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# THE HIGH PRESSURE NERVOUS SYNDROME REVISITED

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As my contribution to this discussion, I would like to take you on a brief guided tour around central nervous system effects of pressures of the order of magnitude we encounter in deep diving.

To begin with, then, allow me to tell you that all vertebrates and, indeed, very many invertebrates that make their living at or near the surface of the ocean show evidence of profound changes in central nervous system functioning when transferred over a reasonable period of time to environments in which hydrostatic pressures are somewhere between 50-150 atmospheres absolute (ATA). Among vertebrates specifically, the two symptoms accompanying this change which are most readily observed are tremors and convulsions. Many years ago, we showed that if one assembles something like a zoological garden of representative vertebrates and one determines under given compression conditions the pressures at which each of these two symptoms develop, the series of data points that result when one plots the two types of pressures against each other for each species fall quite close to a single straight line. This very simple fact is of interest because, while we have seen tremors in man, we have not so far encountered anywhere in the world divers sustaining clear-cut high pressure convulsions. Knowing the tremor threshold pressure, however, and having at our disposal the linear relation between tremor and convulsion threshold pressure for many vertebrate species, we can infer with reasonable accuracy the point at which man (who after all is another vertebrate) might be expected to undergo high pressure convulsions under the same compression conditions.

The overall range of these phenomena is defined by the fact that the most sensitive animals show quite well defined high pressure tremors when exposed to about 20 ATA, while the most resistant ones seem to undergo convulsions when they are exposed to roughly 150 ATA. Multiply each of these values by ten and you have a range from 200-1500m over which symptoms of the high pressure neurologic syndrome can be observed, taking surface dwelling vertebrates as a group. Within that range, furthermore, since human tremors develop at pressures somewhere in the neighbourhood of 25-30 ATA, we can predict with some reasonable assurance that we might expect the mean threshold pressure for high pressure convulsions in man will be little higher than 70 ATA with an uncertainty of approximately ±10 atmospheres given, however, a compression rate which is substantially higher than those in current use. If we factor in the compression effect, the mean threshold is likely to fall around 100 ATA but given a standard deviation for such values of the order of ±10 ATA, this means that we must expect that about 5% of all people will have HPNS convulsions by about 75 or 80 ATA even at the slowest compression rates. You will recognize that regardless of how these figures are analysed they indicate that in the range of depths which are currently of interest for deep diving in support of such things as oil exploration, high pressure effects on the central nervous system can be expected to be of very serious significance.

I think it is fair to tell you that as of to date we really know terribly little about the biophysical mechanisms which underlie these phenomena. I think in a sense it is true for these phenomena, as it is for deep sea biology in general, that our problem is not so much a scarcity of possible effects, but quite on the contrary a plethora of such effects. Almost any process going on in living tissues and contributing to excitability is subject to some degree to modification by hydrostatic pressures of the order of magnitude that we are discussing here. Thus the real problem is to try to segregate out from among these the one, or the ones, that are of real importance. I think most physiologists who are in this business share the suspicion that a very major role in these events should be played by characteristics of the excitable cell membrane, and among these fluidity changes and phase changes of the lipoprotein membrane system are viewed with special suspicion.

Now, to give you only one example of the type of frustration from which we are suffering, let me tell you that there is quite good experimental evidence indicating that melting points of such membranes, which in turn presumably are closely linked to the ease of re-orienting the all important ion channels embedded in the membrane, are indeed affected by pressure: the magnitude of the shift to be expected is of the order of 4° for every 100 ATA. On the other hand, among many other data of this type, let me merely quote to you observations on very young mice which have not yet developed the machinery for actively defending their temperature in high pressure environments and whose deep body temperatures, therefore, can be safely assumed to be very close to those of their environments. In these animals, one can experimentally test the inference that change in hydrostatic pressure should elicit changes in the properties of those very membranes which in turn could be potentiated or reversed by manipulating the temperatures under which the compressions are carried out. The regrettable fact is that when the experiment is performed and one measures the mean pressures required to produce convulsions in these baby mice over a temperature range of approximately 8°C there is absolutely no change in convulsion threshold. Clearly, this observation will make it quite difficult to entertain the hypothesis that change in membrane fluidity can indeed constitute the principal point of attack giving rise to development of the high pressure syndrome. Indeed, despite 20 years of efforts in quite a number of excellent laboratories, we are still largely in the dark as to the real mechanisms brought into play to modify brain function in animals exposed to high pressure environments.

By and large, such neurophysiologic changes as are observed would lead us to predict that in high pressures animals ought to calm down and go to sleep, rather than to undergo exaggerated activity and show locomotor changes culminating in these vicious seizures.

In our ramble around HPNS, I would like to take you next briefly to another corner of the forest where interaction of

these phenomena with oxygen supply to the tissues is under review. This subject came up very early when some people, especially those who wished that the whole matter which seemed to limit our ability to penetrate to great depths would go away, suggested that what was being observed was merely a phenomenon secondary to the presumed respiratory difficulties that "must" attend breathing such dense atmospheres, with the actual seizures representing merely a special case of either hypoxic or hypercapnic seizures. That particular debate was probably resolved to a large extent 10-12 years ago when it became quite clear that sensitivity of animals to high pressure convulsions was quite independent of gas density, and quite unaffected by modification of oxygen content of those atmospheres over a range from roughly 0.2 to roughly 1.5 ATA. That conclusion was supported further by blood gas analyses which showed no changes, and by experiments with simulated high density atmospheres, the effects of which were clearly dominated by the narcotic effects of the heavier gases utilized rather than by impairment of respiratory exchange. Indeed, those experiments that involved manipulation of oxygen partial pressures in atmospheres which otherwise included only helium suggested that, in the high pressure environment increase of oxygen partial pressure beyond 1.5 ATA facilitated the onset of convulsions. More recently, we have come back to that particular line of inquiry and have found that if the relation between oxygen partial pressure and convulsion onset is investigated in greater detail two phenomena become evident. In the first place, we find that the convulsion stage of HPNS is not simple, but consists of at least two distinct events, one of which is potentiated by high pressure oxygen, while the other seems to be quite insensitive to it. These data are merely a special case of a more general observation that indeed the two stages of the HPNS convulsive phase which we call Type I and Type II seizures, behave as though they were two quite distinct entities, showing different genetics, different dependence upon compression rates, different response to drugs including narcotically effective gases, and different courses of development in very young animals.

All round, these particular phenomena are one of the examples where the study of underwater physiology has provided substantial and significant input to general medical physiology, in this case documenting for the first time the coexistence of two such quite distinct seizure events. Similar patterns had been suspected in other conditions including epilepsy, but it had never been possible to reproduce them at will and to discriminate them with the clarity with which this is possible in this situation.

Confining our attention now for the moment to the Type I seizure, the one that develops soonest, we found that if we modified oxygen partial pressures through a range from 0.2 to 10 ATA in the presence of various amounts of helium, three quite different patterns of interaction can be observed. There is a zone in which, as the total pressure is increased by helium additions to values up to about 20 ATA, the curves relating oxygen partial pressure to time of onset of convulsions retain essentially the same hyperbolic shade characteristic of uncomplicated hyperoxic convulsions, but displaced to shorter and shorter time intervals as the helium pressure is increased. We feel that this range is best described as the area in which oxygen convulsions are potentiated in the presence of high pressure helium. As the total pressure is further increased the character of this curve changes progressively, and develops a very dramatic plateau between helium pressures of 35 to 50 ATA at all oxygen partial pressure between 1.8 and 3 ATA. This behaviour strongly suggests that in this case we are observing high pressure convulsions potentiated by hyperoxia. Finally, if total pressures are increased further, time to convulsion onset decreases below those required for development of oxygen toxicity and it becomes apparent that we are now looking at high pressure convulsions which are virtually unaffected by oxygen partial pressure.

At the next point, I would like to briefly turn to a problem I touched upon briefly earlier, namely the effect of compression rate upon the onset of the severe stages of HPNS. Quite early in the game, we showed that high pressure convulsions develop at lower total pressures when the compression is rapid than when it is slow. More detailed analysis of this kind of experiment allows us to gain some insight into the scope of this phenomenon. In the case of mice, where we have the most complete data, convulsion threshold pressures at the very slowest compression rates that are practicable, requiring days to reach the threshold and corresponding to months long compressions for man, the maximum seizure threshold that can be attained is in the neighbourhood of 120 ATA. Indeed, there is little difference between compression rates of 1/5 of an atm/hr and of four or five atm/hr for this species. At the other extreme, at compression rates of 1000 atm/hr, picked originally because they bore some relation to the compression rates required in connection with some of the submarine free escape techniques, the same mice have convulsion threshold pressures in the neighbourhood of 75 ATA. The maximum scope of this phenomenon in the case of the mouse, therefore, is of the order of a 60-70% increase in convulsion threshold pressure. Here again, it is worth noting that the figures I have just given you apply to the Type I seizures.

Type II seizures are much less affected by compression rate, and it is possible that the limiting convulsion threshold pressure for very slow compression rates corresponds to the point of intersection between the compression rate dependence curve for Type I and Type II convulsion threshold pressures. Indeed, in the mouse at very slow compressions an increasing proportion of the animals show a seizure type that is intermediate between the clonic Type I and the hyperextension and rigidity of the tonic Type II seizure. Apart from its neurophysiological interest this observation serves to bring into focus a peculiarity of HPNS that seems to me not unimportant, namely, that as one takes measures to alleviate the severity of HPNS at a given depth and uses these measures to penetrate to ever greater depths, the clinical characteristics of the entity change, and more specifically they tend to change in a direction in which the presumed protective measure suppresses the warning symptoms, frequently without suppressing or postponing measurably the most alarming and potentially the most lethal components of this entity.

Here again, I am afraid that we do not have a really satisfactory analysis of the mechanisms which underlie the

compression rate effect. In the case of the mouse, I think one can make a reasonable case for the hypothesis that to an important extent this entity involves activation of central monoamine neurotransmitter pathways which are known to antagonize the development of convulsions in general. Suppression of the action of these neurotransmitters tends to abolish the compression rate effect in the mouse and in a number of other species. While we are far from understanding these events fully, I think one can make an excellent case for the hypothesis that we are looking at a complex event, the time dependence of which reflects its dual character. A largely time-independent effect of hydrostatic pressure on central neurones, is modulated by time-dependent events which appear to be triggered by the high pressure exposure and which tend to postpone or to lessen the severity of the locomotor effects consequent upon modification of central nervous system function by high pressure.

This brings me to the next brief stopover on our excursion, namely to what we are terming "acclimation phenomena". We came to these observations originally via the back door, through studies of interaction between high pressure effects and inert gases that I shall discuss briefly in the last section. Here, I will merely tell you that there is an antagonism between the effects of these two types of agents. When it was shown some years ago that mice can be acclimated to the anaesthetic effect of gases like nitrous oxide by prolonged exposure to sub-anaesthetic levels, we became interested in testing the possibility that such acclimation might entail a change in susceptibility to hydrostatic pressure. Experiments confirmed this suspicion dramatically. Animals that had been exposed for a week or so to half an atmosphere of nitrous oxide, and then transferred to a heliox environment underwent high pressure convulsions at pressures little more than half as high as those of control animals. That being the case, we became interested in the possibility that the reverse phenomenon might also be observable. We were able to show that this is indeed the case. Mice that have been exposed for four to five days to 80 ATA of heliox, when decompressed and recompressed to determine convulsion threshold pressures, undergo their convulsions at pressures which are 30-40 ATA higher than those of normal control animals under the same circumstances. This type of effect is dissipated relatively rapidly, and we wondered whether it might prove to be merely a special instance of activation of the monoamine type of protection we just discussed. However, the pattern of compression rate dependence of convulsion thresholds of such animals does not support this hypothesis. Pressure acclimated mice show exactly the same compression rate effects as non-acclimated ones. Thus, pressure acclimation must represent a more general type either of biochemical or electrophysiological change in the brain.

I might mention that this phenomenon, once again, is not merely a matter of concern to underwater physiologists, but has a rather broader interest. As I have told you, surface dwelling vertebrates in general, including fish, undergo high pressure convulsions at pressures which never exceed 150 ATA. Yet, as we all know, there are many fish that inhabit depths of the ocean corresponding to much greater depths. Working with abyssal fish from Lake Baikal in Siberia, we have been able to show that there is a rough relation between observed convulsion thresholds and capture depths which bespeaks either acclimation or adaptation to the high pressure environment. The fact that pressure tolerance of these abyssal fish does not decrease rapidly with exposure to one or a few atmospheres suggest that, in part at least, these fish must have invoked an adaptational mechanism different from the acclimation one that we have described so far. A theoretical basis for such adaptation exists. We have been able to show that in mice variations in pressure tolerance are to a very large extent under genetic control. Indeed the genetic mechanisms are much simpler and more direct than only a few years ago people would have thought possible for so-called quantitative genetic effects. Thus, it seems likely that the genetic machinery can exist also in fish upon which evolutionary mechanisms could act to increase the pressure tolerance so as to yield pressure tolerant deep sea species. As regards mechanisms that might account for this type of adaptation, the most appealing hypothesis is that these might involve changes in brain composition, and in particular perhaps of the ganglioside component which is so strongly concentrated in the synaptic areas of these tissues and which has been shown to be involved in low temperature acclimation of fishes.

I would like, finally, to turn briefly to the problem of interaction of high pressure effects with those of pharmacologically active inert gases. We have recently had the opportunity to undertake a fairly detailed review focussed on an attempt to separate the effects of pressure as such from the pharmacologic effects of helium and hydrogen in particular, and to a lesser extent of nitrogen and nitrous oxide, though these are much more potent narcotics and relatively much less affected by the effects of "pressure as such". That review showed that for the four effects for which sufficiently detailed data are available for such an analysis in excitable tissue or excitable tissue models there was a common pattern. In each case, hydrostatic pressure effects were antagonized to some degree by the so-called "inert gas", and in each case also the potency with which this effect was exerted was least for helium and increased in the order neon/hydrogen/nitrogen/nitrous oxide. At the same time, it became obvious that the balance of these effects was by no means uniform. Thus the "neutral" member of the series, ie. the gas in which a particular hydrostatic pressure effect associated with the total pressure of the gas was just counterbalanced by the pharmacologic, antagonistic, effect of that same gas, varied within the series almost all the way up and down from hydrogen or (rather a gas intermediate between neon and hydrogen) for anaesthesia, or reversal of anaesthesia, to a gas with properties intermediate between nitrogen and nitrous oxide for the phenomena of phase reversal in lipid bilayer models. These phenomena once again are of interest not only from the point of view of the biophysics of high pressure effects, but also from the point of view of diving physiology. They clearly establish the fact that the once hoped for "neutral gas mix" which would "abolish HPNS" simply does not exist, for the reasons that HPNS itself is a complex, not a simple, entity and that the different pressure effects which are responsible for this compound character show widely different sensitivities to the antagonistic effects exerted by the various inert gases.

That same inquiry turned up yet another previously unexpected phenomenon, namely the existence of numerous other effects of hydrostatic pressures which fall altogether outside the pattern of antagonism discussed so far. Here hydrostatic pressure effects either were not antagonized but even potentiated in the presence of pharmacologically active inert gas components. Here again the order of potentiation in producing effects often bore no recognizable relation to the order of potencies characteristic of the excitable tissue phenomena we have discussed so far. Phenomena in this category include such things as cell death, development of cell pathology, and changes in cell replication. I think it is probably not terribly surprising that a group of effects of this type should exist which may well reflect some of the many changes in cell functioning that can be brought about by high hydrostatic pressures without involving excitable cell membranes, or for that matter cell membranes at all as a primary target.

From a practical point of view, the existence of this group of pressure effects suggests the possibility that when we use addition of narcotically active gases to diving mixtures to minimize some of the manifestations of HPNS, in addition to the complexities of modification of the clinical picture by uneven action of these agents, we may be producing additional problems. By creating such conditions we may succeed in exposing our subjects to quite high hydrostatic pressures by suppressing the acute manifestations of HPNS while significant other pressure effects may be exerted upon our subjects which may not be relieved to the same extent, or which may even be exaggerated, by these modifications of our diving atmospheres. This, then, could confront us with the possibility of pressure-induced injury that might not become manifest until sometime after the dive is completed. Since we are dealing with human beings at risk, I think it is appropriate to recognize this possibility, and in future studies directed toward medical problems of extremely deep diving, we must include work designed to probe for, and if possible to dissipate, any such residual injury problems at the level of animal experiments rather than risking possibly painful surprises from the ultimate effects of what must be termed human experiments.

I hasten to add to this that at the present time such dangers constitute no more than a purely theoretical possibility. I would be inclined to question the validity of suggestions that some of the behaviour changes that have been reported in subjects undergoing very deep dives can be interpreted as valid evidence for residual changes of any kind resulting from such dives, although surely they do not allow us to discount that possibility. At the level of animal experiments, we have conducted experiments which involve repeated exposures of animals and which, in the obliging way nature has with such things, yielded equivocal data that would be equally compatible with an affirmative and a negative conclusion in this matter. We have currently underway what we hope will be more sensitive experiments utilizing behavioural criteria and quantifiable memory performance, but the results of those experiments will not be in for another year, and even then I would suspect that they can hardly furnish more than suggestive evidence tending to sway us one way or another.

I have tried to give you some feeling for the lines of investigation of high pressure effects on the central nervous system which have engaged our attention over the last several years. I hope I have conveyed to you three ideas.

The fact that these phenomena are real, and that coping with them is one of the prerequisites for further development of deep diving.

Some sense of the types of real and probable hazards these phenomena impose, and some concept of kinds of working hypotheses we currently entertain as to the biophysical mechanisms underlying them.

Finally, a sense of the fact that in addition to their immediate bearing on problems of deep diving these phenomena are characteristic of many problems in underwater physiology in that they bear upon and provide opportunities for studies of a wide range of problems in basic physiology and in particular in basic adaptive biology.

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## COLD ADAPTATION IN HUMANS
## A LESSON FROM KOREAN WOMEN DIVERS

Suk Ki Hong

I would like to express my thanks to the RAN for inviting me and giving me this opportunity to present some of the experimental results I have obtained over the past 20 years from studies on Korean women divers.

Professor Brauer has described very interesting effects of pressure which is an important environmental variable to diving individuals. There is another very important aspect of diving, body heat exchange in water. To dive, you have to go into water, stay there and pressurize.

I started my research on the physiology of Korean women divers exactly 24 years ago. At the beginning we were concerned with the respiratory physiology of breathhold diving, particularly the effects of pressure. However, it soon became apparent to us that the real problem with Korean women divers was not respiratory physiology but thermal physiology. This is because the water temperature is about 22°C in the middle of summer, which is relatively warm but still cool. In the middle of winter, the water temperature decreases to 10°C.

In that water temperature range these women are exposed to a severe cold stress. To overcome that they should dress