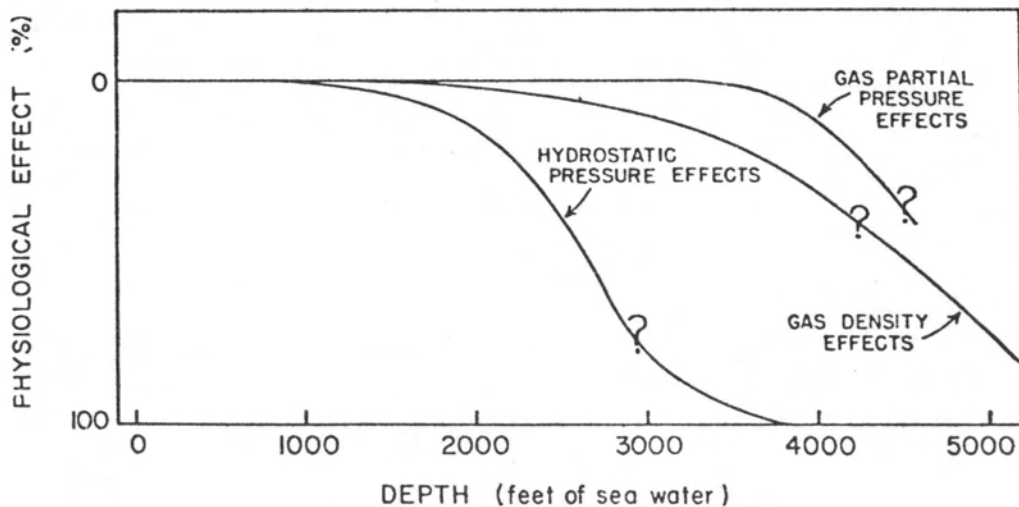
RESPIRATORY GAS DENSITY, AIRWAY RESISTANCE, WORK OF BREATHING AND EXERCISE TOLERANCE \*



\* From Predictive Studies III (1)

Figure 3

"DOSE-RESPONSE" RELATIONS OF LIMITATION BY PRIMARY STRESSES





Limits for both Open Water and Chamber DivingX. FructusEnglish Abstract

This is a summary of our chamber dives (Physalie and Sagittaire) and sea dives (Janus I, II and IV), which provide a basis for suggesting future limits.

The detailed comments on Janus IV - a 460 m sea dive in the Mediteranean - include the observation that the six divers had little manifestation of HPNS and their psychomotor performances were better than those of the divers in Janus III, who were exposed to a similar range of pressures. The difference between these dives may be related to two factors.

1. The later divers were selected on the basis of test dives to 180 m compressed over a 15 min period with a total duration of two hours. We have found that the sensitivity of subjects to this test is a good indication of their sensitivity to higher pressures.
2. Both the compression profile and the use of trimix had been improved.

The result of the Janus IV dive was that the divers were able to make six excursion dives (including one to 501 m) over a three day period. The periods of continuous work in the water ranged from 40 min to 2 hours 21 min.

Based on our experience and other chamber dives (including Atlantic II to 650 m) it is reasonable to predict that man will be able to work below 500 m in the sea and reach 700 m in a chamber dive.

Il nous est difficile de définir avec certitude les limites de la plongée profonde. Toutefois, notre expérience des plongées en caisson (Programmes PHYSALIE et SAGITTAIRE - Voir appendix) et plongées en mer (JANUS I, II et IV et LABRADOR) nous permettent de nous faire une opinion.

Nous limiterons ici nos remarques à l'observation clinique des plongeurs, de leur comportement et de leurs performances, en particulier lors de JANUS IV en mer, par 460 mètres de fond, au large de CAVALAIRE, en MEDITERRANEE (43°07'26" de latitude Nord et 06°31'42" de longitude Est).

Les 6 plongeurs avaient subi, en caisson, une exposition aux mêmes pressions. Ils avaient présenté peu de manifestations due S.N.H.P. Quant à leurs performances psycho-motrices, elles avaient été meilleures que celles des plongeurs de JANUS III A et B dans la même zone de profondeur. Cette nette différence entre JANUS III et JANUS IV peut avoir deux causes:

1° - Les plongeurs de JANUS IV avaient été sélectionnés au préalable en fonction de critères professionnels mais aussi à la suite des résultats des tests pratiqués au cours d'une plongée à 180 mètres à l'héliox: compression en 15 minutes, durée: 2 heures. Il est reconnu que le S.N.H.P. ne se limite pas au syndrome de compression mais l'expérience nous a montré que la sensibilité d'un sujet à la vitesse de compression accompagne généralement sa sensibilité aux hautes pressions. D'où l'utilisation de ce "test des 180 m" pour la sélection des plongeurs profonds.

2° - La courbe exponentielle de compression de JANUS IV représentait un progrès par rapport à celle de JANUS III, et le TRIMIX un autre progrès par rapport à l'HELIOX.

Cet ensemble de facteurs favorables a permis aux plongeurs de réaliser, en 3 jours, 6 excursions, dont l'une à 501 mètres. La durée moyenne de séjour en tourelle fut de 2 H. 40 et la durée moyenne de travail dans l'eau, de 40 minutes mais l'un des plongeurs réalisa 2 H : 21 de travail en une sortie.

En regardant le film on peut constater l'aisance du plongeur au travail sous 460 mètres d'eau de mer. Aucun des six travailleurs n'a eu besoin de monitoring pour accomplir son programme; le self-control a toujours été conservé.

Après une telle expérience et compte-tenu de la profondeur qui vient d'être atteinte en caisson (ATLANTIS II : 650 mètres) il est permis de penser que des hommes pourront travailler au-dessous de 500 mètres dans la mer et atteindre 700 mètres en caisson. A supposer que le facteur limitant respiratoire n'intervienne pas trop à ces profondeurs.

COMEX CHAMBER DIVES BELOW 299 MSW : 1968 - 1979

Date Name Depth (No. Divers)	ELAPSED TIME			BREATHING MEDIA (Bottom)		Tremor	Dysmetria	Myoclonia	Psycho- motor decre- ment	Micro- sleep
	Compression	Bottom	Decompression	I.G.	O <sub>2</sub>					
03 - 1968 PLC 1 335 m (2)	min: 133 (stages)	min: 17	hours: 94 1/2	He (N <sub>2</sub> : 3%)	3.7%	★				
05 - 1968 PLC 3 300 m (2)	min: 85	min: 20	hours: 91	He (N <sub>2</sub> : 4.5%)	2.7%	★★★	★★		★★★	★
05 - 1968 PHYSALIE I 335 m (2)	min: 113 (stages)	min: 20	hours: 97 1/2	He (N <sub>2</sub> : 4%)	2.6%	★★	★	★		
06 - 1968 PHYSALIE II 360 m (2)	min: 115 (stages)	min: 14	hours: 114 1/2	He (N <sub>2</sub> : 4 %)	1.8%	★★	★	★	★	★★

Date Name Depth (No. Divers)	ELAPSED TIME			BREATHING MEDIA (Bottom)		Tremor	Dysmetria	Myoclonia	Psycho- motor decre- ment	Micro- sleep
	Compression	Bottom	Decompression	I.G.	O <sub>2</sub>					
06 - 1968 PHYSALIE III 365 m (2)	min: 123	min: 8	hours: 138 1/2	He (N <sub>2</sub> : 5%)	1.9%	★ ★	★		★	★ ★
09 - 1968 PHYSALIE IV 300 m (2)	min: 180 (1 stage)	min: 10	hours: 103 1/2	He (N <sub>2</sub> : 5.7%)	1.8%	★	★			★ ★
11 - 1970 PHYSALIE V 520 m (2)	hours: 74 1/2 (2 stages)	min: 100	days: 8 1/3	He (N <sub>2</sub> : 0.15%)	0.42 b	★ ★ ★ ★	★ ★	★ ★	★	★
11 - 1971 SAGITTAIRE I 300 m (4)	hours: 164 (4 stages)	days: 7 2/3	days: 5 1/2	He (N <sub>2</sub> : 0.15%)	0.30 b 0.42 b	★				★

Date Name Depth (No. Divers)	ELAPSED TIME			BREATHING MEDIA (Bottom)		★	★		★	★
	Compression	Bottom	Decompression	I.G.	O <sub>2</sub>	Tremor	Dysmetria	Myoclonia	Psycho- motor decre- ment	Micro- sleep
02 - 1972 SAGITTAIRE II 500 m (2)	hours: 49 (non stop)	hours: 100	days: 8	He (N <sub>2</sub> : 0.17%)	0.40 b	★ ★ ★ ★	★ ★	★ ★	★ ★	★ ★ ★ ★
05 - 1972 PHYSALIE VI 610 m (2)	hours: 177 (3 stages)	min: 80	days: 9 1/2	He (N <sub>2</sub> : 0.17%)	0.40 b	★ ★ ★	★ ★	★ ★	★ ★	★ ★
03 - 1973 SAGITTAIRE III 300 m (4)	days: 4 2/3 (2 stages)	days: 15	days: 7	He (N <sub>2</sub> : 0.17%)	0.40 b	★ ★	★ ★	★ ★	★ ★	★ ★
04 - 1974 JANUS IIIA 460 m (3)	hours: 50 (non stop)	days: 6	days: 7	He (N <sub>2</sub> : 0.15%)	0.40 b	★ ★	★ ★	★ ★	★ ★	★ ★ ★

Date Name Depth (No. Divers)	ELAPSED TIME			BREATHING MEDIA (Bottom)		Tremor	Dysmetria	Myoclonia	Psycho- motor decre- ment	Micro- sleep
	Compression	Bottom	Decompression	I.G.	O <sub>2</sub>					
06 - 1974 SAGITTAIRE IV 610 m (2)	days: 10 3/4 (4 stages)	hours: 50	days: 10	He (N <sub>2</sub> : 0.15%)	0.40 b	★ ★	★	★	★	★ ★
12 - 1974 JANUS IIIB 395 m (3)	hours: 50 (1 stage)	days: 6	days: 10	He (N <sub>2</sub> : 0.19%)	0.42 b	★	★	★	★ ★	★ ★
01 - 1975 CORAZ I 300 m (3)	hours: 4 (3 stages)	days: 4	days: 6	TRIMIX (N <sub>2</sub> : 9%)	0.42 b				★ ★	★ ★
04 - 1975 CORAZ II 300 m (2)	hours: 4 (3 stages)	days: 4	days: 6	TRIMIX (N <sub>2</sub> : 4.5%)	0.42 b	★	★		★	★



Date Name Depth (No. Divers)	ELAPSED TIME			BREATHING MEDIA (Bottom)		Tremor	Dysmetria	Myoclonia	Psycho- motor decre- ment	Micro- sleep
	Compression	Bottom	Decompression	I.G.	O <sub>2</sub>					
06 - 1975 CORAZ III 300 m (2)	hours: 4 (3 stages)	hours: 33	days: 6	TRIMIX (N <sub>2</sub> : 4.5%)	0.42 b	★				★
12 - 1975 CORAZ IV 300 m (2)	hours: 4 (3 stages)	days: 3 1/3	days: 6	HELIOX (N <sub>2</sub> ≈ 0.15%)	0.42 b	★★		★	★	★
12 - 1976 JANUS IV 400/460 m (8)	hours: 25 (non stop)	days: 9/7	days: 8 3/4	TRIMIX (N <sub>2</sub> : 4.8%) Progressively	0.42 b ?	★★	★★	★	★	★
03 - 1979 "Selection" 450 m (8)	hours: 38 (4 stages)	hours: 48	days: 10 2/3	TRIMIX (N <sub>2</sub> : 4.8%) Progressively	0.42 b	★	★		★	

Co-operation with  
French Navy

Discussion Session 1: Operational ProblemsC.E.G. Lundgren - Leader

Although some divergence of opinion was apparent between naval and commercial requirements, the following statement was taken as central to the theme of this workshop:

"The need for oil companies to have contingency plans for emergency intervention will justify deep diving for some time to come. The depth which needs to be attained is the maximum at which man can perform useful work in relative safety."

It was stressed that, despite the problems which can occur, Comex have established that hard physical work is possible during open sea dives to 450 m (1476 fsw) and that men have now successfully completed work tasks at a depth equivalent to 650 m (2132 fsw) in a research dive at Duke University (Atlantic II, March 1980).

The discussion following these statements, centered around three topics; the diver vs atmospheric or remote systems, the physiological limitations and the application of selection criteria. This section will deal with the former, the two latter categories will be considered later.

The fundamental advantages of the diver over other systems (e.g. Jim; Wasp; Mantis) were felt to be: 1) the ability to make critical judgements on site and 2) to effect fine manipulations. Consequently it is these skills which must be preserved when the amelioration of the HPNS is considered. In addition to these skills the meeting was reminded that the mobility of the diver, and in particular his vertical mobility, was originally considered a major advantage. Recently this mobility has been increasingly reduced by the umbilical connection employed for safety reasons. Was it not an appropriate time to reconsider the question of mobility and the means of maximising it ?

The areas for improvement in one atmosphere and remote systems were considered. Their essential limitation was felt to be the lack of tactile feed-back, which both limits their operation to conditions of good visibility and prevents fine manipulation. It was suggested, in view of the current research into feed-back systems and the advances of microelectronics, that some two orders of magnitude improvement in remote systems would be evident within 10 years.

In support of the present systems, it was reported that Comex currently preferred to employ one atmosphere systems for tasks below 600 m (1900 fsw).

Finally, the role of proper operator training was emphasised in connection with these systems. As an example of what could be achieved with remote manipulators, the experience of radiological laboratories was cited.

Potential Methods to Prevent the HPNS  
in Human Deep Diving

Peter B. Bennett

In my contribution to the previous workshop (1) I reviewed a number of factors derived from over 23 experimental deep dives between 1965-1975 which appeared potentially able to reduce the signs and symptoms of the High Pressure Nervous Syndroms (HPNS). These included selection of the least susceptible diver; choice of a suitable rate of compression involving an exponential profile with stages during the compression; excursions from saturation at a shallower depth; the use of narcotics such as nitrogen added to the heliox to produce the so-called Trimix; and other factors such as allowing time for adaptation after compression before starting work with cool temperatures.

Since 1975 an additional 19 or so deep dives have been carried out using one or more of the above principles by universities (Duke and Pennsylvania) commercial companies (Comex, K.D. Marine), Navies (U.S.N. Experimental Diving Unit, RN Admiralty Marine Technology Establishment Physiological Laboratory or RNPL) involving four Nations, the U.S.A., U.K., France and Japan and with depths between 600 to 1800 ft.

An additional three further deep dives have been made by AMTE(PL) with helium oxygen to 540 m and by Duke with trimix ( $N_2 = 10\%$ ) to 460 m and to 650 m during the spring of 1980.

This paper will attempt to review the success of these methods in 1975 and afterward since reviews already exist of the 1965-75 era (3,16).

Helium-Oxygen

During the early 1970's, studies at the RNPL (6,7) and by Comex (12,20,24) showed that depths of 1500 ft and 2100 ft could be obtained by slow exponential compressions and stages. Since then there has been less interest in this type of dive. Primarily this is due to the commercially unrealistic lengths of time involved with such compressions (e.g. 10 days to 2,100 ft) and yet often leaving the diver still affected by varying degrees of HPNS which could be incapacitating in an ocean situation.

However, in 1976 the AMTE(PL) carried out a dive to 300 m (15) (AMTE/PL5)\* using a linear compression rate of 1 m/min. There was nausea, unspecified epigastric sensations, intention tremor and

\*For summary of dives see appendix

impending loss of consciousness. Previously in 1969 Buhlmann (10) made a much faster compression to 300 m at 5 m/min producing only mild dizziness and an initial decrement in psychomotor tasks which had gone 2-3 hrs later. The reasons for the differences between these two dives are not clear but it would seem most likely to be due to personal susceptibility.

One clear characteristic of the subsequent dives with very slow compressions (AMTE/PL 6, 7 and 8) is no nausea and possibly little change in the EEG. However, whilst very slow compressions do considerably ameliorate or even prevent HPNS in suitable subjects at 1000 ft, at 420 m (1377 ft) even with 6 days of compression some signs of HPNS are still present, including loss of appetite, periods of unspecified epigastric sensation and persistent intentional tremor with occasional muscle jerks. With a further depth increment 300 ft deeper, these become more severe and are compounded by additional signs and symptoms severely limiting functional ability.

Thus in 1979 AMTE(PL) and the USN Experimental Diving Unit carried out very similar dives. In the British dive (AMTE(PL) 9) to 540 m (1771 ft) there was marked nausea, tremors, dizziness, vomiting and loss of appetite. Marked intention tremor and epigastric sensations persisted.

The U.S. Navy dive was to 1800 ft. Fatigue, dizziness, nausea, vomiting, aversion to food with 8% weight loss, stomach cramps, diarrhea, myoclonic jerking and dyspnea were present and the divers deteriorated rather than improved with time at depth but they were able to work at 100 watts in connection with respiratory studies (Spaur 1979, personal communication).

These studies show that at these very slow rates of compression, which virtually eliminate the effects of compression, the hydrostatic pressure is inducing severely incapacitating HPNS between 1400 to 1800 ft. The recent results are perhaps a little worse than the first British dives to 1500 ft in 1970 and the early French Physalie and Sagittaire series in 1972 and 1974 to 1640 ft and 2001 ft (12). These may be due to the choice of faster compressions and to the stages and linear compressions. The choice of exponential compressions and stages should improve the results. Nevertheless both from the view of getting to the work site and the economics involved, plus the questionable functional ability of the diver on a regular operational basis, the limits of the helium-oxygen only diving without excursions or trimix would seem to be about 1500 ft.

#### Helium-oxygen plus Excursions

During the period 1969-75 there was considerable interest in the potential use of helium-oxygen saturation at a shallower depth

with excursions to the working depth. These studies (2,10,26) and the Ludion (13) and JANUS series I-III by the Comex company showed that some reduction or even elimination of HPNS could be obtained at the working depth by this method, even to depths as deep as 1500 ft (460 m) from saturation at 1277 ft (390 m). Again, however, the greater the depth, the less effective this method appeared to be and the less the excursion depth could be without signs and symptoms of HPNS occurring, such as tremors and EEG changes.

The University of Pennsylvania looked further at this method during Predictive Series IV (18). This large investigation was in two phases. Phase 1 primarily studied a 1 hr compression to 800 ft with excursions to 1200 ft, the first after a 2 hr hold at 800 ft. After no HPNS at 800 ft the first excursion with compression to 1200 ft in 40 mins produced headache, dizziness, slight nausea, tremors and incoordination and some difficulties in concentration, but subsequent excursions to 1200 ft during the 7 and 8 days of saturation at 800 ft showed no problems and is in agreement with the earlier Swiss, French and American work of excursions being a beneficial method of diving to 1200 ft. However, Phase 2 involved a  $3\frac{1}{2}$  hr compression to 1200 ft and after a 22 hr hold, excursions to 1600 ft. As with the Comex Physalie III dive, on arrival at the 1200 ft saturation depth, marked HPNS was present with nausea, vomiting, fatigue, tremors and nervous tension present. After 2 hrs the divers had improved and were self sufficient but exhausted. Performance decrements slowly recovered and there were intermittent EEG theta wave increases.

After the 22 hr hold the first excursion to 1600 ft in 40 mins for 55 mins showed some mental slowness, slowness of responses, prolonged reaction time, increase in error incidence and occasional brief episodes of failure to follow well learned specific test/manipulation procedures with feelings of tenseness or "nervousness" and visible tremors and muscle fasciculations. The EEG showed increased theta and decreased alpha activity. Subsequent compression showed less HPNS and it proved possible to decrease the compression time to only 20 mins without causing appreciable HPNS and permitting useful underwater work at self-competitive rates "with timing and skill generally equivalent to that at the surface involving an oxygen consumption of 2 L/min".

By comparison with the very slow 6-8 day compressions with helium-oxygen described earlier, the time of arrival at 1600 ft of about a day, including the 22 hr hold at 1200 ft, is indeed rapid. However, it resulted in severe HPNS at 1200 ft prior to the excursions, although adaptation did occur with time and the excursions did not appear to make the HPNS worse. On the contrary, there was a gradual improvement. Obviously such a profile is not a practical



method of diving, due to the severe HPNS induced by the  $3\frac{1}{2}$  hr compression to 1200 ft. A natural question that follows is what would be the optimal heliox compression time to reach 1200 ft without causing HPNS? The answer probably lies somewhere between 3 hrs and 2 days. The next question is could you then make similar rapid excursions in 10 or 20 mins to 1600 ft without undue HPNS? How much time should be spent at 1200 ft before such an excursion? From the present data it seems that once severe HPNS has occurred it will never be as bad again no matter how fast the compression. Does the opposite follow that if severe HPNS has been prevented, then very rapid excursions will cause HPNS? Only further experiments will permit answers to these problems. However, assessment of the use of either helium-oxygen alone or with excursions suggests that divers will not be fit to work at 1500-1600 ft without a delay for compressions and adaptation of probably at least 2 days.

#### Helium-Nitrogen-Oxygen (Trimix)

In the search for methods which might allow more rapid compression to the worksite, use of the so-called Trimix (i.e. He-N<sub>2</sub>-O<sub>2</sub>) or narcotic reversal of HPNS has received marked attention. First reported in tadpoles and later mice and rats (8,17,21), the method was first used in man at Duke Medical Center in 1974 in attempts to prevent HPNS in humans compressed to 1000 ft in 33 mins using 18% N<sub>2</sub> (4). Although this did prevent the HPNS, euphoria due to nitrogen narcosis was present in 2 of the 4 subjects.

Therefore further studies were made in 1974 with 5 divers exponentially compressed with 3 brief stages to 1000 ft in 33 mins breathing a 10% N<sub>2</sub> Trimix. No narcosis, tremors or EEG changes occurred and there was no nausea or significant changes in performance ability (5). Work was carried out for 44 mins in 56°F water by a diver in a heated suit who reported mild euphoria.

Similar results were reported with 13% N<sub>2</sub> in Trimix for compressions of 100 ft/min to 1000 ft in the ACCESS series (14) and by the Comex Co. in their CORAZ series (3).

The CORAZ series (11,22) were three dives to 1000 ft with a total compression time of 4 hrs but with different nitrogen percentages of 4.5%, 6.5% and 9%. It was found that euphoria limited ability to perform any work in the water at the 9% N<sub>2</sub> and disturbing paroxysmic EEG discharges were seen in one of the divers during the early part of the dive. Although there was no significant difference in the performance results between the three nitrogen percentages, 4.5% N<sub>2</sub> appeared to overall be best for ameliorating the HPNS without causing euphoria. Krasberg in 1976 (personal communication) also made a 35 min compression to 1000 ft with a 6.4% N<sub>2</sub> Trimix plus

1½ oz. scotch whisky and performed satisfactorily a "typical oilfield task". As a result of these experiments the question arises as to whether there is a correlation between the rate of compression and percentage of nitrogen present, so that the faster the compression the more HPNS is present and the more nitrogen or narcotic is needed to suppress it.

Investigations of Trimix at deeper depths were made in 1976 by a Duke team using the AMTE/PL chamber at Alverstoke and commercial divers. First, a dive was made to 400 m (1312 ft) with a compression time of 1 hr 40 mins using 6% N<sub>2</sub> in HE/O<sub>2</sub>.

This resulted in performance decrement, marked tremors, dizziness, lightheaded feelings and confusion. There were no arthralgias but slight nausea in one subject. The subjects said they would have locked out to work and there was improvement over the 2 hrs at 1312 ft. However, it was felt that the divers would have been in much better condition with either more nitrogen or a slower rate of compression.

Therefore a week after the 6 day decompression from the previous dive an attempt was made at rapid compression to 1600 ft. The first stage of compression was again to 1312 ft but in 2½ hrs instead of 1 hr 40 mins. This time the divers were fit and well with only some mild dizziness. After a 30 min stage compression was resumed at 3 ft/min but at 1521 ft (464 m) the decision was made to stop the dive due to severe HPNS with fatigue, somnolence, nausea, tremors and increased theta activity in the EEG. Interestingly lying against the cold chamber decreased the dizziness.

Atlantis 1 (Fig. 1) is the first dive in a series of dives over the next few years whose primary objectives are first to try to establish the relationship between a given partial pressure of nitrogen and the rate of compression in preventing the HPNS and second to determine the single and combined effects of inspired gas density, hydrostatic pressure and narcosis on various respiratory and circulatory parameters. Arterial blood gases during rest and exercise will be made in investigating the dyspnea reported by a number of deep oxygen-helium divers.

Analysis of the data from Atlantis 1 indicates that during the final stages and immediately after compression, the 3 divers experienced HPNS with variable degrees of nausea and fatigue. Intention tremor was significant but the nitrogen suppressed the postural tremor. By day two, although the divers appeared normal, their performance tests still showed a mean reduction of some 10% from control values compared to a mean 30% decrement for the first day when the compression effects were at their peak. This result seems mainly due to the divers carrying out their tasks more slowly than previously, since all their tests were completed satisfactorily, including the very complex pulmonary function measurements and

arterial catheterization, blood gas sampling and analysis. Although work limiting dyspnea was present during moderate exercise whilst breathing only helium oxygen or trimix, the arterial blood gases were within normal limits. Indeed, the dyspnea seemed worse with helium-oxygen alone and suggests that the dyspnea may be of central origin due to an HPNS effect on the respiratory centers.

The psychomotor tasks were less adversely affected except for the Bennett Handtool test which involved assembly of nuts, bolts and screws with tools. The latter clearly shows (Fig. 2) the biphasic effect of first the 40-50% reduction due to compression effects followed by a 20% reduction due to pressure itself.

The electrical activity of the brain also showed a marked increase in theta (4-6 hz) and delta (2-4 hz) activity during the first two days (Fig. 3) as it did too with the faster frequencies (Fig. 4). However, after the adaptation to the compression phase the delta and theta activities remained increased above normal whilst the faster EEG activities were depressed.

In Atlantis 2 the same compression profile was used by 3 divers (2 the same as Atlantis 1) but the nitrogen was increased to 8.8% (Table 1). There were no signs and symptoms of HPNS: no nausea or dizziness, no tremors or fatigue and the divers slept well. One of three divers experienced dyspnea but the others were not affected and the pulmonary function studies showed that the men could work at remarkably high levels without difficulty.

One significant difference from the early trimix dives was that the compression was with trimix throughout rather than starting compression with air and then continuing with helium as in the earlier trimix dives. Experiments with the *Papio papio* monkey (23) showed that the best method of preventing HPNS in a trimix ( $N_2$  6.5%) dive to 1000 m (3,282 ft) was injection of nitrogen 7 times during compression every 100 m from 300 m rather than just at the start or end.

Comex made a similar trimix dive to 450 m (1476 ft) with 4.8% nitrogen but with a slower exponential compression with stages of 40 hrs by 8 divers. Tremors and myoclonic jerking were suppressed but the EEG theta increase and decrease of alpha remained. Performance decrements were only 6-10%. As with the Duke dive the presence of nitrogen seemed to differentiate between compression and hydrostatic pressure effects and the divers were much improved the second day and better than in previous oxygen-helium dives to this depth. Thus although the Duke 12 hr 20 min compression rate was too fast with the 5%  $N_2$  trimix, the French 40 hr compression was satisfactory. It may be possible to reduce this further or again the use of 10%  $N_2$  may be of more benefit with the more rapid compression.

### Use of Trimix plus Excursions

In 1977 Comex and the French Navy carried out the JANUS IV series (19,25) using virtually all of the principles previously discussed with 4%  $N_2$  in trimix in pre-ocean studies, exponential compression to 460 m (1508 ft) was achieved in 24 hrs including 4 stages. The degree of HPNS was not sufficient to affect the work of the divers. Later in 1977, an ocean dive was made off the south coast of France to conduct pipe line connection operations, at 460 m (1508 ft). Three men also made two ten minute excursions to 501 m (1,644 ft)(9).

Six divers were selected from 20 pre-screened volunteers by means of seven tests for compression sensitivity, high pressure sensitivity, vigilance and EEG stability, manual dexterity, cardio-respiratory function, urinalysis and self-evaluation. Due to equipment problems on the dive ship, initial exponential compression with stages to 430 m with heliox and 4% nitrogen took 30 hrs and a further 30 min was added for compression to 460 m (1508 ft). The study proved that men could perform work as capably at that great depth as they have previously at 700 to 1000 ft. Use of the principles of diver selection, exponential compression rates with stages, trimix and excursions therefore permitted a relatively fast compression to 1508 ft with ability to work effectively and with excursions to 1644 ft. Whether such methods will permit effective operational diving to even greater depths remains an important topic for future research, as does the potential long range effects if any of exposure to trimix. However, this review does show that, as in the past, the keenness of some to draw depth limitations to diving man continues to be confounded by the solution provided by careful and ingenious research solutions.

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TABLE 1

ATLANTIS II TRIMIX DIVE  
Helium/Oxygen 0.5 ata/Nitrogen 10%

- DAY 1 : Compression to 460 m (1509 ft) 12 hr 20 min compression Days 1 to 6 at 1509 ft (Performance tests/Pulmonary function)
- DAY 7 : Compression with He/O<sub>2</sub> only at 0.2 m/min to 500 m (1640 ft) in 3.3 hrs giving 8.846% N<sub>2</sub>. Hold 2 hrs.  
 Compression with He/O<sub>2</sub> only at 0.15 m/min to 560 m (1841 ft) in 6.6 hrs giving 8.234% N<sub>2</sub>. Hold 14 hrs.
- DAY 8 : Compression with He/O<sub>2</sub> only at 0.1 m/min to 611 m (2004 ft) in 8.3 hrs giving 8.011% N<sub>2</sub>. Hold 13.8 hrs.
- DAY 9 : Compression with He/O<sub>2</sub> only at 0.1 m/min to 650 m (2132 ft) in 6.6 hrs. Hold 24 hrs: 7.862% N<sub>2</sub>; %O<sub>2</sub> = 0.914; Density 15.7 g/L.
- DAY 10: Start decompression at 2.5 m/hr reducing nitrogen to 5% by 1500 ft.

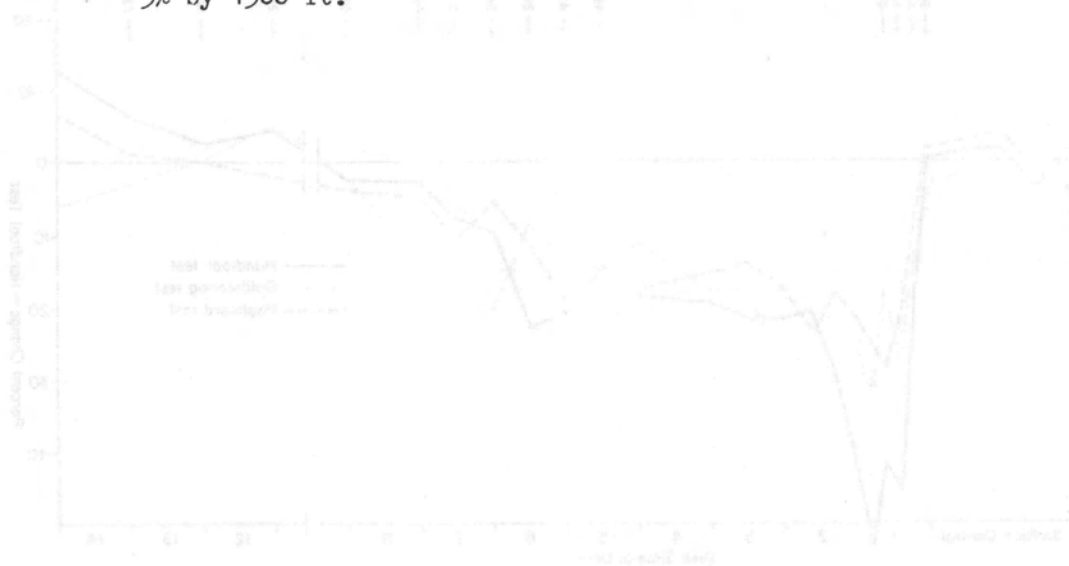


Fig. 2. Mean decrease in the ratio of pulmonary performance in Atlantis I study.

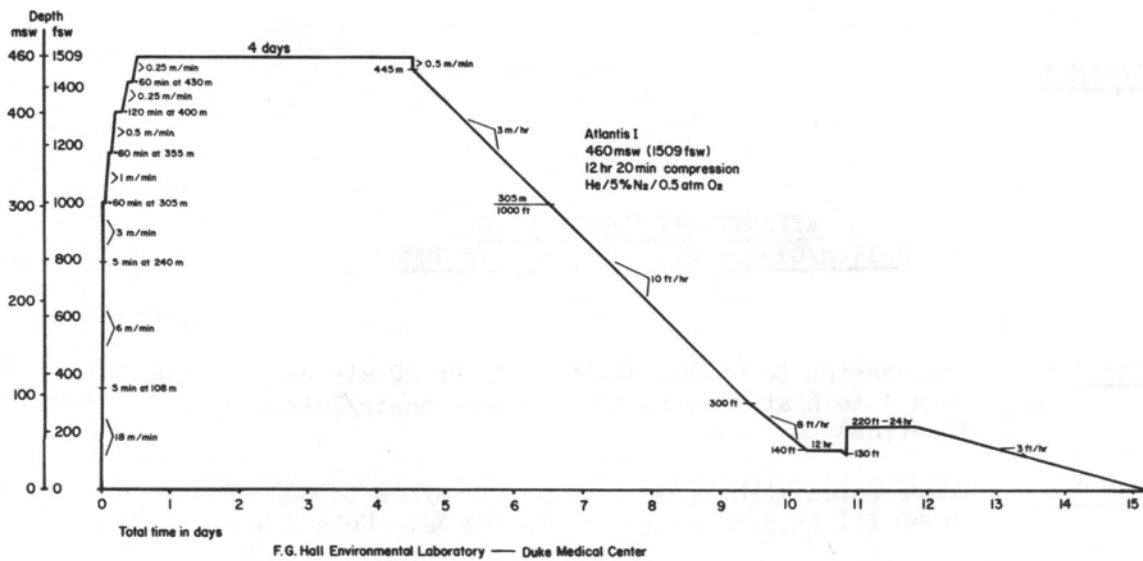


Fig. 1: Profile of Duke Atlantis I experiment in which 3 subjects were compressed to 460 m breathing Trimix.

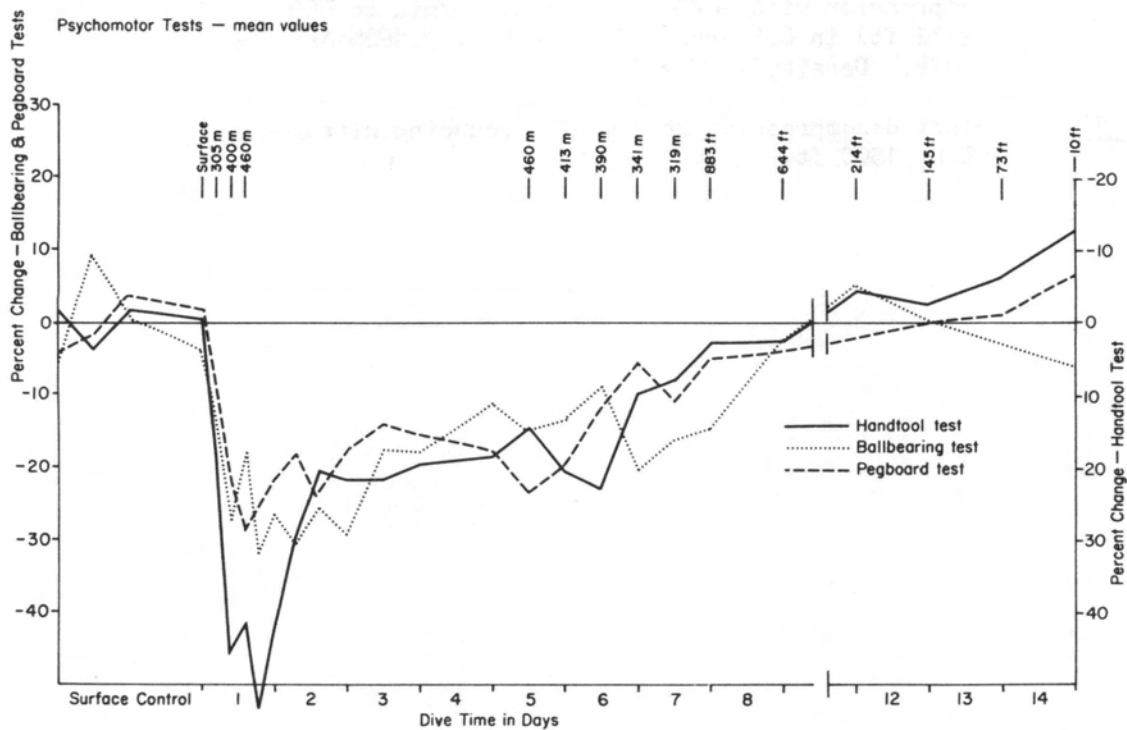


Fig. 2: Mean decrement in the tests of psychomotor performance in Atlantis I study.

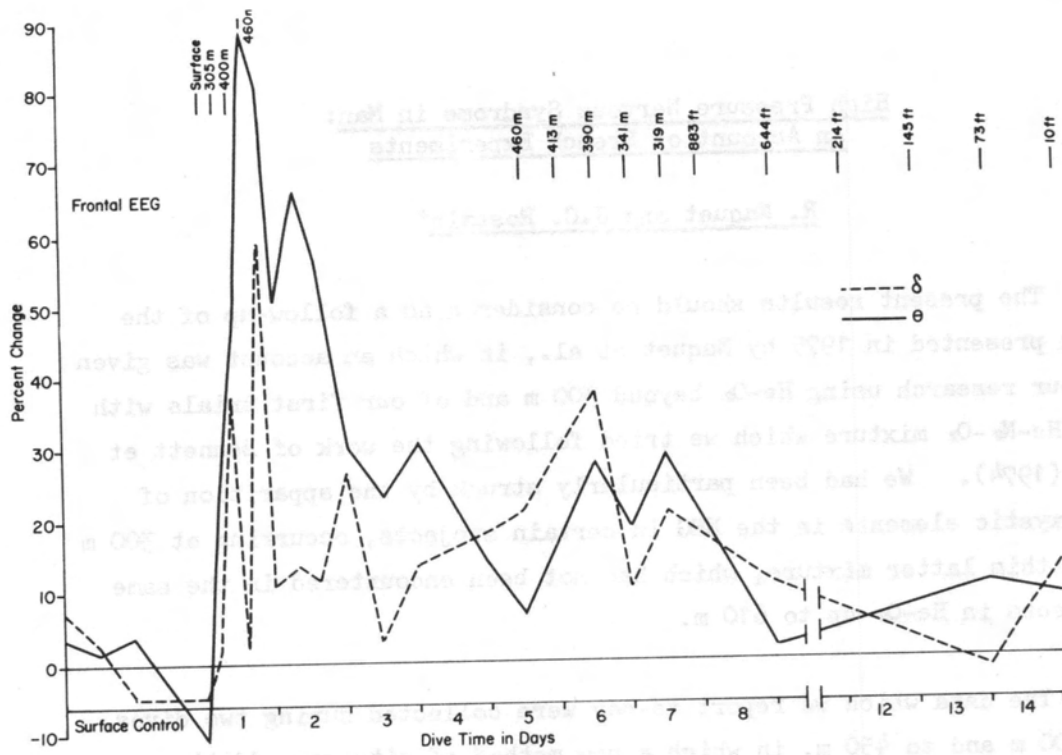


Fig. 3: Mean changes in the delta (2-4 hz) and theta (4-6 hz) activities of the EEG of the subjects in Atlantis I study.

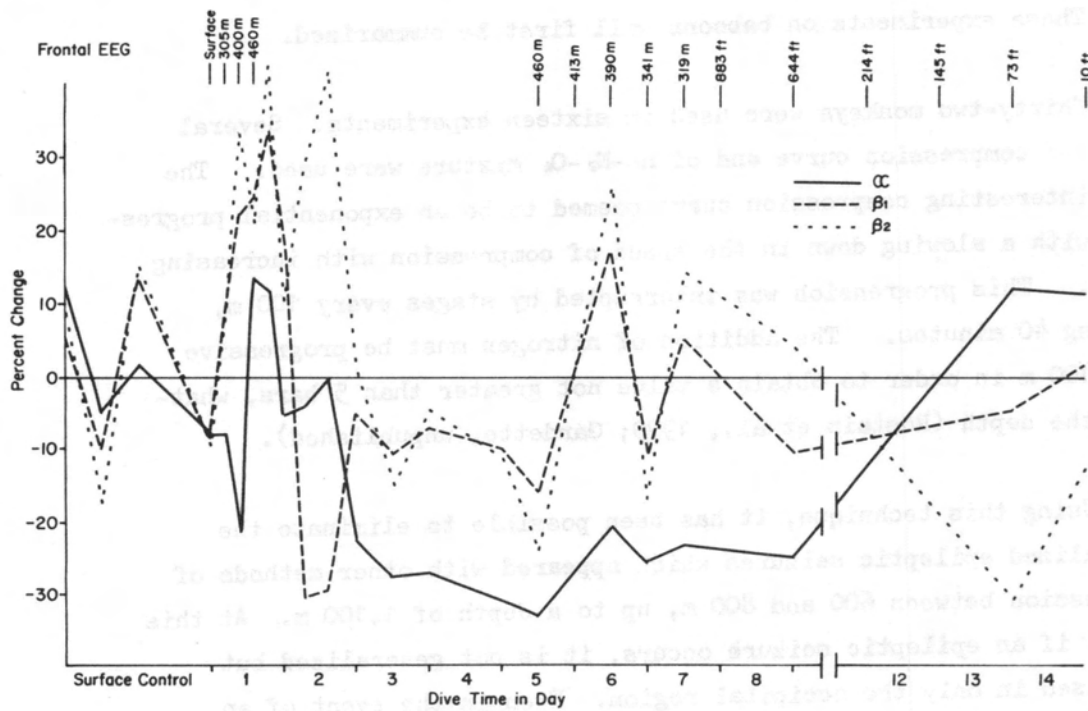


Fig. 4: Mean changes in the EEG fast activities ( 7 - 12 hz, 12 hz) of the subjects in the Atlantis I study.

High Pressure Nervous Syndrome in Man:  
An Account of French Experiments

R. Naquet and J.C. Rostain\*

The present results should be considered as a follow-up of the work presented in 1975 by Naquet et al., in which an account was given of our research using He-O<sub>2</sub> beyond 300 m and of our first trials with the He-N<sub>2</sub>-O<sub>2</sub> mixture which we tried following the work of Bennett et al. (1974). We had been particularly struck by the apparition of paroxystic elements in the EEG in certain subjects, occurring at 300 m with this latter mixture, which had not been encountered in the same subjects in He-O<sub>2</sub> up to 610 m.

The data which we report to-day were collected during two dives, to 400 m and to 450 m, in which a new method of nitrogen addition, developed using baboons (Imbert, 1978; Rostain et al., 1977, 1978, 1979; Gardette, unpublished) was used.

These experiments on baboons will first be summarized.

Thirty-two monkeys were used in sixteen experiments. Several types of compression curve and of He-N<sub>2</sub>-O<sub>2</sub> mixture were used. The most interesting compression curve seemed to be an exponential progression with a slowing down in the speed of compression with increasing depth. This progression was interrupted by stages every 100 m, lasting 40 minutes. The addition of nitrogen must be progressive from 100 m in order to obtain a value not greater than 5 bars, whatever the depth (Rostain et al., 1979; Gardette, unpublished).

Using this technique, it has been possible to eliminate the generalized epileptic seizures which appeared with other methods of compression between 600 and 800 m, up to a depth of 1,100 m. At this depth, if an epileptic seizure occurs, it is not generalized but focalised in only the occipital region. Even in the event of an epileptic seizure, it was possible to recover the animals subsequently in good condition.

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This technique retards the apparition of tremor and reduces its intensity. Myoclonus, and a new symptom characterized by phases of motor agitation, are still present at great depths. This technique does not eliminate the occurrence of slow EEG elements but their increase remains slight and from 800 m there is a progressive depression of physiological EEG activity.

It was these new techniques of compression which were employed in man in 1976 during a dive to 400 m (JANUS IV) and in 1979 in a dive to 450 m. The compression curve was improved between the two dives and that of 1979 was slower than that of 1976. In both cases, the progressions were exponential and slowed with the depth, with longer staging halts in the latter than in the former (Rostain et al., 1977, 1980a, b) and also used different nitrogen addition procedures in order to obtain 1.6 bars in the first and 2.2 bars in the second. The two dives included a stay on the bottom of several days which made it possible to dissociate the symptoms due to compression from those linked to the pressure or the mixture. The second compression gave better results than the first but the symptomatology was similar in the two dives.

In both cases, the subjects supported the methods of compression reasonably well: they showed no euphoria nor any behavioural disorders. They were much more fatigued by the first dive, after which they required 24 hours to recuperate, than in the second.

Tremor was less marked than with the mixture He-O<sub>2</sub> but was not reduced to zero; the increase was not more than 100% but where it was present on arrival at the bottom, it persisted throughout the stay. In no case was there myoclonus and dysmetria, where it occurred, was slight.

During the initial, most rapid phase of compression, in both cases the subjects could be subject to diurnal drowsiness but this was much greater and more frequent during JANUS IV.

EEG abnormalities varied from subject to subject during the two compressions; they were greater in JANUS IV but in the second dive the percentage increase in slow activity in the frontal region rose by more than 1,000% in certain subjects.

This slow activity diminished in all the subjects during the stay but never completely disappeared.

None of the sixteen subjects showed paroxystic elements in the EEG, analogous to those described during the CORAZ experiments (Naquet et al., 1975; Rostain et al., 1980a,b).

During both dives, but especially in JANUS IV, certain subjects showed frequent modifications of the EEG resembling microsleep, as soon as the eyes were closed in the initial rapid phase of compression.

In all the subjects, in both dives, a greater change in performance was observed on arrival at the bottom than at the end of the stay (Lemaire, 1979; 1980).

This behavioural and electrographic symptomatology, characteristic of high pressure nervous syndrome, varied in severity and was different from subject to subject. In addition, not all the symptoms appeared simultaneously; certain, for instance the tremor and the tendency to sleepiness were immediate; others, for example the modification of the EEG, developed progressively and after a delay. This delay was especially apparent for the initial periods of compression which were the most rapid.

The observed latency of appearance of the EEG modifications is a new and important fact; it may perhaps explain certain divergencies in the data collected by different authors. It has also been encountered during a whole series of rapid compressions to 180 m in 15 minutes, both in the He-O<sub>2</sub> mixture and with the He-N<sub>2</sub>-O<sub>2</sub> mixture.



In the course of these rapid compressions, the maximum EEG abnormalities may occur only after seven hours at the bottom, although the maximum tremor is immediate. These rapid compressions have also been shown to have a test value for the EEG modifications which are found at greater depth in a given subject, particularly when the gas mixture used is the same in the two compressions (Rostain et al., 1980a, b).

Conclusion :

1. The experiments carried out on baboons have made it possible to improve over the last five years the method of compression both for animals and for man, and in the latter, in spite of a reduction in the overall duration of the compression. To give an example, in 1979, eight subjects were able to reach 450 m in 38 hours, while in 1974, with the techniques used at that time, 72 hours were required to reach the same depth with an analogous symptomatology.
2. The association of a certain percentage of nitrogen with the He-O<sub>2</sub> mixture appears to be less dangerous than we thought in 1975. However, animal experimentation has shown that, apart from the percentage of nitrogen, the moment at which it is introduced is also important and the progressive addition procedure, although we cannot properly explain its mode of action, has made it possible to obtain better results both in monkeys and in man.
3. The test dives to 180 m should make it possible to establish a selection of divers for the greatest depths, at least where the EEG is concerned and especially for analogous mixtures. It is necessary, however, to underline that the degree of modification of the EEG cannot be correlated with the changes in performance.
4. The HPNS as it was described in 1969 (Brauer et al.), while remaining valid, must be slightly revised. It seems that some of the symptoms described as characteristic of the HPNS are more likely to be the consequence of the compression than of the pressure alone,

at least for analogous depths. Also the variability of the symptoms according to the subject and to the mixture used suggests that this should not be considered as a single entity, but as the association of multiple symptoms of different origins.

5. Lastly, it is possible, at least with animals, using such a compression profile and a progressive nitrogen addition, to retard the appearance of one of the most serious symptoms of HPNS, the convulsive seizure. However, it should be noted that the disappearance of this alarm signal cannot be without danger since, in its absence, access to greater depths may perhaps reveal other more serious signs, without any warning.

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Deep Diving: U.K. ExperienceZ. Torok

The Deep Dive Programme: Most of the scientific results from the first 6 simulated dives have been described in a detailed report, Hempleman et al (1978). The subject of this presentation is a summary of the following two dives, 7 and 8. 9a in March 1979 was to 180 m, with a comparatively fast uninterrupted linear compression profile of 15 m/minute. 10b (October 1979) was a similar training dive with a 5 m/minute linear compression. Another 180 m dive, No 10a (September 1979), and the most recent experiment in the series, Dive 11 (February 1980) to 300 m, were planned to go on to 540 m but abandoned at the subjects' request. In any human experiment the subject has the right to withdraw at any time, and clearly with hindsight, mistakes were made in selection of the volunteers.

For Dive 9b (May 1979) commercial divers were loaned by Star Offshore Services Ltd and compression proceeded to 540 m as planned. The daily dose of compression was 180 m initially, and 120 m on each of the following 3 days. Compression rates were 5 m/minute to 420 m, 3 m/minute to 480 m, and 1 m/minute to 540 m. Tremor and other motor signs were the most prominent features of this compression.

Decompression: The RN standard helium saturation decompression table was used in one of the 180 m dives. This exception apart, decompression was carried out on an experimental schedule based on a 28 m/day depth-independent rate. We did not decompress overnight. The final days' profiles have been subject to various attempts of slowing in view of the high incidence of limb bends experienced on this type of decompression.

Dives 7 and 8 : In these two 43 bar exposures one of the salient features of design was very slow compression to facilitate study of "depth" and "rate" effects of pressure separately. 60 m of compression was carried out daily, in 6 increments, separated by 2 hours. In Dive 7, 48 hours' hold was imposed at 250 m, due to a throat infection in one subject. In this dive there were only very minor ill-effects at 43 bar, in contrast to Dive 8, where two different men suffered severe HPNS. Most of this developed in the last 30 m, and was severe enough so that further compression, had it been planned, would not have been proceeded with.

Respiratory studies in Dives 7 and 8 were aimed at measuring the maximum voluntary ventilation (MVV) of our subjects at depth and confirming by the use of a bicycle ergometer the relationship between gas density, maximum voluntary ventilation and tolerated workloads. When performing MVV at depth subjects felt that they were working harder than at the surface, but none described their experience as breathlessness or discomfort.

All subjects maintained ventilation and a workload corresponding to 60% of MVV at 420 m. On 150 W load subject DH stopped work after 6 minutes during a rebreathing manoeuvre, due to dyspnoea. Subject PA stopped after  $7\frac{1}{2}$  minutes for the same reason. Subject PD completed the task at 150 W, but stopped work after  $3\frac{1}{2}$  minutes on 200 W due to knee problems as well as breathlessness.

Metabolic Balance: An important study carried out in these 2 dives was based on the concept of metabolic balance (Nardin, 1976). It is possible to design a diet tailored to individual requirements of each subject with key components kept constant within 24-hour periods. When such diet is consumed for a number of days prior to the commencement of a dive, the 24-hourly output from the body of these chemical compounds will become constant, free from the potentially large fluctuations imposed by variations of the intake. The body is then in a steady state, or metabolic balance. Departures from this state coincident with an event such as a simulated dive can now be perceived without much of the noise on the output signal, and causally linked to the coincident event. Success with this technique depends on attention to detail, multiple safeguards such as inert markers, and discipline in providing and consuming the prepared food and collecting all excreta. 48-hourly venous blood samples were taken throughout the dives.

Nitrogen Balance: There was no change in  $Ca^{++}$ ,  $Mg^{++}$  and  $PO_4^{--}$  balance in any of the subjects. Nitrogen balance was maintained down to 360 m, indicating negligible effect of the way of life imposed by confinement in the pressure chamber. Thereafter all 4 subjects showed negative nitrogen balance, with 4-8 g daily deficit. There was a corresponding compensatory nitrogen retention during decompression. An increased urea output accounted for the lost nitrogen at depth.

Musculo-skeletal Proteins: The circulatory level of 3-methyl-histidine is a good indicator of both actin and myosin turnover and can be used as an indicator of catabolism of muscle protein after injury and the following bed rest. The urinary output of hydroxyproline, against the background of constant dietary intake, may be used as index of the integrity of collagen. The serum concentrations of proline-imino-peptidase may also be used as an indicator of collagen catabolism. These three quantities were shown to remain constant during Dives 7 and 8; therefore by the above criteria the measured negative nitrogen balance cannot be due to increased catabolism of protein constituents of the musculo-skeletal system. By inference, other body proteins, such as stores, are implicated.

Amino Acids: Circulatory levels of 21 amino acids have been concurrently studied in Dives 7 and 8. The only significantly (2-3 fold) raised concentration found was that of glycine, with slight increases in lysine, valine and methionine.



Hormones: There were also concurrent increases in blood levels of cortisol, noradrenaline, thyroxine ( $T_4$ ), and thyroid stimulating hormone, and decreased serum insulin. Free fatty acids, urea, triiodothyronine ( $T_3$ ) and unbound thyroxine ( $T_4$  resin uptake) showed no significant changes. In the proposed chain of events  $T_4$  has a key role. Its increased activity during the late compression phase of helium saturation dives is accounted for either by the pituitary-thyroid axis or by  $T_4$  release from peripheral stores and decreased conversion rate to  $T_3$ .  $T_4$  then stimulates catabolism of protein stores, specific in the sense of the resulting raised glycine levels.

Energy balance was studied by assessing separately each quantity of the following equation :

$$\text{Intake} = \text{expenditure} + \text{faecal energy} + \text{urinary energy} - \text{stored adipose tissue}^{\dagger}$$

The dietary control measures were here supplemented by oxygen consumption studies and whole body composition estimates from skinfold techniques and  $D_2O$  dilution measurements for total body water.

Increased energy expenditure at depth and constant dietary intake was represented by negative energy balance. In Dive 8 this was further increased by the subjects' anorexia and temporary departure from the controlled dietary intake of around 3000 calories daily. Overall, in Dive 7, there were slight increases of the body weight of both subjects; in Dive 8 3.1 kg and 0.5 kg decreases of total body weight have been observed. The excess energy expenditure at depth converted into equivalent weight fatty tissue, would account for 0.26 - 3.64 kg loss of body weight in these 4 weeks of the dives. One may speculate that the large losses of body weight in simulated diving observed in other centres are mainly due to reduced intake of subjects whilst suffering from the anorexic effect of HPNS.

Echinocytes: The erythrocyte was the subject of a significant study in these dives. This work originated from Nichol's observation during Dive 6 of the present series (Hempleman et al, 1978) that morphologically unusual red cells ("ball races") appeared in the later stages of decompression, persisting after the dive. Scanning electron microscopy revealed a variety of shapes from echinocytes and spiculed ovoid cells to sphero-vesiculocytes. These cells with unusual shapes contributed during late decompression 6 - 12% of erythrocytes in the blood of all 3 subjects studied (Carlyle et al, 1979). Control studies indicated that this phenomenon is not an artefact, and that blood subjected in vitro to the physical parameters relevant in saturation diving will not affect erythrocytes in this way. Their origin and significance is under further investigation.



Carbonic Anhydrase: Another change observed on erythrocytes of the dive subjects is lowered activity of carbonic anhydrase. Studies with ghost cells indicated a 3- to 4-fold increase in the quantity of the enzyme bound to the cell membrane. Though these changes are associated with increased plasma concentration, it cannot yet be assumed that the origin of the plasma carbonic anhydrase is the red cell, thus indicating a leaky membrane. Similarly the concurrence in the time course of the morphological and enzymic changes in circulating erythrocytes is worthy of note but does not warrant an assumption of causal linkage without further evidence.

Erythrocyte Sedimentation: Grossly accelerated erythrocyte sedimentation is a highly nonspecific finding in its interpretation. Dive 7 provided a good example of this change, when after a rise starting on the 12th day of decompression peak values in excess of 70 mm in 2 hours (Westergreen) were measured in both subjects, returning to pre-dive values of around 20 after a week or so (Nichols, 1979).

In all these 3 areas much further work needs to be done. The potential, however, seems to be there for any of these blood changes to be used as objective indicators for the safety of a given decompression procedure.

Neurophysiology was represented in Dives 7 and 8 by 4 different studies: systematic physical examination of the subjects using the methods and diagnostic approach of the clinical neurologist; a set of oculo-graphic tests aimed at the neural apparatus of the vestibular system; Hoffmann techniques studying spinal cord reflexes; and indices of muscle fatigue derived by electrical stimulation methods. In addition, performance tests were used, and these may be interpreted as information about integrity of the cerebral cortex.

Muscle Fatigue: In experiments using the adductor pollicis muscle and ischaemic acceleration of the fatigue process to save time, force measurements were made on maximal voluntary contractions and electrical stimulation at 20 and 50 Hz of both the ulnar nerve and the muscle itself. Voluntary contractions were used to induce fatigue to a 10% force criterion. The intensity of muscle fatigue was expressed as the time taken (milliseconds) for peak force of a contraction, however produced, to drop to half its value (Edwards et al, 1972). This is consistent with the accepted concept of muscle fatigue, i.e. that it is the inverse ability to sustain the force of contraction. Expressed in this way, fatigue was more intense on the 4th day of decompression at 325 m (Dive 8, one subject) than at 420 m, and greater still 4 days later at 216 m. The time course of the recovery process from ischaemic fatigue was shown to be unimpaired at 43 bar, when the same technique was used to compare the subject's time and force measurements to his pre-

dive control values (McKenzie, 1977). This important finding is best seen in the context of diffusion and availability of transmitters and related enzymes as well as metabolites and availability of oxygen at key sites upon termination of peripheral ischaemia. An attempt to analyse peripheral components, if any, of the often profound feeling of fatigue reported by most subjects on completion of a dive has not met with notable success.

Spinal Cord Reflexes: This study (Harris, 1979a,b) arose from the consideration that if an essential feature of HPNS is general disinhibition throughout the nervous system, then the spinal cord with its established methodology presents a particularly convenient experimental bed for study.

With the aid of a jig to ensure consistency, graded mechanical stimuli were delivered to the Achilles tendon. By measuring the force produced, 2- to 3-fold increases against control values were studied. The effect was most marked at depth, with a secondary peak towards the end of decompression. The size of electromyographic potentials, recruitment ratios calculated from responses to electrical stimulation and to a lesser extent, H reflex excitability gave similar results. These features constitute a description of "hyperbaric hyperreflexia" without providing information as to its mechanism.

Electro oculographic techniques and direct observation of the subject's eye movements through magnifying goggles contributed the following. The ocular dyskinesias, i.e. opsoclonus, dysmetria and rebound, are manifestations of cerebellar lesions. Break-up of smooth pursuit pattern whilst following a clockwork-driven visual target may originate in the brain-stem or cerebellum. Nystagmus on lateral gaze, present in 3 out of the 4 subjects studied, could be caused by brain-stem or peripheral vestibular lesions. Most of the above appeared on compression at around 300 m, and persisted up to the 3rd day of decompression. Opsoclonus was the first positive sign to present at 200 m. Spontaneous and paroxysmal nystagmus were always absent, and there were no reductions in the velocity of saccadic eye movements. Gross lateral asymmetry of the optokinetic reflex was ruled out using a striped drum. Of the non-ocular motor signs intention tremor and ataxia were most conspicuous, both pointing at the cerebellum.

The horizontal vestibulo ocular reflex is one of the compensatory eye movement mechanisms, with the purpose of enabling vision during whole body or head movements. When the head is rotated to the left at velocities stimulating the vestibular organ, smooth or nystagmic eye movements are induced to the right and vice versa. Even with the aid of compensatory reflexes vision during motion can practically

never be continuous. If the objective is considered to be the acquisition of visual samples during certain parts of the sinusoidal oscillation in the present experiment, then the task is to return the line of sight by a given amount of axial displacement. The reflex gain is therefore best considered in terms of displacement of the stimulus versus displacement of response. Alternatively, if the objective is vision during certain parts of motion, then relative axial movement between eye and object is best minimised by matching the velocities, and the reflex gain in terms of velocity is the most appropriate concept. Both have been calculated and used here.

Ideally the amount of eye movement caused equals the movement initiating it, resulting in the gain of the reflex being unity. In practice, however, a wide range of gains has been observed by different authors, e.g. 0.43 and 1.0, depending on a number of experimental variables. The problem as to what these should be was circumvented by considering changes during the dive from control values.

In the present study generally the velocity gains were higher than the displacement gains and pre- and post-dive displacement control results are closely similar. The post-dive velocity gains, with the eyes closed in slow (100 degrees/second) and fast turns (150 degrees/second) were considerably higher (0.84 and 0.63 against 0.55 and 0.54). Experiments at 420 m resulted in even higher velocity gains and some rise in the displacement gains. The post-dive control experiments were obtained 12 days after the end of decompression still showing the above increase of velocity gains (but not of displacement gains). These observations are consistent with Gauthier's (1976) work on velocity gains only, including the persistence to 4 days after the dive of some of the initially observed rise (0.50 to 0.65) at 59 ATA. The admissibility of the cerebellum as a control site for the gain of the vestibulo ocular reflex (Robinson, 1976) removes most of the localising value of the above results. These can originate in midbrain, cerebellum or end organs.

It is generally accepted that the semicircular canals are overdamped accelerometers. If it was demonstrated that the velocity of the ocular response is directly related to the velocity signalled by the end organs, that is to the signal before its second integration (to displacement) by the pons reticular formation, a very powerful localising technique would be obtained. Minor disturbances to vestibular end organ function could be followed with significant benefits to designers of diving tables. An indication that this may be the case is the observed discrepancy between the time course of the velocity and displacement gains outlined above.

VOR Asymmetry: The experimental technique permitted comparisons between the vestibular ocular reflex gain obtained during left versus right turns. Results from two subjects indicated an 11.0% and 12.8% asymmetry at 420 m, against 2% normal control values. This statistically significant result was interpreted as evidence of direct vestibular end organ effect by the hyperbaric helium environment.

Psychological Tests: From the large variety of carefully controlled psychological tests there were a number of significant decrements at 420 m. The most important ones were impairment of short-term memory and slowing of decision-making processes. The ability to select specified visual stimuli was impaired, yet a self-rating test indicated that in the subject's view no lowering of alertness occurred.

Conclusion: It is apparent that the plethora of ill effects on the nervous system described above must take effect at several sites and probably also levels. There were effects on the vestibular end organ, myoneural junction, spinal cord, mid-brain, cerebral cortex and cerebellum. The involvement of the cerebellum is especially conspicuous. What we know as HPNS is therefore a mere collection of hyperbaric ill effects under specific circumstances, until a more unified causative mechanism is found.

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Compression and Decompression Data on AMTE/PL Dives

(all dives:  $P_{O_2} = 0.4$  bar)

Dive	Time(Days)			Comments on Decompression
	Compression	Bottom	Decompression	
5 (300 m)	2.27	7.56	10.27	CIRIA/UEG 6 (Modified)
6 (300 m)	1.02	6.80	10.25	CIRIA/UEG 6 (Modified)
7 (420 m)	8.41	2.04	15.64	Hybrid decompression with 4 x 12 hr and 1 x 34 hr holds. CIRIA/UEG 5 for last 250 m.
8 (420 m)	6.46	3.4	15.54	28 m/day (4 m/hr x 7 hrs/day) last 25 m on Table 1; 5 m drops at 4 m/hr.
9b (540 m)	3.21	2.65	20.15	As above but last 30 m on USN/Sat table.



Recent U.S. Navy Experience in Very Deep Saturation DivingW. Spaur

Since 1973 the Navy Experimental Diving Unit has conducted four very deep experimental saturation dives. In chronological order, these were to 1600, 1400, 1500, and most recently to 1800 fsw equiv. Respectively, these dives had 16, 19, 10 and 17 days at depths of 1000 fsw equiv. or greater. Each dive had six subjects. This is 372 man-days deeper than 1000 fsw equiv. The NEDU dives are primarily for equipment and procedure testing and ordinarily involve days and days of severe exercise in cold water. Experiments are usually conducted during compression at the bottom and throughout decompression back to the surface.

All the dives produced symptoms attributed to the great depth and all except the 1500 feet of seawater dive, which had the shortest time below 1000 ft, were marked by body weight loss. The 1600 and 1400 fsw equiv. dives caused a 6% loss of body weight and mild symptoms similar to that experienced on the recent 1800 fsw equiv. dive.

Methods

The six subjects on the 1800 fsw equiv. dive were non-smokers who were well trained and had already been subjects on saturation dives. They underwent 10 weeks of intense physical training and were well trained for the experimental procedures to be conducted.

The dive was conducted in the commodious chambers of the Experimental Diving Unit which has five dry living chambers and a life support system to precisely control temperature, humidity, carbon dioxide, and oxygen atmosphere. The chamber atmosphere oxygen partial pressure was maintained in a range between 0.4 and 0.45 atmospheres, an increase of .05 atmospheres over the usual U.S. Navy oxygen levels.



The divers compressed on the first dive day to 640 feet of seawater at 3 ft per minute. At 640 fsw they conducted graded exercise and carbon dioxide absorbent canister studies of a U.S. Navy semi-closed underwater breathing apparatus. On dive day eight and nine, the divers were compressed to 1000 feet for experiments. On dive day ten, the compression continued to 1400 fsw equiv. for experiments and then to 1520 fsw equiv. on dive day eleven. This compression from 640 ft to 1520 ft was conducted at 30 ft per hour. On dive day twelve, the compression at 30 ft per hour continued to 1600 fsw equiv. and then at 15 ft per hour to 1800 fsw equiv. The divers reached 1800 fsw equiv. on dive day twelve. They remained at 1800 fsw equiv. for five working days to conduct graded exercise in-water studies using a low resistance breathing apparatus. On the evening of dive day seventeen, the divers commenced a standard U.S. Navy saturation decompression which continued to 1530 fsw equiv. At that depth, the divers were recompressed to 1560 fsw equiv. Twelve hours later, decompression was again commenced and continued to the surface. The divers surfaced on dive day 38. Additional experiments at 1800 fsw equiv. and during decompression were studies of cold gas inhalation and pulmonary mechanics, a study of a communications system involving in-water reading of word lists. A weight loss study was also conducted which included blood and urine collections and water loading tests.

### Results

The effects of the very deep dive cannot be easily quantitated and are difficult to organize into cause and effect relationships or a categorical review of systems. The weight loss the divers experienced followed their general feeling of being ill. Weight loss began with compression deeper than 1000 fsw equiv. and continued throughout the bottom time and well into the decompression. The days of least body weight were 10 to 13 days after beginning decompression.

These non-smokers experienced respiratory symptoms at depths greater than 1400 fsw equiv. At 1800 fsw equiv. they had dyspnea with mild exercise while working about the chamber. The dyspnea was remarkably worse in the evening. Dyspnea was also experienced with chewing and speaking. The divers were observed to breathe with pursed lips at times and used the accessory muscles of respiration with all but light work. The divers breathed through their mouths deeper than about 1400 fsw equiv. The maximum exercise tolerated was 5 or 6 minutes of 100 watts on the pedal ergometer immersed. This resulted in tremendous air hunger and extremely distressing post-exercise recovery. Exercise dyspnea was improved by 10 cm of water positive pressure breathing. Ten cm of water negative pressure worsened dyspnea. Raising of the oxygen partial pressure caused no subjective change. The immersed maximum oxygen consumption was 1.5 - 1.6 l/min.

Constant attention to breathing caused concern for some of the divers. Sneezing or coughing, which was seldom, caused aching pain felt in the region of the lung apices and trapezius muscles or radiating in an ulnar nerve distribution. This aching lasted for five to ten minutes.

All divers experienced symptoms of orthostatic light-headedness, nausea and imbalance with head movement throughout the deep period of the dive. This caused movements to be slow and careful, both to prevent nausea and to maintain equilibrium while moving about. The divers had mild tremor all the time but had very gross distressing tremor following exercise. Fasciculations at 1800 fsw equiv. were described by the divers but not observed by the medical personnel. The most disturbing symptom was myoclonic jerks which caused the divers to spill coffee and which persisted into the sleep, awaking the divers frequently during the night with their gross body movements. Sleep was poor because of close temperature requirements and because of the myoclonus. The divers also suffered nightmares, often associated with flying. By the afternoon of each day, the divers were suffer-

ing from exhaustion and the completion of each days' experiments was a result of extraordinary dedication and effort. The divers suffered from a feeling of having a short attention span and slow thinking.

Nausea was constant and anorexia severe. Two of the divers had vomiting throughout the five days on the bottom. The divers survived by selecting only fruit juices, toast and tea, or grapes. Eating resulted in an exaggerated post prandial gastrocolic reflex. There was an urgent need to defecate which was often productive of nothing or soft stools or diarrhea. This complex of gastrointestinal symptoms lasted throughout the deep period of the dive and continued through the decompression to about 700 fsw equiv. on about dive day 29.

The schedule of decompression was altered on several days so that the stop could be during the day to perform experiments. After a period of overnight decompression, one of the divers awoke in the morning with acute vomiting, diaphoresis, light-headedness and vertigo without nystagmus. He belched large quantities of gas. He was recompressed from 1530 to 1560 fsw equiv. and slowly regained his former level of well being. The diver thought that he began to experience relief after belching and that the recompression had no significant further effect. The cause of this episode was probably acute gastric distention. Other divers in the chamber suffered from this 30 ft recompression at 10 ft a minute and had a return of tremor, nausea and light-headedness.

The comfort zone at 1800 fsw equiv. was  $91^{\circ}\text{F} \pm 0.5^{\circ}\text{F}$ . Even with the close control of the chamber atmosphere, the divers had distressing alternate sweating and shivering and poor sleep.

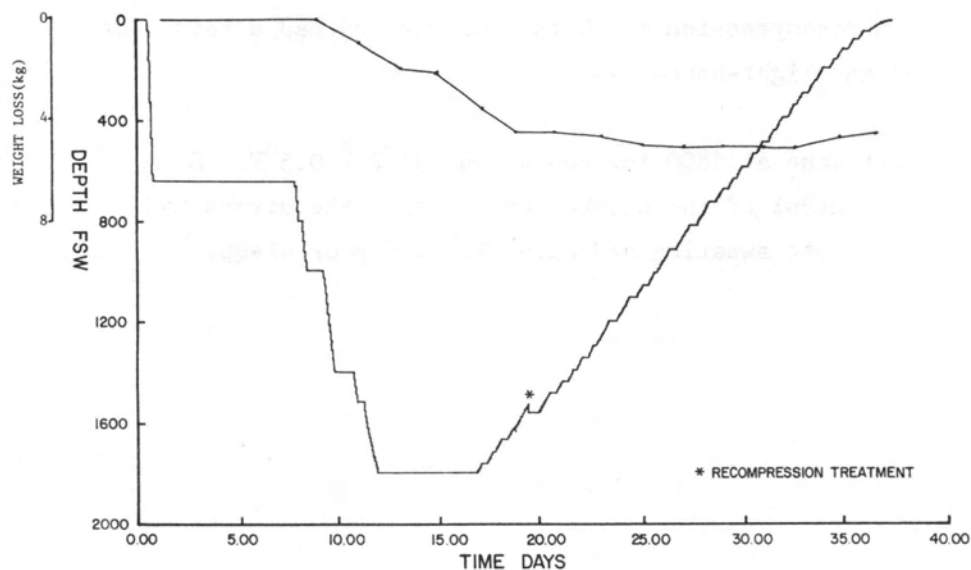
Joint pains following exercise were severe and persistent and were experienced on all studies on the bottom and during decompression.

During the decompression, the divers suffered itching when exercising in the water. This itching would subside in approximately one half hour after completing the immersed portion of the studies.

The decompression was without incident and the divers suffered no symptoms resembling decompression sickness. The two to four weeks after the dive were marked by varying complaints of difficulty in thinking and poor attention span in three of the divers. Several divers had joint pains in the shoulders or knees weeks after the dive. All suffered malaise, weakness and easy fatigue and required long hours of sleep.

### Discussion

The 1800 fsw equiv. dive recently completed demonstrated to our satisfaction that 1800 fsw equiv. is too deep to conduct working dives using helium-oxygen alone as the breathing media.



Discussion Session II : HPNS in ManR.W. Brauer - Leader

A considerable number of issues were raised in this session including the effect of adding nitrogen, different compression profiles, respiratory and gastrointestinal symptoms (which have only recently been ascribed to an effect of pressure), the possibility of acclimatisation to pressure, and metabolic changes. In addition, the possibility of identifying end-points which might be used as a basis for selection was discussed. These end-points will be dealt with in the discussion following Session IV.

The first point raised was the striking difference between trimix and heliox dives (trimix: Duke University to 650 msw equiv; 1979 Comex to 460 msw. heliox: U.S. Navy (NEDU) to 549 msw equiv.) During the heliox dive severe HPNS was experienced by all the divers including dyspnoea, light headedness, nausea, imbalance, pronounced tremor, myoclonic jerks, poor sleep, nightmares and anorexia with some vomiting. In general all the divers felt unwell and were unable to perform work satisfactorily. In contrast the trimix dives demonstrated that the majority of these symptoms were suppressed by the addition of nitrogen (in the range of 5 - 10%) without attendant marked euphoria and that the divers were able to work and exercise efficiently. A major advantage of trimix was thought to be in the increased flexibility in compression.

It was the concensus opinion that exponential compressions were far superior to linear compressions (which result in compression being far too rapid at depth). This was best illustrated by comparing the 1976 Comex dive Janus IV to the 1979 dive. In these two dives the same proportion of nitrogen (4 - 5%) was used but the 1979 dive compressed over 38 hours with 4 stages compared to 25 hours non-stop for Janus IV. In the dive with the longer and staged compression, tremor and dysmetria were much reduced and myoclonic jerks and micro-sleep prevented. In contrast the NEDU heliox dive compressed to

549 msw equiv. (1800 fsw) over 12 days but there were still the severe symptoms described above (see also Section 2.4). An even more striking comparison is the Atlantis II dive at Duke University where compression to 460 msw equiv. was achieved in 12.3 hours without attendant HPNS. Two additional points were raised in connection with compression rate. First, it was suggested that if recovery from HPNS was complete at depth, then further compression could be performed quickly without reoccurrence of HPNS. This effect had been observed during experimental dives at Pennsylvania University. Second, the experience of Comex suggested that the initial phase of the compression should also be slow in order to avoid abnormal EEG. Ideally, they would select a compression profile which was approximately sigmoid in shape.

Considerable discussion was related to three signs which may now be included in the catalogue of HPNS: dyspnoea at rest which is aggravated by exercise, gastrointestinal problems and vestibular problems. It was firmly suggested that the dyspnoea exhibited by one of the 4 divers involved in Atlantis II was related to the ambient pressure and not gas density. This effect was not suppressed by the added nitrogen; increasing the concentration breathed from 7.8% N<sub>2</sub> to 10% N<sub>2</sub> neither worsened nor improved the condition. This dyspnoea occurred in the presence of normal blood gases, normal arterial/venous differences and normal tidal volumes. The condition did not deter the subject from exercise although it did limit the time he felt able to perform. In support of the hypothesis that this is indeed an effect of pressure, it was reported that experiments at Harvard with mice demonstrated pronounced mouth breathing at 90 ATA independent of the gas density - or addition of anaesthetics.

The question was raised as to whether the gastrointestinal problems observed on the NEDU 549 msw equiv. (1800 fsw) dive were



a common feature of heliox dives ? Comex had not experienced these problems up to 610 msw equiv. (20001 fsw). On the other hand the U.K. experience at AMTE/PL was that approximately 50% of their subjects reported these symptoms and the associated diarrhoea was observed. It was mooted that alternative causes may exist for this condition, virus or bacterial infection being the obvious choice. However, this was dismissed on a number of accounts; a) stools were cultured for bacterial or viral infection and none was found, b) the onset of symptoms was unrelated to length of stay in chamber but to exposure to pressure, c) trimix prevented occurrence of these symptoms d) these symptoms are not seen during long commercial saturation dives (lasting months at a time) where "the lack of hygiene in the chambers is unbelievable". It was further reported that these gastrointestinal symptoms appeared in about 20% of squirrel monkeys exposed to high heliox pressures. By analogy with acute oxygen toxicity, it was suggested that these gastrointestinal symptoms may be serious pre-convulsive signs. Alternatively it was argued that they may be a stress reaction unrelated to any subsequent event. Neither argument was supported by experimental evidence and further research is clearly indicated.

The observations on the vestibular ocular reflex (VOR) generated some controversy. In one study at 305 msw equiv (1000 fsw) VOR disturbance was observed but with no asymmetry. However, no specific vestibular end organ dysfunction could be identified. In contrast the AMTE/PL study has shown a statistically significant asymmetry of some 12% at 420 msw equiv (1378 fsw) which was interpreted as direct evidence of vestibular end organ effect. These observations may or may not be linked to nystagmus which appeared in some subjects at 300 msw equiv. (984 fsw) and disappeared on decompression. It was suggested that the asymmetric response to a sinusoidally rotating chair stimulus may be "isolated directional preponderance", which is

not related to vestibular end organ dysfunction but to a central nervous system disorder. It was thought that the type of left-right asymmetry of VOR observed was unlikely to be of central origin. However, more research is again needed to fully describe this effect.

The possibility of acclimatization to pressure was discussed, the term being carefully chosen to avoid confusion with adaptation which has specific genetic meanings. It was suggested that slow compression of men was having the same effect as rapid compression of small rodents followed by holding at pressure; namely, allowing them to acclimatize. If nitrogen is added, is acclimatization accelerated, hence giving protection, because the final pressure is achieved more rapidly and hence more time is spent at pressure? Conversely, by protecting against HPNS by adding nitrogen is acclimatization prevented? In man, if nitrogen is removed from breathing mixture at pressure HPNS comes on. It was reported that this has been done experimentally at 305 msw (1000 fsw). Furthermore, following the stay at 650 msw equiv. (2132 fsw) on the Atlantis II dive, as the nitrogen was removed on decompression HPNS occurred in all three subjects (light sleep with nightmares, myoclonia, shivers). This subject will be investigated at the Institute of Marine Biomedical Research in a genetic programme with small rodents. Some evidence for a lack of acclimatization at pressure of small rodents was given by the Harrow experiments in which convulsions at pressure were "switched on and off" by intermittent pulsed infusions of short acting intravenous anaesthetics over a four hour period.

The question of metabolic changes associated with exposure to high pressure was discussed. The Predictive Studies III at Pennsylvania University found little change in basal metabolism after exposure of 366 msw equiv. (1200 fsw) with excursions.

This is apparently supported by the available Russian work. However, work with small animals in which oxygen uptake was measured showed a correlation between the oxygen uptake changes and the log basal metabolic rate and these changes were unaffected by changes in temperature. From these studies a 15 - 20% increase in oxygen uptake would be predicted. This was considered significant in view of the metabolic changes recorded during the 540 msw equiv. (1772 fsw) chamber dives at AMTE/PL (See Section 2.3).

The final question raised was the possibility of convulsions occurring without warning, given that it is known that in animals certain aspects of the HPNS can be selectively suppressed by choice of the appropriate drug. This was thought exceedingly unlikely when using the gaseous anaesthetics. They affect all the HPNS end-points approximately equally and postpone them to higher pressures. Similarly it is unlikely that, if convulsions are suppressed using nitrogen, unexpected death would occur. Presently the use of alternative drugs to ameliorate HPNS in man is not considered appropriate until further animal research has been completed.

High Pressure Neurological Syndrome - Fundamental AspectsRalph W. Brauer

The fact that hydrostatic pressure changes are capable of profoundly and usually reversibly modifying CNS activity in a wide variety of animals makes these phenomena interesting not only in themselves, but also as extraordinarily flexible and controllable tools for the study of a wide variety of fundamental biological questions. Table 1 attempts to provide a brief overview over the most significant questions as they occur to me at this particular moment. I have grouped them into three clusters, a first cluster relating to the question of underlying mechanisms; a second cluster relating to modification of these effects, and to problems of biological variability; and a third cluster which includes effects which seem to be linked to the direction of pressure change, pressure related changes occurring at relatively low pressures, and effects of high pressures on sensory or perceptual phenomena. This is a long list, but even it, undoubtedly, is incomplete. Thus, I have deliberately not listed such questions as changes in ion transport processes, or changes in the activity of specific enzymes as one step too far away from the subject of our deliberations. To stay within our present time frame, therefore, only a somewhat arbitrarily chosen fraction of these topics can be discussed. To lead into subsequent presentations in this section, and to conform to the overall theme of seeking to clarify research strategy, I have chosen to focus on the first cluster, i.e. on the problem of mechanisms underlying the HPNS-like effects of hydrostatic pressure on the CNS.

When the HPNS was first recognized as such and studied systematically in vertebrates, it was perceived as a succession of manifestations occurring in mammals at successively higher pressures. In clinical terms, it appeared meaningful to consider these as successive effects attributable to a common etiologic cause, i.e. increase in hydrostatic pressure. This view of the subject was incorporated in the designation given the syndrome by us in 1968 and since widely adopted. In the meantime, more critical investigations have shown that while the general sequence seems to persist over a wide variety of compression conditions, and in a wide range of vertebrate species, individual stages within the entity are distinguished by substantial differences in the way in which they respond to a variety of experimental manipulations as well as in the precise way in which they manifest themselves in different species.

This suggests that before any successful attack on the mechanisms underlying HPNS effects can be mounted, it becomes necessary to attempt to dissect the syndrome so as to seek to determine to what extent the

successive phenomena observed in the course of a compression experiment can be considered as links in a coherent causal chain. The most complete data in this respect are perhaps those we have accumulated with regard to the convulsion stage of the HPNS. Table 1 shows characteristics of the two successive seizure events which are typically seen in the mouse. As you can see, these differ kinetically, pharmacologically, ontogenetically and electrophysiologically. The radioautographic patterns of deoxy-glucose retention, which bespeak activation of glucose metabolism in the specific regions of the brain involved in seizure activity, reveal wide neuroanatomic differences between the two seizure types (1). Recent data show, furthermore, that susceptibility to the two seizure patterns is under genetic control, and that the patterns of genetic determinacy for the two types of seizure likewise are widely different.

The differences between the two seizures are so many and so profound that it seems to me presumptuous to hypothesize that they should represent merely different manifestations of a single common underlying neurophysiologic change. While similarly complete data are not available for any other stages of the HPNS, the limited information on hand would certainly be compatible with the assumption that differences between tremor and convulsion stages, or convulsion stages and high pressure death, to mention only a few, are at least as profound as those we have shown for the two components of the convulsion stage.

Exploring an entity of such complexity clearly requires use of model systems both in an effort to fully describe and systematize the phenomena observed, and as an aid to simplify the test system to the point where one may, with some reasonable hope of success, probe mechanisms at the molecular level. HPNS Type I convulsions appear to be a manifestation unique to mammals and even there are not altogether universal. Type II seizures, or a curious compound seizure containing traits of both Type I and Type II seizures, on the other hand, are present in all vertebrate orders. Furthermore, there is evidence strongly suggesting that while TYPE I seizures may depend upon suprasegmental centers, probably including at least diencephalic structures, Type II and compound seizures clearly can be elicited in the spinal cord isolated from the brain.

Invertebrates subjected to hydraulic compression, likewise, develop a sequence of changes in behavior reminiscent of those seen in vertebrates: successively, there is a state of exaggerated activity; convulsion-like bursts of uncoordinated motor activity; and a state of progressive immobilization frequently referred to as tetany by invertebrate physiologists. Of the three stages, the last immobilization, in all probability, does not have a neurologic basis, but is the result of action of hydrostatic pressure upon the contractile system of the general musculature. The stage of enhanced activity may represent an analogy with the vertebrate tremor stages; the burden of evidence, in our opinion, makes it more likely, however, that this stage represents an indirect effect in



which pressure increases produce some more generalized change, such as altered osmotic relations, which is perceived by the animal as an aversive stimulus eliciting avoidance or escape behavior. This leaves the invertebrate convulsion stage which may well prove a valid analogue of the vertebrate Type II HPNS seizure.

Figure 1 illustrates one distinguishing characteristic of the invertebrate high pressure seizure in crustaceans: if one compares crustaceans acclimatized to deep water conditions with closely related species acclimatized to shallow water conditions, compressing all of them from the same baseline pressure of 1 atm, then it would appear that only the convulsion stage shows unmistakable evidence of adaptation. Threshold pressures for the inactivation stages, as well as the less clearly defined threshold pressures for the early activation stage, for deep and for shallow water gammarids, either are not distinguishable at all or are separable only to a statistically marginally significant extent.

High pressure convulsions or convulsion-like hyperactivity can be elicited in many invertebrate phyla. Figure 2 shows a summary of all the data that I have been able to come across in terms of a phylogenetic tree. The most interesting result of this analysis is that high pressure convulsions or convulsion-like phenomena have been seen in virtually all of the triploblastic coelomate phyla, but disappear when one steps below that level of organization to flat worms and the coelenterate and ctenophore diploblasts. These three groups go along swimming happily and undisturbed up to pressure levels at which their activity slows down and eventually ceases. The distinction, I believe, may be highly significant when one considers the structure of the nervous systems in the several phyla: it would now appear that HPNS-like high pressure convulsions are observed only in those phyla the nervous system of which displays well differentiated central ganglia with integrative properties. Certainly this observation suggests that the exaggerated activity elicited under high pressure in the more developed invertebrates is a function of levels of integration higher than those present at the level of a simple network of synaptically connected neurons. While the acetylcholine system as a neurotransmitter seems to be absent in the coelenterates, it is present in the flat worms, as are monoamine neurotransmitters, pretty well excluding the possibility that neurochemical differences, rather than more complex integration mechanisms, might underlie the sharp division suggested in Figure 2.

An interesting further observation pointing to the role of complex integrative mechanisms in the development of HPNS seizures comes from recent and I believe as yet unpublished observations in the lobster: well defined, seizure-like phenomena can be elicited and recorded from the abdominal nerve cords in this species, but transection of the abdominal nerve cord abrogates the seizure-like events in the segments distal to the transection. It is interesting



to note that in contrast to the lobster, transection of the mammalian spinal cord reduces the intensity of observed locomotor seizures, but does not seem to abrogate electromyographically recognizable manifestations of either Type I or Type II HPNS seizures (2). Thus the complexity of the mammalian spinal cord seems to attain a level sufficient for development of HPNS seizures.

If one turns from intact animals to more or less isolated preparations of excitable tissue, the effects of increased hydrostatic pressure provide a complex spectrum. I have tried to summarize the available literature - altogether some eighteen papers - in Table 2. The data are clearest with regard to synapses and the myoneural junction: all investigators found decreased transmission and increased thresholds for such preparations, and synaptic fatigue, where it was studied, also was found to be accelerated. With regard to axonal preparations, all observers concur in finding prolonged action potentials. Changes in excitability are less clear: three papers found no change, three others reported increases in excitability. As you can see from Table 2, I tend to be more convinced by the former. Pressure-induced repetitive firing was reported by three investigators, and was not observed by five other observers. I am sure we shall hear more about this later on during this session. Cardiac pacemaker and conduction tissues present a clear cut picture: there is a decrease in firing rate, decrease in excitability, and decrease in conduction rate. Rhythmically firing molluscan burster neurons show a transient increase in firing rate even though burst frequencies may be reduced. Related synaptically driven neurons from the same species show markedly accelerated adaptation so that the number of action potentials elicited by a single current injection were decreased at high pressure; there seems to be some question about increased excitability of such neurons.

All told then, my reading of the data is that, with the possible exception of data on burster neurons, the effect of pressure increases on the various types of preparations does not seem to supply a reasonable basis for predicting the enhanced and exaggerated CNS controlled motor activity characteristic of the HPNS. I suggest to you that these data are of a piece with the conclusions derived above from the phylogenetic considerations in suggesting that HPNS-like effects are manifestations of the action of hydrostatic pressure upon nerve networks of considerable complexity and that the lowest level of complexity in which these effects have been convincingly demonstrated in vertebrates so far is at the level of the isolated spinal cord.

During the later half of the 1960's, observations that the action of anesthetics in many cases could be reversed by high hydro-

static pressure, and conversely that some of the effects of high hydrostatic pressures could be postponed or eliminated by treatment with anesthetic agents, raised the hope that this interaction takes place at a molecular level and might provide a common key to an array of phenomena ranging from blocking of nerve function by anesthetics through elicitation of high pressure convulsions. Even at the whole animal level, it would now appear that this hope for a unifying molecular hypothesis is becoming increasingly untenable: profound differences in interaction between dose response curves for general anesthetics and hydrostatic pressure have led to recognition of what appear to be chemically very substantially different receptor sites for anesthesia and/or at least four stages of the murine HPNS (3). Again, using injectable anesthetics substantial differences in the time course of development of the different effects suggest substantial differences in anatomical distribution as well as in molecular properties of the sites involved (4).

At the level of isolated preparations, observations have been reported concerning interaction of pressure and anesthesia for the same group of systems for which the effects of pressure alone were summarized above. Table 3 presents my summary of twelve papers. In many cases, the data are confined to modification by pressure of the effects of anesthesia upon such preparations. In general, it would appear that the effects of pressure and anesthesia upon axons may be directly opposed to each other. Similarly, the effect of high hydrostatic pressures upon cardiac pacemaker tissues can be reversed by anesthesia. On the other hand, the effects of hydrostatic pressure upon synaptic and myoneural junctions do not reverse the effects of anesthetic agents upon these preparations or may even enhance them. Similarly, it would appear that in burster neurons the effects of pressure and anesthesia are not antagonistic but rather summate. The same seems to be true for synaptically driven repetitive firing nerves from the same species. As pointed out in Table 3, the induction of repetitive firing in axonal preparations by high pressures or low temperatures is said to be antagonized by anesthetic agents.

It seems to me that this very brief review of available literature suffices to make it clear that it is most unlikely that the antagonism between pressure and anesthetic agents which is observed in intact animals can still be regarded as reflecting a simple antagonism at the molecular level. It seems more likely that this antagonism represents the interaction of almost fortuitously opposed effects which may well be asserted at altogether different sites in the CNS. It appears to me that the effect of pressure upon the action of anesthetics may well continue to furnish a useful tool for the unraveling of the mechanisms of anesthesia, but that the antagonism of HPNS effects by anesthetics

must be analyzed as a complex pharmacological problem rather than as a simple key to the molecular mechanisms underlying HPNS.

What is the bearing of all of this information upon the formulation of a research strategy aimed at exploring the mechanisms by which exposure to high hydrostatic pressures elicits the changes collectively referred to as the HPNS?

It appears clear now that at least four entities, in conjunction, constitute the complex of the HPNS. Three of these, the tremor stage and the two components of the convulsion stage, clearly have a neurophysiologic basis and are almost certainly manifestations of changes in CNS function. The fourth component comes at rather higher pressures, and it seems to us a tenable working hypothesis that this represents an effect at the level of the contractile system, rather than the nerves or even the neuromuscular junction. Further progress in understanding HPNS in vertebrates would seem to depend upon further analysis of the neurologic basis for every one of the stages, each treated as a separate entity in terms of its neuroanatomical representation and its neuropharmacologic characteristics. In pursuing such analyses, one should not overlook the possibility that one or all of these stages may prove not to be the result of any direct effect of pressure or pressure change upon any particular neuronal elements in the CNS, but rather indirect effects i.e. responses of the CNS to some more general pressure induced disturbances, such as, for instance, disturbances of ion distribution among CNS compartments or metabolic changes such as those which are hinted at by the pressure-related changes in oxygen consumption rate, in nitrogen metabolism, or in hormonal balance.

We believe that it is a reasonable hypothesis that no one of the three neurogenic stages of the HPNS can be described in terms of alterations of the properties of single neurons. It would thus appear to be a meaningful question to enquire after the simplest neuronal network capable of displaying HPNS-like activity. With regard to HPNS tremors and Type I seizures, the burden of evidence would seem to point to requirements of considerable complexity not even encountered at the level of the mammalian spinal cord. By contrast, Type II seizures can be generated regularly in the isolated spinal cord and this would seem to offer a most promising substratum for further investigations aimed at defining the neurologic substrate for that component of the vertebrate HPNS.

The extent to which invertebrate models can provide valid analogies for exploration of neurophysiologic changes leading up to HPNS-like effects seems less well defined and further experimental studies seeking to validate or to reject such analogizing would appear to us to merit attention. For the present, we suggest that the activation stage be considered a response pattern peculiar to invertebrates, and more specifically perhaps to aquatic invertebrates, and that it most likely does not have a parallel in the

vertebrate models. A good case could also be made for the fact that the immobilization stage does not have a neurophysiologic base and, hence, is not in the strict sense of the word pertinent in present context. By contrast, the invertebrate convulsion stage shows a number of similarities with Type II HPNS seizures and may well provide a useful working model especially when observed in forms in which the CNS has a relatively simple makeup that lends itself to detailed electrophysiologic exploration. In addition to whatever limits the exploration of the effects of pressure on invertebrates may prove to have in conjunction with exploration of the HPNS, it is worth noting that key phenomena here, such as the convulsion stage and such behavior patterns as pressure modification of temperature preference behavior are providing important insights into mechanisms of adaptation to high pressure regimes which, whether or not they prove of interest in conjunction with the HPNS in vertebrates, will certainly be of substantial scientific significance in their own right in connection with the biology of deep sea animals and their special adaptations.

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Figure 1:

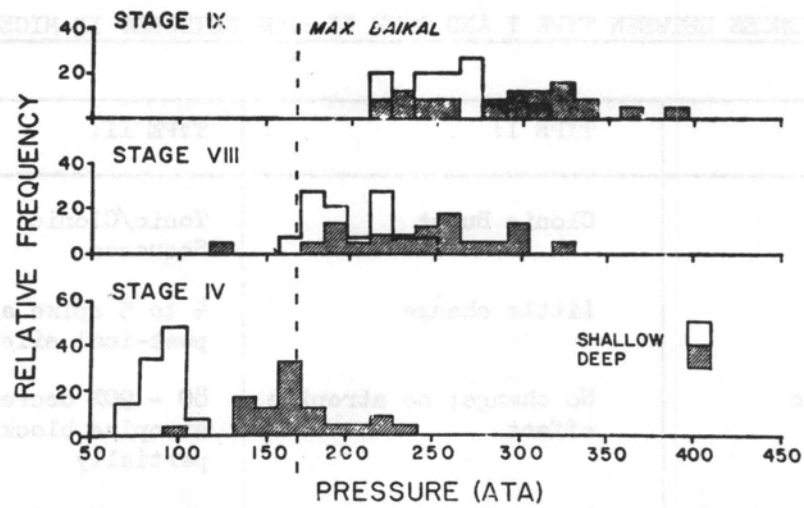


Figure 2:

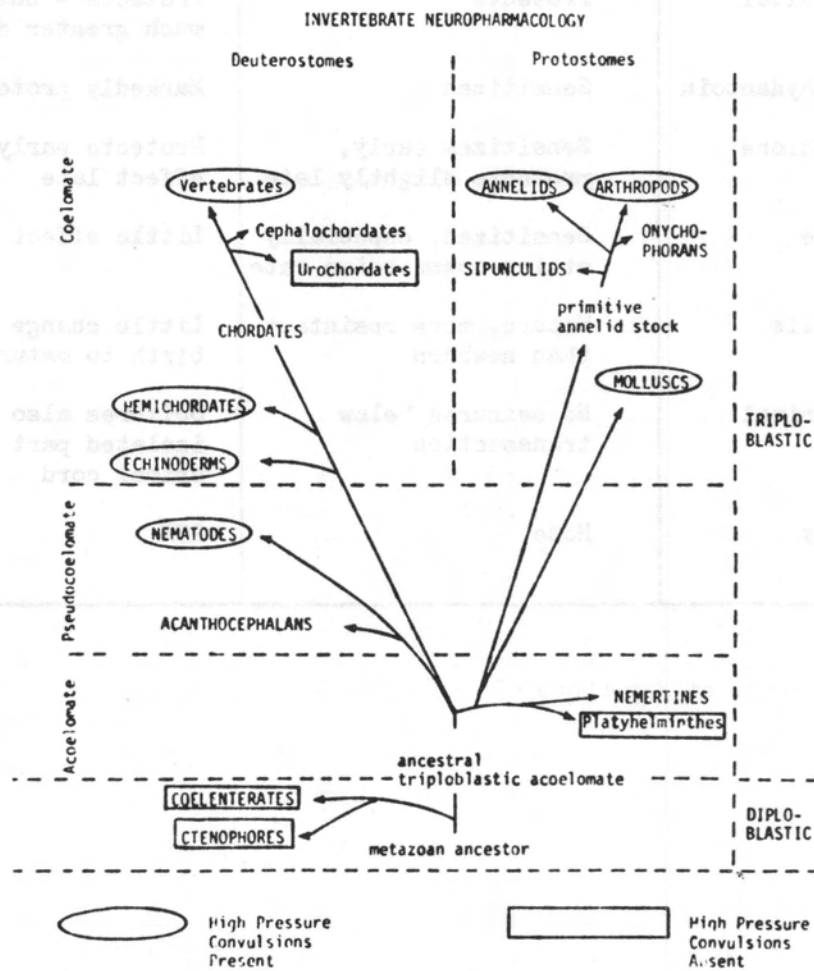


TABLE 1

DIFFERENCES BETWEEN TYPE I AND TYPE II HPNS SEIZURES IN MICE

CRITERIA:	TYPE I:	TYPE II:
Clinical	Clonic Burst	Tonic/Clonic Sequence
EEG	Little change	4 to 5 spike and wave; post-ical silence
Heart Rate	No change; no atropine effect	80 - 90% decrease; atropine blocked partially
Compression Rate	Very - K = 11	None - K = 0 or negative
Strain Differences	Marked	Few and small with one exception
Phenobarbital	Protects	Protects - but to a much greater degree than I
Diphenylhydantoin	Sensitizes	Markedly protects
Trimethadione	Sensitizes early, protects slightly late	Protects early, no effect late
Reserpine	Sensitizes, especially at low compression rate	Little effect
Ontogenetic	Mature, more resistant than newborn	Little change from birth to maturity
Spinal Animal	No seizures below transection	Seizures also in isolated part of spinal cord
Mortality	None	29%

TABLE 2 : Tentative Summary of Data on the Effects of Pressure on Isolated Excitable Tissue Preparations

AXONAL	Slowed Conduction Prolonged Action Potential No Change in Excitability Repetitive Firing Questionable
SYNAPSES, MYONEURAL JCT.	Decreased Transmission Increased Threshold Accelerated Fatigue
RHYTHMICALLY FIRING NEURONS	Transient Increase in Firing Rate
CARDIAC PACEMAKER	Decreased Firing Rate

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Table 3 : Tentative Summary of Data on Interaction of Anesthesia and Pressure on Isolated Excitable Tissue Preparations

AXONS	Anesthesia reversed by pressure Effects of pressure blocked by anesthesia (reported only for repetitive firing)
SYNAPSES AND MYONEURAL JCT.	Pressure does not reverse, or even summates with anesthesia
REPETITIVE FIRING STRUCTURES	Neuronal preps. - pressure does not reverse or summates with anesthesia (except for crayfish claw; see under AXONS)  Pacemaker Preps. -(pressure effect reversed by anesthesia)

The Amelioration of the HPNSKeith W. Miller

The object of this presentation is to examine in detail how far a pharmacological approach may be useful in the control of the HPNS. I shall not be much concerned with other important variables such as compression rate and temperature. The question posed in its simplest form is under given conditions how far do pharmacological agents alter the HPNS and what does this tell us about the underlying mechanisms? Given mankind's rather rudimentary knowledge of his own central nervous system only rather crude mechanistic models can be expected. This talk will cover three aspects of the topic. First, the use of gas-mixtures to ameliorate the HPNS. Here there is a simple model which accomodates the experimental data to a good approximation, makes some interesting predictions and leads to the conclusion that different aspects of the HPNS are mediated by different sites. Second, the latter rather non-specific approach can be replaced by one based on specific drugs. Here the aim is to selectively protect against those aspects of the HPNS which appeared above to have different sites of origin. In essence to perform a pharmacological dissection of the HPNS and to seek rationalizing models based on such data. This is an aspect of the subject which will be discussed by other speakers also. Third, I want to point out some directions for further study. In the CNS classical electrophysiological techniques are difficult to apply; the physiologist gravitates to the periphery. Biochemical techniques can thus fill a gap here. We have done some work which demonstrates the feasibility of doing such studies under hyperbaric conditions. The equipment we have developed should enable specific neurochemical questions to be approached.

All the work described here used mice as subjects. Experiments were carried out in a hyperbaric chamber under well controlled physiological conditions.

Gas mixtures were used to control the HPNS in the very earliest studies. The realization that helium pressure reversed the sedative effects of the anesthetic gas in these mixtures gave impetus to their application. Many of the findings are well known. We have systematically studied the effects of a number of anesthetic gases on different phases of the HPNS. All raise HPNS thresholds and their relative potency in doing so is roughly proportional to their anesthetic potency. When their ability to raise HPNS thresholds is compared on this basis, it is found that different aspects (for example chronic vs tonic convulsions) have their thresholds raised at different rates, suggesting different underlying mechanisms (Figure 1). This actually raises a difficult experimental problem. The end-points of the HPNS often occur quite close to each other on the pressure scale. When these end-points shift by different amounts the order they occur in may invert. It is often difficult to distinguish them. Thus work to better define end-points which occur at lower pressures is clearly important.

It is possible to rationalize most of these observations using the critical volume hypothesis. The purpose of doing so here is to emphasize some points that are not immediately obvious from the experiments. Empirically we observe that helium excites while argon is an anesthetic. Helium reverses argon anesthesia. Helium also acts very much like hydrostatic pressure. In the critical volume hypothesis this occurs because helium is so insoluble that little of it dissolves at the site of action; thus its expanding effect is small. So small in fact that the mechanical compression is large and net compression occurs. Argon is more soluble and

expansion occurs. The model equates compression with excitation and expansion with anesthesia. By mixing gases the two effects can be titrated ---- hence the use of trimix. But will helium always behave like pressure ? The model predicts not and is quite precise about when this happens. At a site where helium is more soluble than usual and where the compressibility is smaller than usual, helium is predicted to cause expansion. When one looks at the physical parameters of the sites we have characterized, the occurrence of sites which helium will expand seems very probable. There are indeed observations in the literature where helium interacts additively with nitrogen. The important conclusion is that we have no right to expect the trimix concept to work universally when helium is used as a pressure transmitter. Therefore for a given aspect of the HPNS which is of practical concern specific experiments should be performed to test the applicability of the trimix concept.

In the second part of this presentation we turn to the use of intravenous agents. We have compared intravenous anesthetics and non-sedative anticonvulsants as well as some other agents (Rowland-Jones, Wilson and Miller, unpublished data). The most striking contrast is seen between phenytoin and phenobarbital which have some structural similarities (Table 1). Our data show that all the end-points studied (tremors, spasms, clonic and tonic convulsions and death) have different pharmacological profiles. Furthermore, the percentage increase in the threshold is greater for some end-points than others.

The anesthetics urethane and phenobarbital gave excellent protection at high doses, in many cases doubling the threshold pressures (Table 1 and Figure 1). Urethane seemed particularly effective at preventing the tremors which showed an unusually low incidence with this agent. Phenobarbital was exceptional against



tonic convulsions and also raised the lethal threshold remarkably. Pressures of 250 Atm (8,250 fsw) were reached without modifying the compression profile (60 Atm/hr) compared to a control value of 130 Atm (4,300 fsw). In these experiments, as well as with trimix, there is a clear tendency for the tonic convulsion threshold to be elevated more rapidly than the lethal threshold. Consequently at high doses death intervenes before the tonic phase occurs, nicely illustrating that these effects have unrelated causes.

The non-sedative anti-convulsant, phenytoin, also illustrates the latter point (Table 1). No tonic phase was observed but death occurred at control pressures. Phenytoin was remarkable for its ability to potentiate tremors and spasms, an observation confirmed independently. It was the only agent to do so.

Other agents have been examined (Table 2). The overall picture is one in which only the anesthetic agents gave a broad protection; other agents gave selective protection, no protection or potentiation. The variety of responses to the non-sedative agents is encouraging. It justifies the systematic search for agents which may selectively protect against the early phases of the HPNS associated with diving. It is difficult to draw mechanistic conclusions from the latter studies. One must realize that many of the drugs effective against epilepsies, for example, have unknown modes of action. Furthermore, one must distinguish at least two types of anti-HPNS agent. The first acts on the primary site of pressure excitation and the second on the neural pathways which transmit the excitation to those areas mediating the behavioural response. By analogy with work on epilepsies several modes of action may be possible in each case. Thus it is much harder to draw conclusions about the specific, than the non-specific, agents. Only detailed studies on simpler systems can be expected to yield useful mechanistic information.

We have tackled the problem of extending HPNS studies to the neurochemical level by developing a filtration apparatus which will enable many of the in vitro CNS preparations to be studied in hyperbaric gases. Presently we are using this to study the properties of the nicotinic acetylcholine receptor from electric fish (a rich source), but the technique will allow one to pose a series of neuro-chemical questions. At present we have studied the effect of helium pressure on the binding of [<sup>3</sup>H]-acetylcholine to its receptor. We find that the binding affinity is decreased without changing the number of sites or the cooperativity of binding. Volatile anesthetics have the opposite effect on binding. Thus the effects of helium and volatile anesthetics oppose each other. Preliminary studies show that other inert gases, such as argon and nitrous oxide, act in the same direction as volatile anesthetics. Thus, while the experimental problems should not be underestimated, it is quite feasible to carry out quantitative neuro-chemical experiments under hyperbaric conditions. One is thus in a position where precise questions may be posed and answered. Since the problem remains so ill-defined, however, and the in vivo neuropharmacology of the HPNS is scarcely charted, the choice of initial questions is difficult to define on a rational basis.

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TABLE 1

Comparison between nitrogen and some drugs (60 atm/hr)

Drug (xAD <sub>50</sub> )	Dose mg/kg	Coarse Tremor	Complete Spasm	Tonic Con- vulsion	Death
<u>Nitrogen</u>					
(0.21)	7.5 atm	ND			+ 28 atm
(1.4)	49 atm	ND		none	90 atm
<u>Urethane</u>					
(0.24)	230	+ 20			
(1.55)	1500	+ 63	+77	+ 100	+ 80 atm
<u>Phenobarbital</u>					
(0.19)	21	+ 24	+ 21		
(1.42)	160	+ 29		none	> 96 atm
<u>Diphenylhydantoin</u>					
	47	- 31		none	
<u>Chlorpromazine</u>					
	15 - 60				
-----					
<u>Helium</u>	50 ± 5	83 ± 4	102 ± 9		129 ± 10 atm

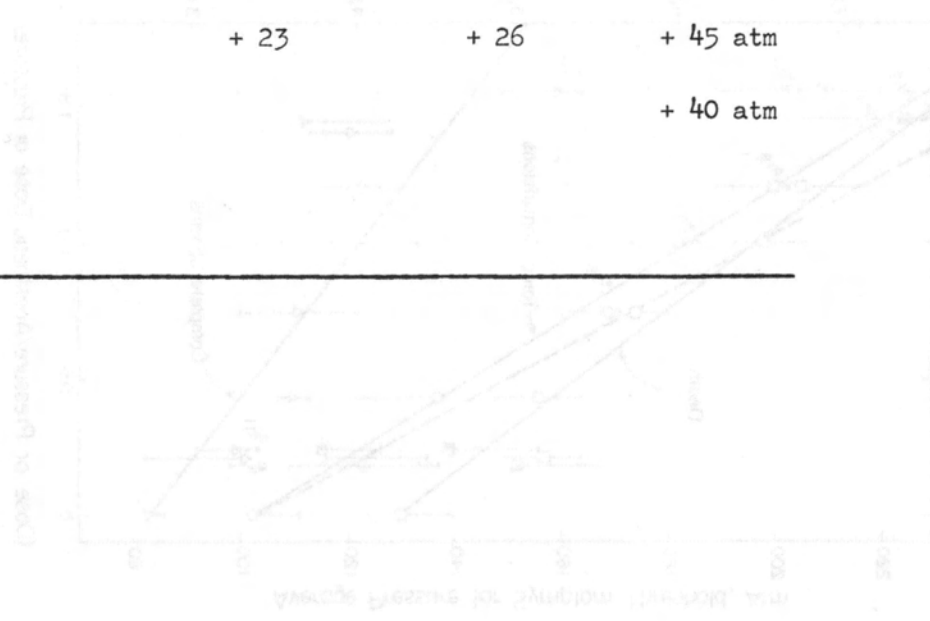
Note: ND = Not determined

Only changes in threshold 20 Atms are reported here

TABLE 2

Effects of 3 non-anesthetics on HPNS (200 Atm/hr)

<u>Drug</u>	<u>Dose mg/kg</u>	<u>Coarse Tremor</u>	<u>Complete Spasm</u>	<u>Tonic Con- vulsion</u>	<u>Death</u>
<u>Helium</u>		36 ± 7	86 ± 7	101 ± 9	117 ± 12 atm
<u>Diazepam</u>	2.5 2.0		+ 23	+ 26	+ 45 atm
<u>Trimethadione</u>	680				+ 40 atm
<u>T.H.C.</u>	60 - 120				



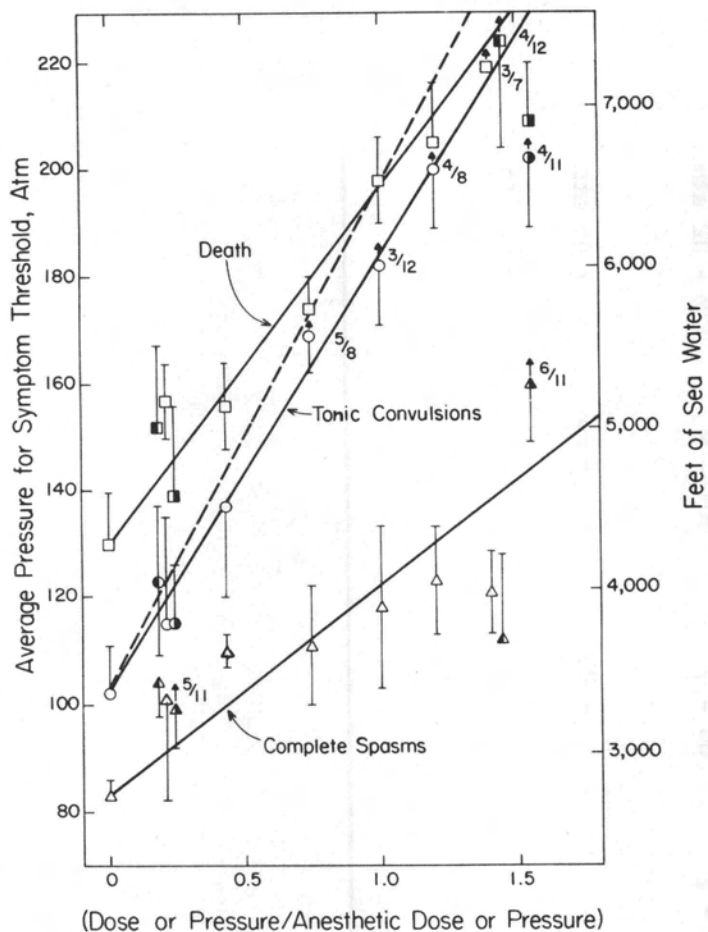


Figure 1:

The effect of nitrogen and two intravenous anesthetics on three HPNS end-points. Experiments were carried out on mice confined in a pressure chamber with excellent environmental control. Compression was carried out with helium at 60 Atm/hr and a  $pO_2$  of 1 Atm. The nitrogen was added at the beginning of the compression. Triangles: complete spasm threshold - rhythmical tensing of the whole body which precedes clonic (Type I) convulsions. Circles: tonic (Type II) convulsions. Squares: pressure induced death. Open symbols are helium plus nitrogen. Symbols solid on the right are urethane and those solid on the left are phenobarbital. Error bars are standard deviations. Lines are drawn by eye. Fractions indicate when not all mice showed a given end-point. Vertical arrows indicate the value shown is a minimum because of the incomplete response in the latter cases. The effect of the anesthetic is greater on tonic convulsion thresholds. The dotted line suggests that the tonic convulsion threshold is raised above the lethal limit.



Pharmacological Aspects of the High Pressure Neurological  
Syndrome (HPNS)

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M.J. Halsey and Bridget Wardley-Smith

The use of anaesthetic additives in diving below 200 m is recognised as a potential major advance both in treating HPNS once present and preventing its occurrence. However, the pharmacological attack on this problem has been limited and the underlying mechanisms of the effects are not understood. We wish to report our rodent experiments with a range of intravenous anaesthetics and anticonvulsants; some of which were selected from our 1975 preliminary screening experiments using tadpoles.

Recent experiments in rodents demonstrated that although some anaesthetics have no effect on HPNS (e.g. thiopentone), no compound unrelated to an anaesthetic has yet been found to have any significant effect in preventing it. It seemed possible that a non-anaesthetic compound with a close structural relationship to an anaesthetic might prove useful in the treatment of HPNS. The steroid anaesthetic alphaxalone (the main component of Althesin) has several non anaesthetic isomers with only small structural changes: since alphaxalone is effective in preventing HPNS these compounds seemed appropriate to study for antiHPNS activity.

We developed a technique for the infusion of agents at ambient or elevated pressure into the tail veins of minimally restrained rats whose behavioural and physiological responses were continuously monitored. The initial experiments involved the continuous infusion of Althesin to provide a constant level of anaesthesia over periods up to six hours. The present experiments have involved intermittent infusion of agents. Results of the generalised effects

on tremor of infusing alphaxalone or its isomers are shown in Fig. 1. Alphaxalone was the most effective, but anaesthesia occurred very shortly after tremor had ceased.  $3\beta$ -hydroxy- and  $\Delta^{16}$  alphaxalone both reduced the severity of tremor, but were not as effective as alphaxalone. Neither isomer had any anaesthetic effect. Once tremor had returned, usually about 3 min after the initial drug infusion, a second dose was given;  $\Delta^{16}$ -alphaxalone was still effective, but  $3\beta$ -hydroxy-alphaxalone had less effect on tremor during second or subsequent doses, suggesting that its metabolized form partially blocked the HPNS receptor.

The use of structural isomers of anaesthetics is an approach which may make it possible to distinguish between separate molecular receptors for anaesthesia and HPNS, and thus to enable a drug to be found which is safe and effective in treating HPNS. Isomers of an anaesthetic already shown to be effective in preventing tremor could have considerable potential as a pharmacological approach. Our results so far are encouraging, but a number of further questions remain. It has been suggested that the isomers of alphaxalone are non-anaesthetic simply because they do not reach the molecular receptor for anaesthesia. The fact that we found the isomers only partially effective in preventing tremor could be due to an insufficient concentration at the molecular level, but the existence of any effect on HPNS demonstrates at least a partial concentration of the drug being available to the receptor. It is possible that isomers of the newer water soluble steroids (e.g. Minaxolone) would be more successful since a much greater reservoir of the drug should be available to the molecular receptor, and we are currently testing this idea.

Attempts to find a drug not related to anaesthetics to treat HPNS have so far not been successful. A study in which we screened anticonvulsant drugs for antiHPNS activity in mice showed that only

those compounds which were anaesthetic at higher concentrations, e.g. diazepam, were of any value. Non anaesthetic anticonvulsants such as phenytoin were completely inactive against HPNS in our preparation. This provides further support for the concept of some interaction between anaesthesia and HPNS receptors. However, it seems certain that the receptors are not identical in view of the considerable variation between different anaesthetics in their ability to prevent HPNS in rats.

This idea of linked receptors is not inconsistent with other experiments in intact animals, which have demonstrated that the area of the brain affected by anaesthetics and pressure is the same i.e. in the somatosensory pathway leading to the cerebral cortex. These experiments looked at the reduction of the evoked somatosensory cortical response by urethane followed by its recovery on increasing ambient pressure. These data also suggest that the effects of pressure, both alone and on anaesthesia, are not due to a general excitation, such as might be mediated by catecholamine release.

It is thus of potential importance to understand more about the precise receptors for anaesthesia and HPNS, since the separate sites would allow the possibility of a drug entirely effective in treating HPNS without undesirable anaesthetic "side effects". Hopefully, the study of inactive isomers of anaesthetics shown to be of value in ameliorating HPNS will continue to provide promising results.

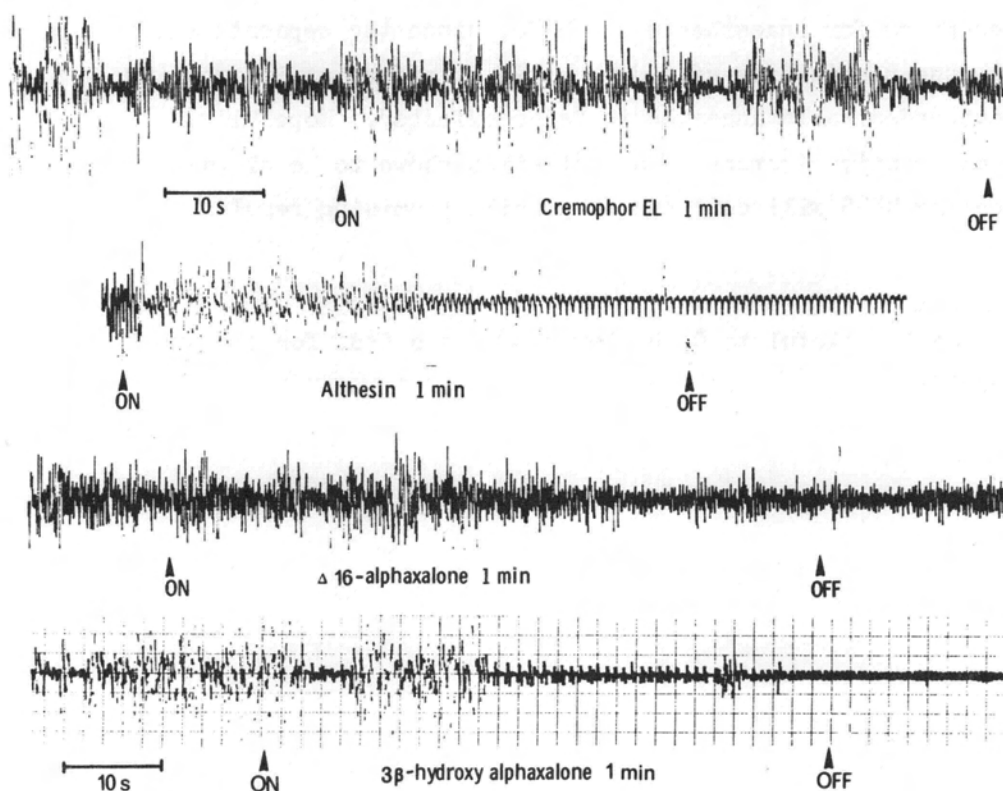
#### Acknowledgement

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Figure 1



Effects of Pressure on Nervous TransmissionJoan J. Kendig

Our laboratory has approached the problem of HPNS and its amelioration by posing two questions: How does the hyperbaric environment alter the electro-physiological manifestations of nerve cell functions? How does it alter the nerve membrane structure which supports these functions? The present report summarizes our progress to date in answering these questions.

Synaptic Transmission at Hyperbaric Pressures

At the time when we began hyperbaric studies in 1972, it was a cliché in anesthetic pharmacology that anesthetics act by selectively depressing synaptic transmission. We therefore elected to examine the synapse as a promising site for pressure anesthetic antagonism, using the mammalian sympathetic ganglion as a test preparation. Surprisingly, the cholinergic synapse of the ganglion does not appear to be affected antagonistically by anesthetic agents and pressure; instead both pressure and anesthetics depress transmission through this synapse in an additive fashion<sup>1</sup> (Figure 1). This was observed at pressures as low as 35 atmospheres. The depressant effect of high pressure has since been observed at other synapses, including the slow excitation of the sympathetic ganglion<sup>2</sup>, the neuromuscular junction<sup>3</sup> and, by other laboratories, molluscan<sup>4</sup> and crustacean<sup>5</sup> synapses. In no case does pressure antagonize anesthetic effects on synaptic transmission or vice versa. Thus although synaptic mechanisms may be involved in HPNS, it seems unlikely that direct antagonism at the synapse is a basis for anesthetic amelioration of HPNS or pressure reversal of anesthesia.

### Impulse Conduction

When we looked at conduction of the action potential in electrically excitable membrane, we did find pressure-anesthetic antagonism<sup>1</sup> (Figure 3). Pressure itself, up to 200 atmospheres, had relatively little effect on the propagated action potential except to slow conduction velocity and slightly depress amplitude. When conduction had been partially blocked by anesthetic agents, however, hyperbaric pressure between 70 and 100 atmospheres did relieve the block to some extent. Pressure-anesthetic antagonism in axons has now been observed for a number of agents, including local anesthetics, which share the common property of hydrophobicity<sup>6</sup>. It thus seems likely that the electrically excitable axon membrane provides a site of antagonistic effects of high pressure and anesthetic agents, and therefore we have chosen to concentrate our recent efforts on this membrane. We have endeavored to find out how pressure alters axon membrane function, and how lipophilic agents act in the membrane to block sodium channel function.

### Axon Hyperexcitability at High Pressure

In many of the experimental studies described above, the recordings gave the appearance of low-level asynchronous activity in axons exposed to hyperbaric pressure. This was hard to quantify in vertebrate nerves, with their large populations of small-diameter axons. In crustacean nerves, however, activity in individual large axons can often be distinguished. In this study, crayfish claw nerves were exposed to pressures up to 200 atmospheres in a temperature controlled recording chamber. Repetitive and spontaneous impulses were reliably evoked by compression, even to pressures at the lower end of the range (20 atmospheres)<sup>7</sup>. The repetitive impulse generation was blocked by anesthetic agents<sup>8</sup>. It has been suggested that axon repetitive firing is related to some types of convulsant activity. This effect of pressure on axon membranes is therefore a phenomenon of considerable interest



to explore as a possible basis for HPNS, particularly in view of the prevention of pressure-induced repetitive activity by anesthetic agents. There is also the possibility that it might be related to pressure reversal of anesthesia.

We have begun to explore the membrane basis for pressure-induced repetitive impulse generation by examining the responses of a voltage-clamped single vertebrate axon to high pressure. The technique of voltage clamping allows ion channel function to be monitored directly, rather than indirectly by observing the action potential. Our preliminary studies suggest that at least some axons respond to even modest compression (<10 atmospheres) by generating a depolarizing net inward current. Such a current would produce repetitive rhythmic action potentials in an axon with suitable properties. As has been described by others in invertebrate axons, very high pressure (above 70 atmospheres) also alters the time constants of the voltage-dependent ion-permeable channels. These results are tentative, and the basis for the pressure-induced changes in membrane properties remains to be explored.

#### Anesthetic Actions in Nerve Cell Membrane

It is clear that pressure antagonizes the anesthetic effects of a wide variety of agents, including general inhalation anesthetics, inert gases, and local anesthetics. Pressure appears also to relieve conduction block by those agents which have lipophilic properties related to their potencies (Figure 3). We have proposed that the lipid-soluble agents share common properties in the way in which they interfere with sodium channel function, via a common action on hydrophobic components of the sodium channel or on the lipid bilayer surrounding the channel. This thesis has been supported by experiments on the sodium channel of the voltage-clamped node of Ranvier. Barbiturates, local anesthetics, and general anesthetics appear to alter channel function in a similar

fashion, promoting channel inactivation and binding selectively to channels in the depolarized membrane<sup>9</sup>. The common basis for interference with a membrane-active channel suggests that the agents act in part in similar fashion in the central nervous system, and that there may be a common basis for pressure antagonism to their anesthetic effects as well as a common path for anesthetic amelioration of HPNS. These common properties offer the possibility of developing an anti-HPNS agent with minimal undesirable side effects. We are pursuing the question of whether pressure directly interacts with anesthetic agents at the membrane level, or rather exerts an unselective effect on a membrane variable which indirectly opposes the anesthetic effect.

#### Nerve Membrane Structure

In parallel with our studies on membrane function, we have explored the opposing effects of anesthetics and pressure on structure in the lipid bilayer of membranes, and more recently on lipid-protein interactions. These studies have been carried out by Dr James Trudell of our laboratory, and I will report on them briefly.

#### Pressure-anesthetic Antagonism in Lipid Bilayers

Since the potency of anesthetics is correlated with their lipid solubility, it has been our hypothesis that both anesthetic and pressure effects are mediated by actions on nerve membrane lipids. In initial experiments in phosphatidylcholine bilayers, anesthetic agents were observed to increase the mobility of the hydrophobic fatty acid chains in the bilayer interior, while pressure had the opposite effect.<sup>10,11</sup> Although the effects were significant and clearcut within the anesthetic range, and within the range of pressures associated with HPNS, they were small. It was difficult to envision a direct effect of these small changes in membrane lipid

fluidity on nerve cell function. A more promising phenomenon was then explored, namely shifts in the phase transition temperature of phospholipids. In defined lipid bilayers, anesthetics produced a marked downward shift in the phase transition temperature, at which lipids change from a solid to a liquid-like structure. Again, pressure acted in the opposite direction<sup>12</sup>. Since phase separations have been strongly suggested to be important in membrane protein function, shifts in transition temperature may be a mechanism whereby anesthetic and pressure effects on membrane lipids may interfere with membrane protein function.

#### Lipid Mobility Changes in Nerve Membranes

In order to test the applicability of the results on model systems to living nerve, we employed the same techniques of spin-labeling membrane lipids of an actual nerve and monitoring lipid configuration via electron paramagnetic resonance spectroscopy. These experiments confirmed that pressure and anesthetic agents induced the same changes in real nerve as in model membrane systems, pressure making the lipid more rigid and less mobile and anesthetics making it more fluid and disordered<sup>13</sup>. The nerve preparation was the same one used in the studies on increased excitability at high pressure, and it was therefore possible to correlate the membrane lipid changes with changes in nerve function.

#### Lipid-protein Interactions

Our most recent studies in this area have begun to explore the structural interactions between surface charge, lipid composition, and protein admixture. Preliminary results show that negatively charged dipalmitoylphosphatidic acid bilayers behave quite differently from, e.g. dipalmitoylphosphatidylcholine in response to pressure. In the latter, pressure and anesthetic agents exert symmetrically opposing effects on phase transition temperatures. In membranes bearing a surface charge, however, hyperbaric pressure

had little effect itself but completely antagonized the effect of methoxyflurane. This is the first demonstration of a true antagonism of pressure to anesthetic effects in a model membrane system.

Our second approach has been to incorporate a single species of polypeptide into defined lipid bilayers. Polymyxin, a positively-charged, antibiotic polypeptide exhibits an asymmetric distribution of hydrophobic and hydrophilic parts. It strongly binds to negatively-charged phosphatidic acid bilayer membranes causing a phase separation in the lipid matrix. Domains of protein-bound lipids are determined which are characterized by a lowered phase transition ( $\Delta T \sim 20^{\circ}\text{C}$ ). This effect is due to an expansion of the lipid matrix. The lipid protein interaction is shown to be cooperative. The effects of high pressure on the organization of the lipid-protein-complex have been examined. One result is a loss of the cooperativity of the binding process at 100 atmospheres helium pressure. A second result is the reorganization of cluster proportions. The lipid-protein-domain exhibits two regions of different binding properties. One shows only hydrophobic, whereas the second one is characterized by hydrophobic and electrostatic interaction. The heterogeneity of the domain is strongly affected by high pressure compensating the effect of membrane expansion caused by the protein.

Our experiments show clearly that pressure may alter lipid-protein interaction and may control cooperative processes. Enzymatic reactions in biological systems are known to be cooperative. The results suggest how high pressure could alter biochemical functions of membrane-bound protein assemblies.

In summary, studies from this laboratory have begun to define the nerve membrane events which underlie anesthesia, the high

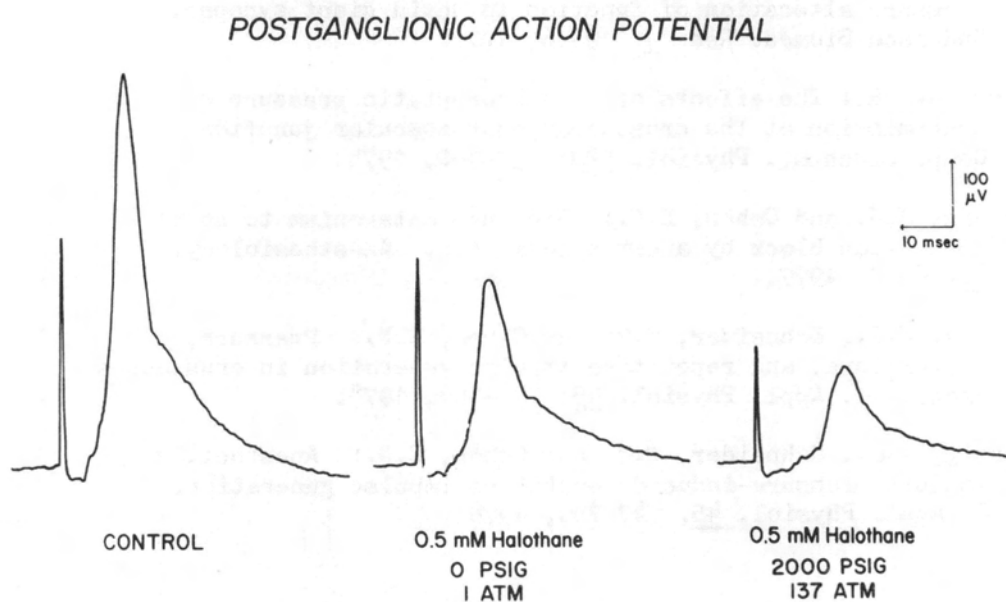
pressure nervous syndrome, and the antagonism between anesthetics and hyperbaric pressure. Defining these events at the level of membrane ion channels and lipid-protein interactions will clarify the way in which the opposing physical agents, anesthetics and pressure, distort nerve cell function by their actions in membrane lipids and/or membrane functional proteins. With respect to human capabilities, the results of these studies will allow us to predict the extent to which divers can function at very great depths, and the degree to which the high pressure nervous syndrome may be safely ameliorated by exposure to agents which induce anesthesia.

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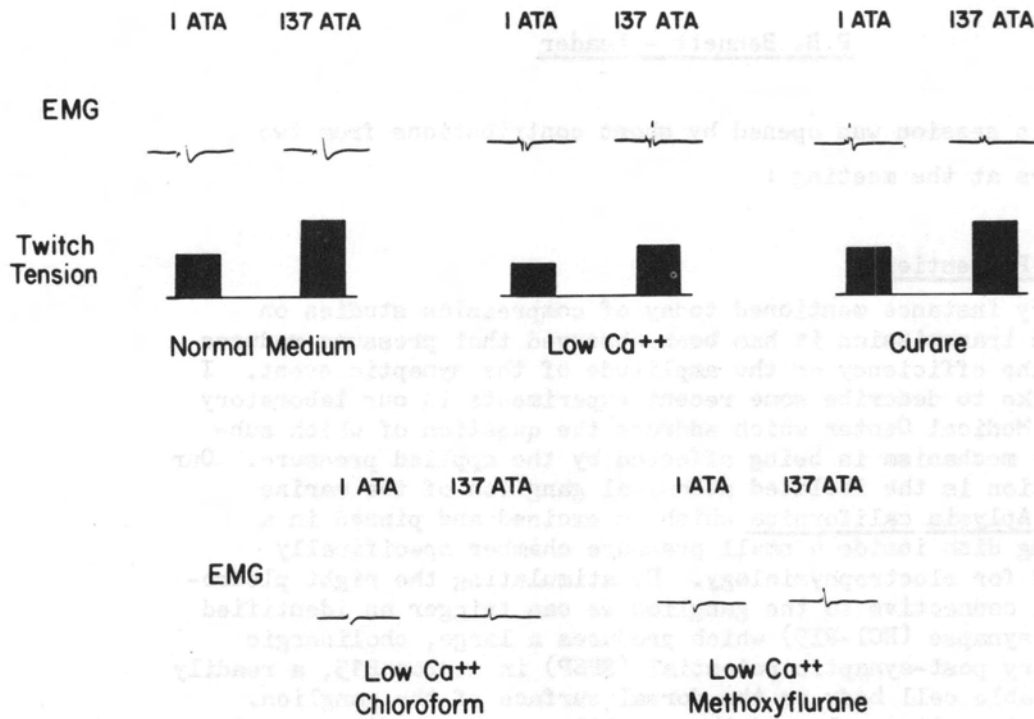
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**Figure 1:** Additive depression of synaptic transmission by pressure and by anesthetic agents. Recording is the postganglionically monitored response to stimulation of the preganglionic nerve of the rat superior cervical sympathetic ganglion.

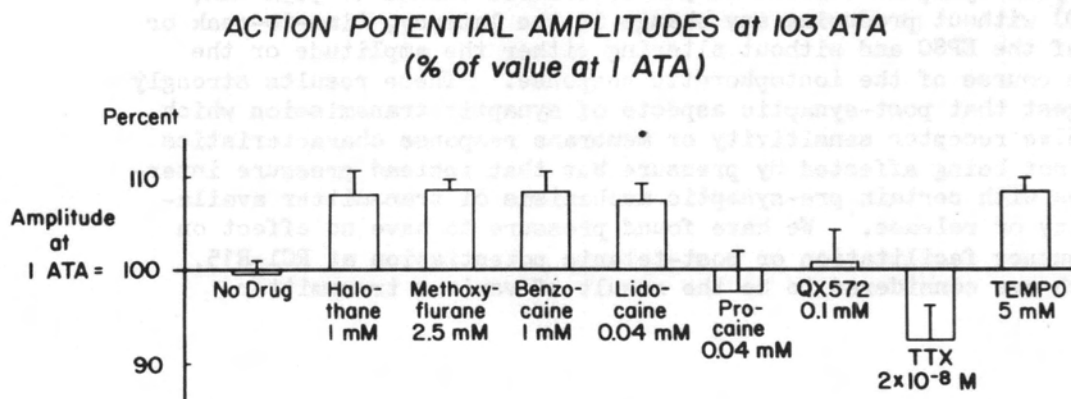




**Figure 2:** Depression of the diaphragm EMG by pressure and anesthetic agents.



**Figure 3:** Pressure antagonism to conduction block by a variety of lipophilic drugs.



Discussion - Session 3: HPNS Mechanisms and Potential  
Methods of Amelioration

P.B. Bennett - Leader

This session was opened by short contributions from two observers at the meeting :

Dr J.L. Parmentier :

"In every instance mentioned today of compression studies on synaptic transmission it has been observed that pressure reduces either the efficiency or the amplitude of the synaptic event. I would like to describe some recent experiments in our laboratory at Duke Medical Center which address the question of which sub-synaptic mechanism is being affected by the applied pressure. Our preparation is the isolated abdominal ganglion of the marine mollusc Aplysia californica which is excised and pinned in a recording dish inside a small pressure chamber specifically designed for electrophysiology. By stimulating the right pleuro-visceral connective to the ganglion we can trigger an identified central synapse (RCl-R15) which produces a large, cholinergic excitatory post-synaptic potential (EPSP) in neuron R15, a readily identifiable cell body on the dorsal surface of the ganglion. When R15 is voltage clamped the resulting monosynaptic event is recorded as an excitatory post-synaptic current (EPSC) which has a rapid rise time, a fixed threshold and time-to-peak, and a single exponential decay phase with a fixed time constant of decay ( $t_D$ ). With a second microelectrode we can simultaneously apply acetylcholine iontophoretically to the soma of R15 and record the rapid, Na<sup>+</sup> dependent excitatory response produced by the extrasynaptic ACh receptors on the cell surface.

Hydrostatic compression of this preparation to 100 ATM, using mineral oil as the compressive medium, resulted in a reduction of the peak synaptic current to 54% of control values ( $\pm 3.5\%$  SEM, N=20) without producing any change in the latency, time-to-peak or  $t_D$  of the EPSC and without altering either the amplitude or the time course of the iontophoretic response. These results strongly suggest that post-synaptic aspects of synaptic transmission which involve receptor sensitivity or membrane response characteristics are not being affected by pressure but that instead pressure interferes with certain pre-synaptic mechanisms of transmitter availability or release. We have found pressure to have no effect on frequency facilitation or post-tetanic potentiation at RCl-R15, which are considered to be the result of various transmitter

mobilization and storage properties of material flow within the pre-synaptic terminal. At the present time we suspect pressure may interfere with certain  $\text{Ca}^{++}$  conductances which underlie excitation-secretion coupling in the synapse and that this effect may explain observations of pressure reduction at many other central and peripheral synapses as well. We are presently investigating pressure effects on an inhibitory central synapse in order to test the hypothesis that a reduction of synaptic efficiency of inhibitory synapses may explain the resulting hyper-excitability effects which normally follow compression of whole animals."

Dr B.B. Shrivastav :

"Precise measurements of ionic currents and related permeabilities in excitable membranes under different conditions of hydrostatic pressure and temperature will provide new insight into the physico-chemical mechanisms involved in generation and propagation of the action potential. Hodgkin and Huxley (J. Physiol. 117, 500-554, 1952) have provided a quantitative description and plausible explanation for the observed changes in membrane  $\text{Na}^+$  and  $\text{K}^+$  conductances, by a set of equations which define the opening and closing of the ionic channels as both voltage and time dependent. From these equations it is possible to calculate rate constants for the channel opening mechanisms. It is then possible to apply Eyring's Absolute Rate Theory to pressure-induced changes in processes to determine aspects of the free energy changes which are involved in both the normal functioning of these channels and the alterations of that normal functioning when exposed to increased pressure. Such free energy changes at constant temperature will change reaction rate and can be written as follows :

$$\alpha_2 = \alpha_1 \exp - \left\{ \frac{\Delta V^* (P_2 - P_1)}{RT} \right\}$$

where  $\alpha_1$  and  $\alpha_2$  are the forward rate constants at pressure  $P_1$  and  $P_2$  respectively. R and T have usual meanings. From this equation any change in volume of activation,  $\Delta V^*$ , for a reaction will be reflected in alteration of the reaction rate at increased pressure. An increase in volume will decrease reaction rate and vice versa. Therefore, by measuring the rate of channel opening at different pressures it is possible to calculate  $\Delta V^*$  and determine the effects of free energy change involved in making or breaking the non-covalent bonds seemingly responsible for control mechanisms of opening and closing of these ionic channels.

Recently, we have been very successful in voltage clamping squid giant axon at increased hydrostatic pressure. These studies at 1, 100 and 150 ATA indicate that for both the sodium and the potassium

channel systems the forward rate constant  $\alpha$  decreased with increase in pressure and the associated change in the volume of activation,  $\Delta V^*$ , for the opening of these channels is independent of the change in pressure. The calculated  $\Delta V^*$  values are +30 ml/mol and 40 ml/mol for the sodium and potassium channels respectively.

Comparing these data to the change in  $\Delta V^*$  for the breakdown of hydrogen bonds or with the formation of hydrophobic interactions and/or ionic bonds at increased pressures, we conclude that changes in the noncovalent bonds are involved in opening these ionic channels upon membrane depolarization."

The subsequent discussion concentrated on the problems of relating the in vitro and in vivo animal work to the phenomena of HPNS as observed in man. It was recognised that HPNS in man is a complex mixture of signs and symptoms, many of which of necessity cannot be observed in animals (e.g. "epigastric sensations"). Conversely convulsions which have been observed in animals have not yet occurred in man at pressure. It was noted that the animal convulsions had only occurred at pressures higher than those to which man had been exposed and so this might be a false dichotomy. One of the differences between the experimental protocols used in the majority of animal and human studies was the rates of compression. In general compression times in human work are of the order of several days whereas those in animal work are several hours. However, it was noted that the effect of compression times in animal studies had been investigated (see for example Brauer in the 8th Undersea Medical Society Workshop Report, 1975: The Strategy for future diving to depths greater than 1000 ft). It was clear that for most species increasing the compression rate increased the sensitivity to and severity of HPNS but there was also a compression rate independent component. Other differences between human and animal research that were discussed included the dosages of drugs used in the amelioration of HPNS. However it was pointed out that in the case of the general anaesthetics the "clinical" concentrations of agents were remarkably species

independent. In any case the majority of pharmacological investigations were comparative studies and not intended to define specific doses for man.

There was a considerable discussion on the merits of earlier approaches to the mechanisms of HPNS such as the critical volume hypothesis. It was realised that these were "black box" models which had originally provided some successful predictions. However most participants felt that the study of HPNS had now reached a point where things were so complicated that such simple models were inappropriate and it was necessary to analyse the data in a more sophisticated way. This complexity applied as much to the human data as to the in vitro preparations (See Section 3.1) and it was not yet clear what were the unifying criteria which could be applied as the framework for the assessment of different experimental approaches. The consensus of opinion was that at this point information on the basic mechanisms of what is termed HPNS is woefully lacking and that an attack on the problem at all levels of organisation is both in order and seriously needed.

Physiological and Medical Monitoring of the DiverC.E.G. Lundgren

As recently as 1978 the U.M.S. organized a workshop entitled "Monitoring Vital Signs in the Diver" (3), and some of you must have asked yourselves as I did if there is anything more to say on this occasion. Well, for one thing, by virtue of my role as a Chairman and Editor of the Proceedings of that earlier workshop I had to retain a certain minimum of impartiality which I can now happily do away with, and that in itself is an irresistible temptation. Furthermore, because of time constraints or by choice on the part of the organizers in 1978 there were certain aspects of monitoring of the diver which were not dealt with and which I would like to address briefly today.

These are the monitoring problems related to the adequacy of decompression. In addition there is the postdive short- and long-term medical monitoring. The latter will probably be best dealt with in the discussion after Professor Walder's presentation on the Chronic Hazards of Deep Diving.

With regard to the question of what to monitor, there are a number of general considerations on which it has been easy to reach agreement earlier. The parameters monitored:

- a) should have predictive value with regard to either the diver's immediate or longterm medical safety and/or ability to perform.
- b) should offer clues as to what went wrong in case of accidents (cf. the in-flight recorder in aircraft).
- c) should be manageable from the practical point of view; i.e. recording and presentation should be such as to allow evaluation and corrective action in real time when parameters under a) are considered.



Also, from the point of view of practicality, the monitoring should be done in such a way as to impose a minimum of inconvenience to diver and dive crew and a minimum of cost to the diving contractor.

Unfortunately, there is likely to be a lot of disagreement when we come to discuss specifics. There is disagreement as to what parameters are useful as well as what is practically feasible. Having said that I am not going to repeat all the arguments and counter-arguments that have been given earlier; I will instead exercise my prerogative of a personal view.

There are a few parameters or types of monitoring that are likely to be immediately useful, and these should be given consideration for in-sea application:

- 1) Voice communication is widely considered the most important and clearly also the one already most widely monitored - and it should be taped and stored at least until the completion of the dive.
- 2) Heart rate - to give an indication of the diver's exertion level and well-being. Cutoff points, i.e. excessively high and low heart rates, should preferably be determined on an individual basis, that is, in connection with exposing the individual diver to graded physical stress in simulated dives (cf. Ackles and Wright and discussion in (3)).
- 3) Ventilatory pattern - breathing frequency and tidal volume. The product of the two, minute volume, has been described as the physiological parameter best correlating with dyspnea in underwater exertion, a high minute volume tending to be linked more closely with dyspnea than high end tidal carbon dioxide concentrations (cf. Thalmann in (3)). Magnetometers (5) or other similar devices mounted on the diver's torso are now becoming available which will make pneumograph monitoring of

minute volume feasible and independent of the type of breathing gear worn.

- 4) Carbon dioxide in end tidal air may reach excessive values in divers in the absence of high exertion levels. Hypercapnia has been given as one explanation for loss of consciousness under water (cf. 6) in individuals with a tendency for hypoventilation at depth (4). In other cases hyperventilation in response to psychological stress has been implicated (1). In either case a continuous readout of  $P_{CO_2}$  in the mouthpiece or breathing mask could provide advance warning in addition to allowing the diving supervisor to check the technical function of the breathing gear. A further extension of this would be a readout of the oxygen tension which might be of value when using gear in which the oxygen content of the breathing gas mixture might vary.
- 5) The temperature balance of the diver is a very critical aspect of his safety and performance. Measurement of core temperature or perhaps heat flow across the skin (cf. Webb in (3)) should allow monitoring of the diver's thermal status. Various technical solutions for this, such as the "radio pill" and heat flow disks, are emerging that will make this feasible. The measurements should be presented against time because, as Webb (3) has pointed out, this would make it possible to guard against dangerous high rates of heat loss before a too low body temperature has been reached. This monitoring will also give forewarning about the treacherous slow cooling which may proceed to low temperature levels without the diver ever beginning to shiver or being aware of the danger.
- 6) Adequacy of decompression still has to be judged primarily on clinical criteria. The question of whether ultrasound or other physical monitoring for gas-liberation have any predictive value is certainly not yet settled. However, if it is

ever going to be of any value, it is important to do monitoring not only in the laboratory setting but also during in-sea conditions. The possibility of provoking decompression sickness experimentally in human subjects is limited by ethical constraints and therefore the cases of decompression sickness that do develop during operational diving are very valuable for determining the prognostic potency of the various bubble monitoring and bubble scoring techniques. Automated methods for quantitative treatment of bubble signals are becoming available these days and seem to make this type of monitoring more feasible (e.g. Kisman (2)).

- 7) Any evaluation of the adequacy of decompression has to be related to the depth-time history of the dive. Here again recent technical developments hold promise of allowing a much better record than the old-fashioned depth-time log kept by the dive tender. Thus, the U.S. Navy is presently testing a decompression meter which has the potential for storing depth time profiles of 12 hours duration (E.D. Thalmann, personal communication). This can be done in a little package 3x3x2 inches large which can then be connected to a tape recorder for permanent recording of the profile.

Again, it cannot be stressed enough that various kinds of monitoring to judge a diver's safety in real time are only meaningful if proper, easily implemented standards for acting on the information exist. The hardware for data treatment and presentation exists, but the physiological or medical background knowledge is in a more precarious situation although as I indicated some relatively firm guidance probably can be given for interpretation of information of temperature balance and certain respiratory and circulatory parameters. Some of the monitoring, such as the bubble monitoring, would mostly be justified because

it would provide data for further investigation.

Now, it is only to be expected that the interest among divers and diving companies in engaging in cumbersome and costly monitoring to provide research material for scientists is going to be lukewarm at best. When it comes to monitoring parameters that may be of more immediate application we can perhaps hope for more interest. However, there is still the cost/benefit consideration as well as concerns about legal aspects. As far as the cost effectiveness aspect goes, we can probably only expect a more positive attitude from the diving community if the scientific community contributes more toward educating divers and diving supervisors about the benefit aspects as well as how to monitor and interpret data. When it comes to further development of methods and the physiological basis of monitoring, it is our selling job to granting agencies that counts.

It has been suggested that implementation of monitoring can be enforced by legislation. This would be a political decision, but I personally would not recommend it as long as there are relatively few solid physiological facts on which to base rules for how to act once monitoring signals are coming in. However, with regard to longterm monitoring of divers, there are already some firm rules pertaining to yearly physicals and long-bone x-rays and we can expect the list to become longer. When it comes to health monitoring of divers for longterm effects of diving the research aspects weigh very heavily because for practical reasons we obviously cannot perform experiments in man to investigate these effects of diving. Regular monitoring of such parameters that are of potential interest should be implemented. This should probably be less controversial in one way than monitoring of the diver during the dive because the diving supervisor is not immediately involved and he is not required to act on the findings.

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Respiratory Problems at DepthE.M. Camporesi and J. Salzano\*

Physiological limitations encountered during deep diving are usually multi-factorial. Respiratory problems represent only a facet of the problem but have received wide attention in the last few years, since various limitations have been observed both at rest and during work at depth.

I would like to summarize some aspects of the hyperbaric environment which have been shown to induce limitations on the respiratory system. The hyperbaric environment may be characterized by the following:

1. Increased density of the breathing mixture.
2. Increased hydrostatic pressure,
3. Different (usually increased) O<sub>2</sub> tension and
4. Elevated partial pressure of inert gas.

In deep dives, the breathing medium usually will be altered for all these parameters at the same time: gas density is usually maintained at a tolerable level by changing the inert gas species (e.g. He). Therefore, it is difficult and often impossible to study the independent effects of gas species, pressure per se or density on the respiratory system.

Gas density Breathing mixtures used for deep diving are denser than normobaric air: as an example a Heliox mixture containing .4 ATA O<sub>2</sub> at 1000 fsw would have a specific gravity of 5.8 g/l, more than 5 times denser than 1 ATA air. With the increasing trend toward trimix usage (He + N<sub>2</sub> + O<sub>2</sub>), gas density will increase even more dramatically, and could become a barrier to human performance. The decrement of overall ventilatory ability induced by breathing of dense gas mixtures has been documented up to 25 g/l in the Predictive Dive series (1): maximum voluntary (MVV), the largest volume of gas

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that can be moved in and out of the lungs in 15 sec, decreases as an exponential function of gas density ( $d$ ), in the general equation form  $MVV_{(D)} = MVV_{(1)} \cdot d^{-a}$  where  $MVV_{(D)}$  = MVV at gas density  $d$ ;  $MVV_{(1)}$  = MVV breathing a gas with density = 1 g/l; and  $a$  is an exponent ranging between .4 and .5, as described by several authors.

MVV is an exhaustive, sprint-like maneuver, often performed by using unfamiliar respiratory cycle parameters, which leads to exhaustion in a few seconds. For these reasons it is probably unwarranted to extrapolate from the MVV value to levels of ventilation required to provide gas exchange during sustained activity. Additionally, the breathing of dense gas mixtures has been shown to be accompanied by neuro-mechanical adjustments of the respiratory system. An increased respiratory drive during  $CO_2$  stimulated breathing has been demonstrated when gas density is increased (2).

Hydrostatic pressure Pressure per se has been shown to induce the complex symptomatology of HPNS. Furthermore it appears to be responsible for alteration of the respiratory regulation of resting and steady-state exercise  $PaCO_2$ , usually found slightly elevated at pressure (3).

Oxygen tension The respiratory problems of  $O_2$  toxicity induced by an elevated oxygen tension while diving with compressed air are not quite transferable to gas mixtures used for deep diving. Commonly, synthetic gas mixtures are used for deep diving, in which  $O_2$  is maintained at .4 - .5 ATA, a level which apparently can be tolerated for several days with no ill effects and appears to offer a larger safety margin to the diver. These levels are well in excess of the tensions needed to maintain full saturation of hemoglobin. The alveolar arterial (A-a)  $O_2$  gradient has not been determined at pressures deeper than 1000 fsw, (4) and appears as yet another unknown variable during deep diving.

An additional limitation to work performance while breathing a gas mixture with a density approaching 7 g/l has recently emerged. Inspiratory dyspnea has been reported to be the primary work-limiting factor in immersed divers at great depth in two chamber dives to 43 and 50 ATA, breathing heliox.(5,6) In each study the dyspnea appeared not to be chemical in origin. More recently, (Spaur, this publication) resting dyspnea was observed at rest at 56 ATA in heliox, with mastication, speech and other activities interrupting respiration even for short bouts.

In the last two years at Duke University we have completed two 3 man dives to 46 and 65 ATA (Atlantis 1 and 2). Breathing mixtures consisted of He, .5 ATA O<sub>2</sub> and 5% or 10% N<sub>2</sub> (trimix). We have studied resting and steady state exercise gas exchange.

All subjects were physically fit and had reached a training plateau: they exercised in the dry on a calibrated bicycle ergometer. A low resistance breathing circuit provided for delivery of humidified fresh gas to the subjects and collection of expired gas for analysis and volume measurements. Arterial blood samples were drawn during the 6th min of exercise and analyzed for Po<sub>2</sub>, Pco<sub>2</sub> and pH. Chest and abdominal antero-posterior and lateral diameters were continuously measured with 4 pairs of magnetometers in order to detect shifts of lung volume during exercise. Surface 1 ATA studies were performed up to  $\dot{V}O_2$  max levels, breathing air or .5 ATA O<sub>2</sub> in N<sub>2</sub> (gas densities: 1.1 and 1.2 g/l). At 47 ATA 3 inspired gas mixtures were used differing in He and N<sub>2</sub> content, with a constant inspired O<sub>2</sub> of .5 ATA, and with densities of 7.4, 10.3 and 12.2 g/l. The gas density of 65 ATA was 15.1 g/l. Profound and sudden inspiratory dyspnea limited work performance at 47 ATA in 2 of 3 subjects breathing heliox (7.3 g/l) at 63 and 70% of  $\dot{V}O_2$  max respectively, with relatively normal blood gas values, and at ventilation levels exceeding 70% of maximal voluntary ventilation

(15 sec). With the 2 denser gases, containing 5% and 10% N<sub>2</sub> respectively, all subjects were conscious of the great respiratory effort required and described some inspiratory difficulty at high work levels, but were able to complete similar or slightly higher work loads than in heliox and had no frightening sensation of dyspnea. Instantaneous lung volumes were continuously calculated from chest wall diameters with a computerized algorithm. A slight decrease of end-expiratory lung volume was observed during exercise both at 1 and 47 ATA. No increase in end-expiratory volume was observed at the time respiratory difficulties were experienced. Resting dyspnea was experienced to various degrees by all subjects while eating, chewing or talking, but more with 5% N<sub>2</sub> (Atlantis 1), and far less while breathing 10% N<sub>2</sub> trimix (Atlantis 2). None of the subjects experienced nausea and in fact all gained weight during the deepest part of the dive. It appears that trimix breathing, despite increasing the respiratory gas density, attenuated not only signs of HPNS, but also resting dyspnea. The respiratory sensation during exercise with trimix may be related in part to the high gas density. Manipulation of gas species in the breathing mixtures appears therefore a useful area of research in order to overcome several respiratory problems at depth.

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A Chronic Hazard of Deep Diving: Bone NecrosisD. N. WalderIntroduction

There are several long-term disabilities which it has been claimed may affect deep-sea divers more commonly than the general population. Perhaps the most insidious of these chronic complications of diving is the aseptic necrosis which is found at certain characteristic sites in the long bones because secondary arthritis or the actual collapse of a joint surface with pain and limitation of movement may be the catastrophic first indication to a diver that anything is wrong in the absence of x-ray or related surveillance.

Fortunately the lesions can be detected by radiography, and appear as areas of altered bone density. The lesions identified by x-ray examination can be divided into two categories :

1. Those adjacent to a joint surface and called juxta-articular. Even after many years these may eventually break down to give rise to an irregular surface with pain, limited movement and the subsequent development of osteoarthritis. When this occurs they may require surgical intervention to relieve the disability.
2. Those in the shafts and other less important parts of the long bones. These lesions do not give rise to the sort of symptoms associated with juxta-articular lesions. It is possible that some of them may give pain though this is difficult to confirm. There is also a slight chance that after many years they may become the site for neoplastic change. I believe that this is only a remote possibility. Both these matters are being considered at present.

Thanks to careful studies carried out by the Royal Navy, the U.S. Navy and, in the North Sea, the M.R.C. Decompression Sickness Central Registry for divers, we now have an accurate idea of the prevalence of bone necrosis in both military and commercial divers. At first sight the figures for the 4463 commercial divers passed medically fit to dive in the North Sea appear to be reasonable. Of these men 2.8% have shaft lesions, 0.9% of men have the potentially disabling juxta-articular lesions but only 0.2% of men have joints which are so damaged that they have had or will require surgical intervention.

However, if we consider only those men who have taken part in diving from 50 - 200 m and who have had decompression sickness, the prevalence is found to be 6.4% for shaft lesions, 2.4% for potentially disabling juxta-articular lesions and 0.8% for those with severely damaged joints.

If we examine the prevalence of definite bone lesions amongst the 4463 divers whose maximum depth is known it can be seen that there is a close relationship between depth and bone lesions (see Table). No lesions at all are seen in men whose experience has been at 30 m or less, whereas more than 8% of the men who have dived to more than 100 m have definite radiographic evidence of bone damage. Obviously the development of safe deep diving will require some careful consideration to be given to the problem of avoiding bone necrosis.

The idea that the lesions result from impacted bubble emboli is logical and attractive. However, animal experiments have not been very helpful, mainly because in small laboratory animals the bone lesions which follow decompression are not like those seen in humans, and in large laboratory animals (mini-pigs) very severe



decompressions have been used which would be excluded from human experience because of the danger of decompression sickness. However, as Cox (1973) managed to produce convincing lesions in rabbits using glass microspheres to simulate bubbles, it could be claimed that previous failures in the smaller laboratory animals were merely due to the short persistence time of bubbles in these animals.

Histological study of the early stages of bone lesions in rabbits make it clear that marrow necrosis is invariably present as well - in fact it seems that marrow necrosis might be the primary event. Walder and Stothard (1978) were able to confirm that this indeed might be so. It was therefore decided to explore Johnson's suggestion (personal communication) that fat in the marrow space was the key to the etiology of bone necrosis. His hypothesis is that clusters of fat cells lie in compartments made up of the bone trabeculae and that when fat cells swell up because gas is released from them during decompression (Gersh, et al., 1944) their blood supply is restricted and blood flow may even stop altogether.

Unfortunately further evidence to support the idea that a fat cell supersaturated with gas will spontaneously bubble has not been forthcoming. Nevertheless, Johnson's hypothesis is attractive because it would explain the way in which bone lesions are found to be distributed in the long bones because they do occur in regions where red marrow is known to be replaced by fatty marrow in adults.

In order to investigate this idea the clearance of a radioisotope marker from the marrow of the femur of intact rabbits has been studied, and it has been found that this is influenced by changes in the ambient pressure. Pooley and Walder (1979) showed

that after 4 h at an air pressure of 2 ATA the clearance of Xenon was diminished. This diminished clearance persisted for at least an hour after the end of decompression.

As this could not be explained by the osmotic effects of dissolved gases an alternative explanation was sought. The effect of high pressure air on populations of isolated fat cells suspended in liquid was studied using a Coulter counter and channeliser. In this way it has been possible to show that a marked increase in the size of fat cells occurs as a result of exposing them to air at pressure for a period of a few hours. Furthermore, it has been shown that it is the partial pressure of oxygen which is the critical factor and not the air pressure per se.

There is some evidence that this effect of oxygen on fat cells is due to an interference with the sodium pump mechanism and this would explain the swelling (Robinson, 1975). It can be estimated that the intracellular pressure of the enlarged fat cells probably reaches a level sufficient to embarrass the intramedullary bone circulation. The effect can be prevented by Lithium salts.

The present position, therefore, is that we believe a critical factor in the etiology of bone necrosis may be fat cell enlargement in the closed medullary cavity of the bone. This so reduces the blood supply that it either results in marrow necrosis with a secondary effect on bone to give the picture we know as bone necrosis, or it makes the surrounding marrow and/or bone particularly vulnerable to a relatively short-lived embolus such as a bubble.

This looks like an interesting story but it is not yet complete as we have yet to demonstrate that it is the change in fat cell volume which affects the marrow blood flow.

If this hypothesis could be substantiated then it would follow that bone necrosis could be eliminated by avoiding the use of too high a partial pressure of oxygen for prolonged periods. Perhaps a more practical solution would be to protect fat cells pharmacologically.

In the meantime, what is to be done now to protect divers from the serious effects of bone necrosis? In the first instance all divers who descend to depths greater than 30 m and all saturation divers should undergo regular monitoring by annual radiography. The sites at risk from juxta-articular lesions are the shoulders and the hips, but it is also important to examine the shafts of the bone above and below the knees because they may turn out to be an indicator of the man's susceptibility to bone damage. It is essential that films of diagnostic quality are obtained and that they are read by at least one expert who has experience in the recognition of divers' lesions.

Secondly, the introduction of a large-scale serum ferritin screening programme for divers particularly at risk should be considered. A significantly elevated level 24 hours after decompression seems to indicate some interference with bone marrow metabolism. Any man who displays this rise could then be specially monitored to detect other evidence of bone necrosis as soon as possible.

Finally, if the use of bone scanning in man (by means of  $^{99m}\text{Tc}$ -labelled diphosphonate and the gamma camera) can be shown to be of value in assessing the early onset of bone necrosis, then it could be used to confirm at an early date whether or not the raised ferritin had been associated with significant bone damage. At present the exact significance of a positive scan has not been determined.

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Maximum Depth	Total men	(1) Men with definite HNS Lesions		(2) Men with definite J.A. Lesions		(3) Men with damaged joints	
		No.	%	No.	%	No.	%
0 - 29 m	555	0	0	0	0	0	0
30 - 49 m	978	3	0.3	4	0.4	0	0
30 - 99 m	1127	8	0.7	9	0.8	3	0.3
100 - 199 m	1622	89	5.5	24	1.5	6	0.4
200+ m	181	27	14.9	4	2.2	0	0

Aseptic necrosis of bone and maximum depth in 4463 commercial divers

Decompression and Therapy at DepthT. E. Berghage1. Decompression problems associated with deep diving

There are three aspects of this problem which we have considered separately; gas uptake, pressure reduction and gas elimination.

a) Gas Uptake: The basic premise in diving from 1 ATA has been that gas uptake is an exponential function of time. The question was whether this remains true if the initial pressure is greater than 1 ATA ? A study was conducted, using rats, in which the initial pressure was varied from 1.3 ATA to 20 ATA and where excursion exposures to 10 ATA greater than the initial pressure were made for various exposure times, with each excursion being followed by an abrupt decompression. Based on the  $ED_{50}$  times for each of these excursions, it was concluded that the pattern of gas uptake was not altered by increasing the initial pressure.

b) Pressure Reduction: Pressure reduction tolerance has generally been believed to vary in a linear, or close to linear, fashion with respect to exposure pressure. Using rats, saturation exposures varying between 6 and 60 ATA were made which were followed by abrupt decompression. Twenty minutes after the decompression the incidence of decompression was observed. The  $ED_{50}$  pressure reduction was plotted as a function of exposure pressure, Fig. 1. A linear relationship was found to an exposure pressure of approximately 42 ATA but beyond this no such relationship was apparent. The cause of this discontinuity is presently unknown. A further observation made from these experiments was that the slope of the dose-response relationship between incidence of decompression sickness and pressure reduction was progressively reduced by increasing the exposure pressure. This is shown in Fig. 2 where the gradients of the dose response curves are plotted against exposure pressure. In



consequence, at low exposure pressures there is a sharp distinction between those pressures which produce no decompression sickness and those which produce 100% decompression sickness, whereas at 60 ATA there is a change of about 11 ATA moving from an incidence of 95% to 5%.

The retention of CO<sub>2</sub> at elevated pressures may have an adverse effect on pressure reduction tolerance. In a study with mice an increase in surface equivalent percent of CO<sub>2</sub> to 5% was found to approximately halve the pressure reduction tolerance at all three exposure pressures studied; 12, 14 and 16 ATA.

We have conducted two studies to examine the effect of oxygen. In the first it was found that increasing exposure pressure increased markedly the relation between incidence of decompression sickness and oxygen partial pressure. In the second, the oxygen partial pressure was varied for different exposure pressures and times of exposure which were followed by abrupt decompression. It was found that the optimum oxygen partial pressure decreased with both time and pressure.

We have conducted one study, using rats, to explore the impact of time on the selection of an inert gas combination. This study indicated that, with the exception of very short dives (5 min), the longer the exposure the greater the proportion of helium required in a mixture of helium and nitrogen.

The Haldanian concept of decompression depends on the maintenance of the greatest possible pressure differential between tissue pressure and ambient pressure. In deep diving the question is, how long can this differential be maintained? We have approached this problem by exposing guinea pigs to pressures

equivalent to 2000, 1500 and 750 feet of sea water, abruptly decompressing to produce a pressure differential and then gradually decompressing toward the surface at a rate calculated by assuming a 10 min tissue half time, to maintain this differential. The differential pressure was maintained until all animals had died and the results were expressed as mean survival time against differential pressure. The results are shown in Fig. 3, where the mean survival time is shortest for the greatest pressure differential and for any given pressure differential the greater the initial exposure the longer the survival time.

c) Gas Elimination: In contrast to Haldane's original hypothesis, it is now generally accepted that gas uptake and elimination are assymetrical. We have examined the effects of exposure pressure and pressure reduction magnitude on gas elimination. In the first instance rats were saturated at 30 ATA and subjected to two successive abrupt decompressions separated by a decompression stop of either 5, 40 or 120 min and where the magnitude of the initial decompression varied from 3 to 15 ATA. These experiments suggested that gas elimination was taking approximately 10 times longer than gas uptake. In a second series of similar experiments the initial exposure pressure was varied. These experiments showed an inverse relationship between initial exposure pressure and gas elimination time. This would imply a marked advantage from deep decompression stops. A final observation made during this study was that there was an optimum time at each decompression stop for maximal gas elimination.

In summary the gas uptake process does not appear to be greatly affected, but both pressure reduction tolerance and gas diminution are affected by the magnitude of the exposure pressure.

2. Treatment of decompression sickness occurring during deep dives

Deep saturation diving appears to be accompanied by a higher than normal incidence of decompression sickness (DCS); 20% of the U.S. Navy's DCS now occurs on saturation dives, despite the fact that this type of dive constitutes less than 0.3% of the total number of dives. A survey of DCS following saturation dives showed 86% of cases concerned limb bends at relatively shallow depths. More recent studies have shown that the abrupt pressure changes associated with excursions from saturation dives are associated with central nervous system disorders (predominantly vestibular symptoms) and that the symptoms which occur under pressure do not respond well to recompression, with only 35% total relief being reported. In practice diving supervisors have been reluctant to use large recompression ratios at depth because of the substantial decompression obligation incurred.

To assess the importance of the variables involved in therapy, 14 variables from 84 cases have been subjected to a factor analysis. Seven of these variables proved cogent and have been related to 3 measures of treatment effectiveness; two of these related to treatment adequacy, treatment outcome and time to relief and the third to total treatment time, which really relates to treatment economics and is only of secondary importance. Of the seven variables only 3 (age of patient, depth of onset of symptoms and delay in treating the symptoms) had a statistically significant correlation with treatment adequacy. Most significantly the amount of recompression did not relate to the treatment adequacy and it would thus appear that the most important therapeutic tool is of no benefit when treating deep decompression sickness.

The efficacy of recompression from 1 ATA has already been demonstrated and thus our programme was designed to examine the

efficacy of recompression magnitude, oxygen partial pressure and time for treating DCS under pressure. The procedure involved; a) exposing rats to 30 ATA helium/oxygen for a time sufficient for saturation, b) abruptly decompressing to a level which would have produced a 50% incidence of DCS but instead of waiting until all 50% were affected they were recompressed after 2 min, the amount of recompression, the oxygen partial pressure and the length of treatment time were all varied, c) following treatment the animals were abruptly decompressed to various pressures to allow an  $ED_{50}$  to be calculated. Comparison of pre- and post-treatment  $ED_{50}$ 's allowed an assessment of the relative importance of the three factors. These experiments confirmed that recompression did little to improve the clinical picture when symptoms appeared below 2 or 3 ATA; of the other two variables the greatest benefit was from long stable exposures to high oxygen partial pressures. The relationship between oxygen and time appeared to be a simple additive one and there did not appear to be any synergistic benefit in their simultaneous use.

Excluding recompression, the four remaining therapeutic tools are oxygen, time, fluid administration and drugs. The final experimental study was to determine the optimum oxygen intermittency regime. It was found that a simple time weighted average of the oxygen exposure provided an accurate means of predicting the time to oxygen convulsions. This method has since been applied to values of oxygen intermittency in the literature with good success. Currently a small calculating device for evaluating toxic effects of oxygen therapy is under development with the Naval Ocean Systems Center (NOSC).

With the statistical and experimental evidence that below approximately 60 feet of sea water recompression has lost most of its efficacy we must turn to the remaining tools. Animal experi-

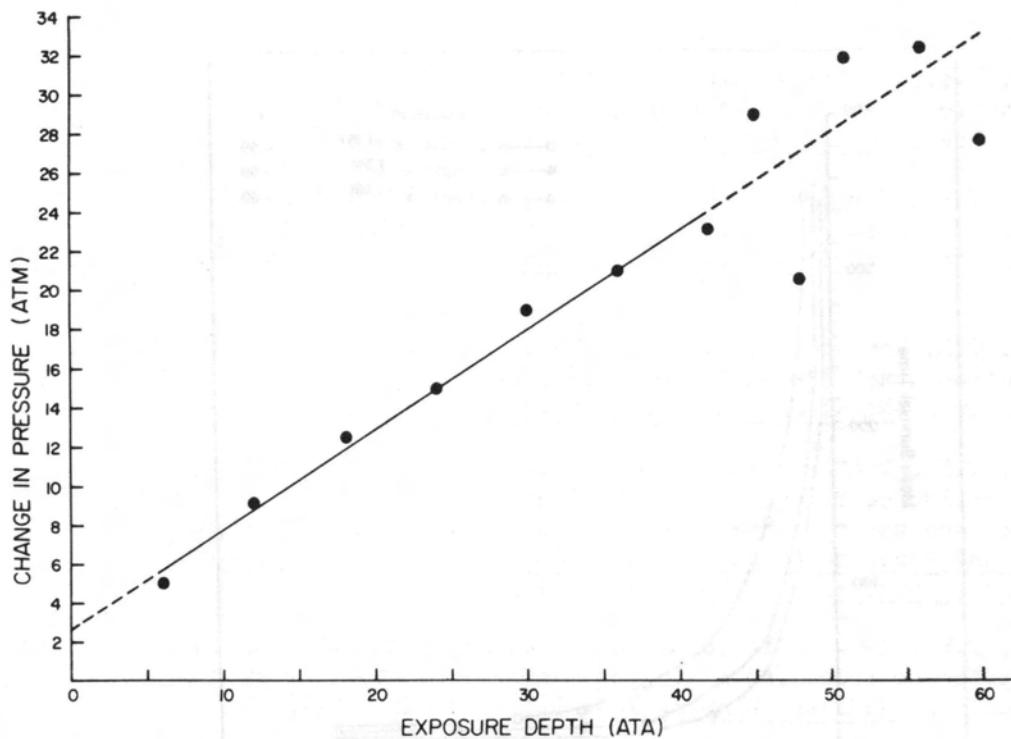
ments have indicated that oxygen partial pressure and time are effective therapeutic tools and it remains for research to determine the usefulness of fluid administration and drugs.

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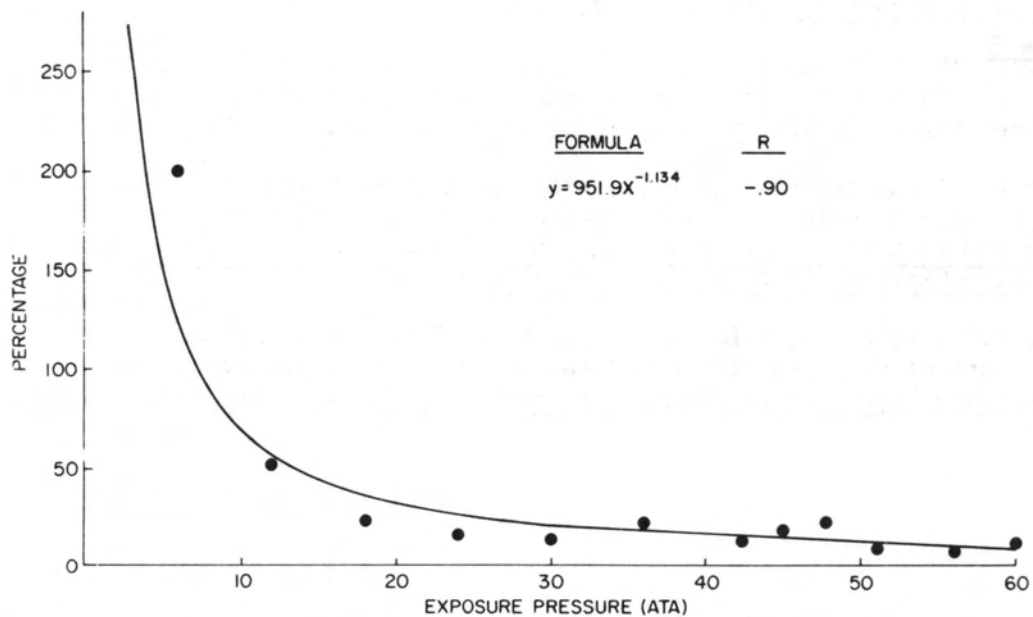
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**Fig. 1:** Reduction in pressure necessary to produce decompression sickness in 50% of the rats following a saturation helium-oxygen exposure.



**Fig. 2:** Change in the incidence of decompression sickness associated with a 1 atm change in pressure at various saturation-exposure pressures. The formula is for the least-squares best fit for the data, where  $y$  is percentage and  $x$  is exposure pressure in ATA

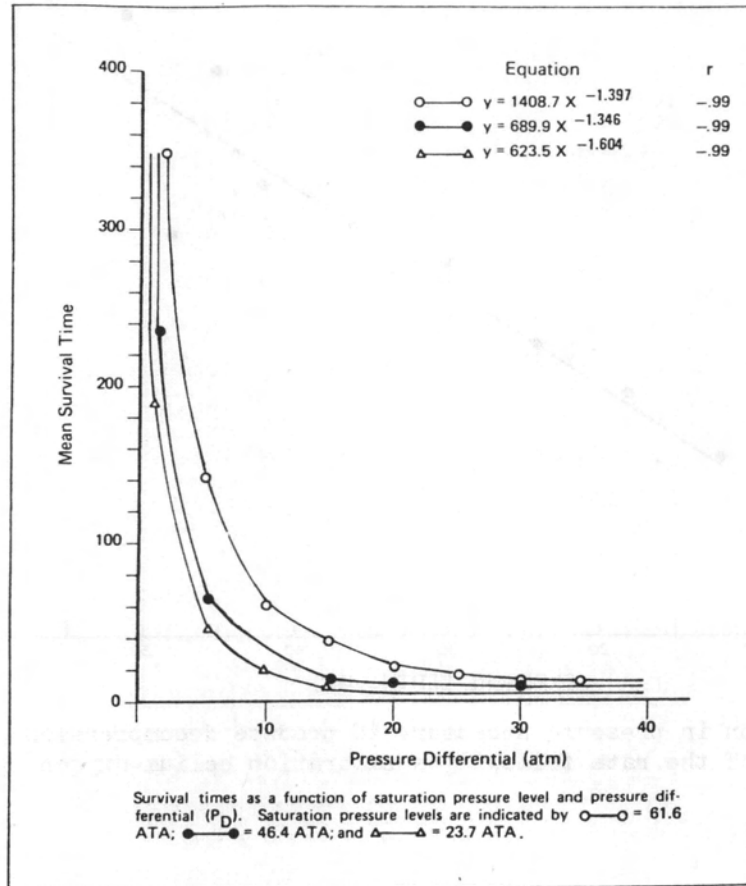


Figure 3

Discussion on Additional Environmental Problems

C.J. Lambertsen, Leader

This section will be mainly concerned with the question of diver selection and the manner in which the various aspects of deep diving already discussed relate to selection. There was, in addition, discussion of monitoring of divers, the problems of thermal balance and temperature perception and the question of decompression from depth and decompression related injuries. Dr C.W. Shilling summarised the problems involved in selection as follows :

"The first step in selecting divers is Task Analysis. This may be summarised by a series of questions. What type of diving is involved: scuba, commercial, bounce diving or saturation diving? What will be required of the diver to complete his task? What type of individual and what abilities are required? The most important attribute of any tests used for selection is that they must have predictive value. These tests must also be cost effective, both in terms of money and in time and annoyance to the subject. Some of the points which should be included in any assessment of an individual are: their age, level of intelligence, their psychological adjustment to confined space and their ability to handle small group interactions. The physical characteristics which must be considered are: their strength in relation to the task required (this may affect the decision to choose between a male and a female diver), their manual dexterity, their endurance and their size in relation to the equipment which is to be used - a 7ft. individual would find life very difficult in a diving bell. What chronic diseases should disqualify a person from diving : epilepsy (even if pharmacologically under control), emphysema, bronchitis or asthma? Similarly, what chronic physical conditions should disqualify a subject: low back pain, deafness (aural communication under water is extremely restricted anyway), blindness (visibility is normally very poor)? Are there any habits which should be counter-indicative: alcoholism, drug dependence (consider anti-histamine used for suppression of allergic reactions such as hay fever), smoking? An assessment of a diver's psychological and physical condition immediately before the dive should be considered essential.

Independent of all these factors, perhaps the most vital preparation, is adequate training, both general and specific to the types of jobs required. Finally, it must be considered whether the environment can be altered to assist the diver or whether machinery can be designed to either assist or replace the diver."

The first question to answer, before assessing potential selection criteria, is "Are any of the HPNS end-points stable?" In addition, the range of variation between individuals must be assessed. The question was raised as to whether any end-points for an individual could be established or, conversely, is HPNS similar to the susceptibility to oxygen toxicity in varying from day to day for any individual? It was suggested that the EEG modification (enhancement of slow theta wave) was stable and that Dr Brauer was a good example. When he was a subject in some experimental dives carried out in France he always demonstrated the first EEG abnormality at 280 msw equiv. (920 fsw). However, the problem with EEG changes as a predictive sign is our lack of understanding of their basis. Frequently EEG changes are seen without apparent behavioural modification in which case, although they no doubt reflect a modification to the central nervous system, they would be considered of no relevance by a neurologist. A further complication was stated in that, even when only considering the theta wave, two types of modification can be recorded - an enhancement of the slow component and a depression of the fast component - which is the most significant? Two final points were made in connection with the possible use of EEG modifications as a basis for selection. First, on one French dive the person who showed the most enhancement of the slow component of theta actually performed his fine manipulative task at depth extremely well. Second, in the Comex series of dives two divers showed EEG modification on one dive but not on subsequent dives.

In primates it was reported that the convulsion threshold is stable over an individual's life time. It was suggested that experiments could be done to specifically test this by selectively breeding those individuals which showed a) the greatest b) the least susceptibility. This sort of experiment has already

been attempted using the response to anaesthesia as the end-point with some success.

A specific test which has been applied both at Duke University and by Comex, is to rapidly compress an individual to 183 msw equiv. (600 fsw) at  $30.5 \text{ msw equiv. min}^{-1}$  ( $100 \text{ fsw min}^{-1}$ ) and to reject those individuals who showed undue distress. However, it was reported that experimental work, using primates, showed that although a good correlation was obtained when comparing a second fast compression to an initial fast test compression, no such correlation was found when the subsequent compression was slow. These experiments had used behavioural observation for determining the end-points and it was reported that by using EEG modification as the end-point, then fast/slow compressions could be compared.

It was suggested that "self-selected" professional divers have proved most resistant to HPNS and that furthermore they exhibit a high "determination factor" which results in their withstanding high degrees of discomfort. For these reasons perhaps for the immediate requirements, selection of individuals for very deep dives should be limited to this population.

The question of limiting respiratory problems was discussed. In this context it was suggested that cigarette (pipe and cigar ?) smokers should be excluded as well as individuals who have any demonstrable pulmonary dysfunction. It was concluded that exercise linked respiratory difficulties require considerably more research. Whilst under "normal" conditions the diver does not have to work maximally, this is not necessarily the case for a diver in trouble. One feature that was felt most important was the design and suitable testing of breathing apparatus. For work at great depths no present equipment was considered satisfactory.

The meeting was reminded that when considering selection the technical ability of the subject was of vital importance. It is possible to train a technician as a diver but the converse is not necessarily possible. It was also stressed that a major problem lay in quantitating these tests; without due care the false rejection rate may be high.

One final point in connection with selection was the willingness of an individual to co-operate at any particular time. In this context the following statement was made :

"I would like to point out the dynamic aspects of selecting men for a particular dive from a group of divers already proven to be capable of performing similar tasks. A man may be fit in a general sense, yet unfit to dive on a particular morning for some psychological reason or reasons. An intended 540 msw equiv. (1772 fsw) simulated dive was abandoned at 180 msw equiv. (591 fsw), because one experimental subject was unable to face further exposure. There is no question about his suitability in general, he has been to 420 msw equiv. (1378 fsw) before in the same facility. That day, however, he was unable to stand up to the well known stresses of the exposure.

This problem represents a second dimension or order of magnitude in difficulty over and beyond selecting a population fit to dive. I have no answer."

The second major area of discussion was diver monitoring. The question was raised as to whether there are clear objectives for monitoring? It was pointed out that even after careful selection things may go wrong. In this context there are two clear roles for diver monitoring, a) to enable difficulties, whether environmental or physiological, to be predicted and hence to allow corrective action to be taken and b) to function as a "black box" to allow subsequent analysis of any incident in order to prevent its reoccurrence. It was felt most important that any monitoring should not present the diving supervisor with additional problems of interpretation although, at the same time, the training standards for supervisors should be improved to allow for increasing responsibility. The role of automated systems in streamlining the presenta-



tion of data and in performing basic judgement functions was stressed.

The most important monitoring system was felt to be voice communication. Considerable improvement in this technology is an urgent priority. Television monitoring was recommended whenever possible. The basic physiological parameters which should be monitored were felt to be heart rate, body temperature and ventilatory pattern. The topic which was extensively discussed was temperature monitoring. There appeared to be technological problems of measurement and control, but in addition physiological problems of a progressive narrowing of the comfort zone, a suitable method of assessing thermal balance and problems of temperature perception at depth.

The first point raised was that the "radio pill" as a method of monitoring core temperature appears unreliable; unexplained and sudden battery discharges which result in false readings have been reported. Second, the question was raised as to whether core temperature is a reliable indicator of the state of thermal balance? It was suggested that urinary temperature might be a better indicator.

It was pointed out that in high pressure environments and particularly when diving suits are worn, the routes of heat loss are different from normal, i.e. the skin is not the primary route of heat loss. Core temperatures may not therefore relate well to brain temperatures under such conditions.

The increase in metabolism due to breathing cold gases is small whereas it is large in response to reduced skin temperatures. Evidence was reported that primates could be trained to regulate

their environmental temperature in response to changes in skin temperature, but not in response to changes in hypothalamic temperature. Furthermore, in these animals evidence is being found for a disturbance of thermal perception at depths greater than 305 msw equiv. (1000 fsw). It was suggested that further investigation of the fundamental changes in thermoregulation at pressure be considered a high priority. In man, the problem is further complicated by the "determination factor" which affects the degree of discomfort tolerated. Furthermore, work has suggested that a subjective feeling of warmth is not a sufficient criterion of thermal balance (Keatinge et al, 1980, Br. J. Med. 280, 291).

Some concern was expressed at the apparent relationship between the incidence of dysbaric osteonecrosis and depth. However, as yet no definite relationship has been established which allows an assessment of the potential hazard. Furthermore, the relation of this problem to "inadequate" decompression still appears reasonable and it is to be hoped that improvements in the techniques of decompression, based on a more sound understanding of the problems involved, will be forthcoming. In relation to decompression it was felt that measurements of gas transport at pressure are vital. It was emphasised that although decompression from depth can be handled empirically, further experiments to elucidate to basic mechanism are needed.

Discussion Session V: Clarification of Future Strategy

E.B. Smith - Leader

This session was devoted to the assimilation and assessment of both the theoretical and practical proposals arising from the Workshop. Emphasis was placed on the integration of research discoveries into practical diving situations. In the long discussion a number of clear themes emerged.

1. Deep diving depths

There is a continuing commercial and Naval requirement for very deep diving. A number of alternative mechanical systems are being developed and until these are completely reliable, divers will also be needed in a back-up role. Commercially it is frequently just as attractive to use divers as to use mechanical alternatives and so for the foreseeable future, divers are irreplaceable except in special circumstances.

We can now meet this need for deep diving. The successful open sea dive to 460 m (1509 ft) - see section 1.6 - has provided a base line for deep water work. The successful chamber dive to 650 m (2133 ft) - see section 2.1 - has set the base line for human research. The medical problems now need to be pursued in order that man will be a viable operator in diving to depths greater than 600 m.

2. Oxygen-helium diving

The problems with conventional oxygen-helium diving are related, at least in part, to compression rate and duration. Severe problems have been encountered in the 457-549 m (1500-1800 ft) range. In many but not all dives there was evidence of diver deterioration with increasing time at depth. The present evidence suggests that,

without further discoveries, oxygen-helium diving below 1500 ft will not be a reliable technique (See Section 2.3 and 2.4)

### 3. High Pressure Neurological Syndrome (HPNS)

The major problems with present diving are those associated with HPNS. We now recognise that this is a set of signs that are more complex than had previously been thought. There is evidence that HPNS can be seen in the effects of pressure on single neurons but it appears to be more fully characterised in structures with considerable integrative capabilities. Many more in vitro experiments and in vivo animal studies are now required, but it must be recognised that these are unlikely to be able to be extrapolated quantitatively to humans.

### 4. Amelioration of HPNS

The pharmacological techniques for ameliorating HPNS have now proved to be of practical value. Specifically the use of trimix (containing 10% nitrogen as the ameliorating additive) is substantiated in the first dive to 650 m (2133 ft). Both the video tapes and independent observer reports to the workshop supported the hypothesis that the limits for this diving technique have not yet been reached (see Section 2.1 and 2.2). It was concluded that trimix appeared to be beneficial in the region of 50 - 650 m. The early problems with euphoria seem to have been overcome but compression rate remains important.

Although the use of nitrogen is proving to be effective in man, there have not been enough studies to assess its safety, reliability or freedom from toxic hazards. Alternative gases (e.g. nitrous oxide) may help with some of the density problems. The use of hydrogen could be investigated further if density proved to be a limiting factor. Intravenous anaesthetics and various anticonvulsants have been studied in animals. (Section 3.2 and 3.3).

## 5. Additional problems

Temperature control is currently of considerable concern in working dives because of both subjective and objective changes in thermal balance. The solutions involve difficult technology rather than unknown physiological problems. This problem is not restricted to deep dives but it is exacerbated at depth by the narrowing of the comfort zone (see Section 1.5).

Respiration in chamber dives is not a general problem but dyspnea exacerbated by exercise is present (see Section 4.2). This could become a limitation in future deep dives. The phenomenon appears to be unrelated to gas density but is an aspect of HPNS that is not alleviated by nitrogen (see Section 2.5). There does not appear to be any adequate breathing apparatus for open water diving below 1500 ft.

Monitoring of working divers was dealt with in another recent workshop (UMS Workshop Report available) but it was agreed that very deep diving may provide additional complications. In particular, temperature monitoring (see above) and voice communication while breathing trimix were considered. (see Section 4.1 and 4.5).

Decompression from deep depths is proving possible. We do not yet know if any new principles are involved when decompressing from great depths. Research in this area is important because conventional treatment involving recompression or a change of gas breathing mixture may prove difficult. (see Section 4.4). The effects of varying  $P_{O_2}$ , total pressure and exercise were discussed.

## 6. Chronic hazards

Apart from bone necrosis, no permanent effects of exposure to depths have been recognised at the moment (see Section 4.3).

However, the number of men who have been below 300 m is very limited and it is important to detect any chronic hazards as early as possible. One of the most reliable methods of achieving this is the careful monitoring and comprehensive long term follow-up of deep sea divers (See Section 4.5).

#### 7. Basic research

The recognition of the practical possibilities and problems of deep sea diving has increased the urgency of basic research into the underlying mechanisms. The principles and mechanisms involved in almost all the effects discussed in this report are unknown. These include both the equilibrium effects of pressure and the kinetic effects associated with varying compression rates. The complete range of physical, in vitro and in vivo experiments will contribute to the elucidation of the problem as defined by the human research. (See Section 2.5 and 3.5).

#### 8. Diver selection

As men push to new limits, selection could become increasingly important. This has been the experience with other extreme environments. We may need to select for more than one attribute. These will include HPNS resistance, respiratory fitness (specifically lack of dyspnea), general diving skills and tolerances (e.g. to psychological stresses). The selection processes apply not only to acceptance into a deep diving programme but also for any particular dive. We do not yet know how to devise such multi-layered selection procedures but the evidence is that they should be possible. (See Section 4.5).



APPENDIX: Dives below 300 m

Designation	Max. Depth	Breathing Gas	No. of Divers	Comments	Ref.
USN/Duke 1968	305 m	heliox	5		1
PLC 1 - 1968	335 m for 17 min	heliox (+ 3.1 N <sub>2</sub> )	2	See Section 1.6	
PLC 3 - 1968	300 m for 20 min	heliox (+ 4.5% N <sub>2</sub> )	2	"	
Physalie I - 1968	335 m for 20 min	heliox (+ 4% N <sub>2</sub> )	2	"	
Physalie II - 1968	360 m for 14 min	heliox (+ 4% N <sub>2</sub> )	2	"	
Physalie III - 1968	365 m for 8 min	heliox (+ 5% N <sub>2</sub> )	2	"	2
Physalie IV - 1968	300 m for 10 min	heliox (+ 5.7% N <sub>2</sub> )	2	"	
Airco - IUC 1968	339 m for 5 min	heliox			3
RNPL/Swiss 1969	340 m for 5 hours	heliox	3		4
RNPL 1500 ft 1970	457 m for 10 hours	heliox	2	Problems in decompression from max. depth.	5
Physalie V - 1970	520 m for 1.7 hours	heliox	2	See Section 1.6	6
Sagittaire I - 1971	300 m for 7.6 days	heliox	4	"	
Sagittaire II - 1972	500 m for 4.2 days	heliox	2	"	6

Designation	Max. Depth	Breathing Gas	No. of Divers	Comments	Ref.
Physalie VI - 1972	610 m for 1.3 hours	heliox	2	See Section 1.6	6
CEMA-CERB III 1972	500 m for 1.5 days	heliox	2		7
Predictive Studies III 1972	366 m for 6 days	heliox	4	Gas density experiments to a heliox depth equivalent to 1520 m	8
Sagittaire III - 1973	300 m for 15 days	heliox	4	See Section 1.6	
Duke 1000 ft. 1973	305 m	heliox	4		9
Duke trimix 1973	305 m	trimix (18% N <sub>2</sub> )	4		9
Access II 1973	305 m	trimix (13% N <sub>2</sub> )			10
Sagittaire IV - 1974	610 m for 50 hours	heliox	2	See Section 1.6	
Janus IIIA - 1974	460 m for 6 days	heliox	3	"	
Janus IIIB - 1974	395 m for 6 days	heliox	3	"	
U.S. Navy 1600 ft 1974	488 m for 8 days	heliox			11,12
Duke 1000 ft. 1974	305 m	trimix (10% N <sub>2</sub> )	5	See Section 2.1	
Coraz I - 1975	300 m for 4 days	trimix (9% N <sub>2</sub> )	3	" 1.6	

Designation	Max. Depth	Breathing Gas	No. of Divers	Comments	Ref.
Coraz II - 1975	300 m for 4 days	trimix (4.5% N <sub>2</sub> )	2	See Section 1.6	
Coraz III - 1975	300 m for 33 hours	trimix (4.5% N <sub>2</sub> )	2	"	
Coraz IV - 1975	300 m for 3.3 days	heliox	2	"	
Predictive Studies IV 1976	488 m for 1.6 hours	heliox	4	See Sections 1.5 and 2.1	13
AMTE/PL5 1976	300 m for 7.6 days	heliox	2	See Sections 2.1 and 2.3	14
Duke - AMTE/PL 1976	400 m	trimix (6% N <sub>2</sub> )		See Section 2.1	
Janus IV - 1976	460 m for 7 days	trimix (4.8% N <sub>2</sub> )	8	See Section 1.6	
AMTE/PL 6 1977	300 m for 6.8 days	heliox	2	See Sections 2.1 and 2.3	14
AMTE/PL 7 1977	420 m for 2.04 days	heliox	2	See Sections 2.1 and 2.3	
AMTE/PL 8 1978	420 m for 3.4 days	heliox	2	See Sections 2.1 and 2.3	
AMTE/PL 9b 1979	540 m for 2.7 days	heliox	2	See Sections 2.1 and 2.3	
Atlantis I 1979	460 m for 4 days	trimix (5% N <sub>2</sub> )	3	See Section 2.1	
U.S. Navy 1800 ft 1979	549 m for 5 days	heliox	8	See Section 2.4	
French Navy SSS6	300 m for 10 days	heliox	2		

Designation	Max. Depth	Breathing Gas	No. of Divers	Comments	Ref.
Seadragon IV 1979	300 m for 14 days	heliox	4	Conducted at JAMSTEC, Yokosuka.	
"Selection" 1979	450 m for 2 days	trimix (4.8% N <sub>2</sub> )	8	See Section 1.6	
AMTE/PL 11 1980	300 m	heliox	2	See Section 2.3	
Atlantis II- 1980	650 m for 24 hours	trimix (8.8 - 5% N <sub>2</sub> )	3	See Section 2.1	

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