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Hydrostatic Pressure Effects on the Central Nervous System: Perspectives and Outlook [and Discussion]

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Hydrostatic pressure effects on the central nervous system: perspectives and outlook

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The high pressure neurological syndrome (h.p.n.s.) represents a complex of behavioural changes observed in all vertebrates when exposed to progressively increasing pressures. The general characteristics of the syndrome will be described and discussed in the light of alternative hypotheses about its aetiology and biophysical characteristics. Recent investigations in this area have dealt with the problem of the discretion of the several stages of the h.p.n.s. in their dependence on compression parameters; with the problem of individual variability in sensitivity to h.p.n.s. development, the genetic basis thereof, and its implications from the point of view of personnel selection; and with exploration of the characteristics and nature of the antagonism between high pressure and general anaesthetics in the production of h.p.n.s. symptoms. A final part of the discussion will deal with the current status of investigations into the problem of hazard assessment, and with the several possible approaches to controlling the h.p.n.s. associated hazards encountered in deep diving operations.

Pressure as an environmental parameter on a par with temperature

The phenomena that are the main subject of this symposium are the result of the effect of changes in hydrostatic pressure upon excitable tissues. Most biologists, used to working with living systems collected on land or in shallow waters, have tended, and indeed continue to tend, to disregard this factor in the description of the environments in which they do their experiments. Yet, in the quantitative relations that govern equilibria or rates of biological processes under terrestrial conditions, temperature and pressure are the two paramount parameters that appear in similar fashion in analogous forms of virtually all thermodynamic and kinetic equations (see, for example, Johnson *et al.* 1954). In the biosphere of the Earth, pressures range from a small fraction of 1 atm (absolute) to more than 1000 atm (absolute). Of this range, the overwhelmingly greatest part is the pressure change from the surface of the world ocean down into the abyssal and trench waters. It is in this part of the pressure spectrum that the magnitude of hydrostatic pressure effects becomes important in affecting biological processes. Among these, the effects of hydrostatic pressure on excitable tissues are most readily elicited and most prominently observed.

Phylogenetic patterns and the substrate for pressure effects like h.p.n.s.

Figure 1 shows a phylogenetic tree in which those groups that show one particular manifestation of such pressure effects, namely changes in locomotor behaviour that are most readily described as 'convulsions' when they are subjected to a pressure change of the order

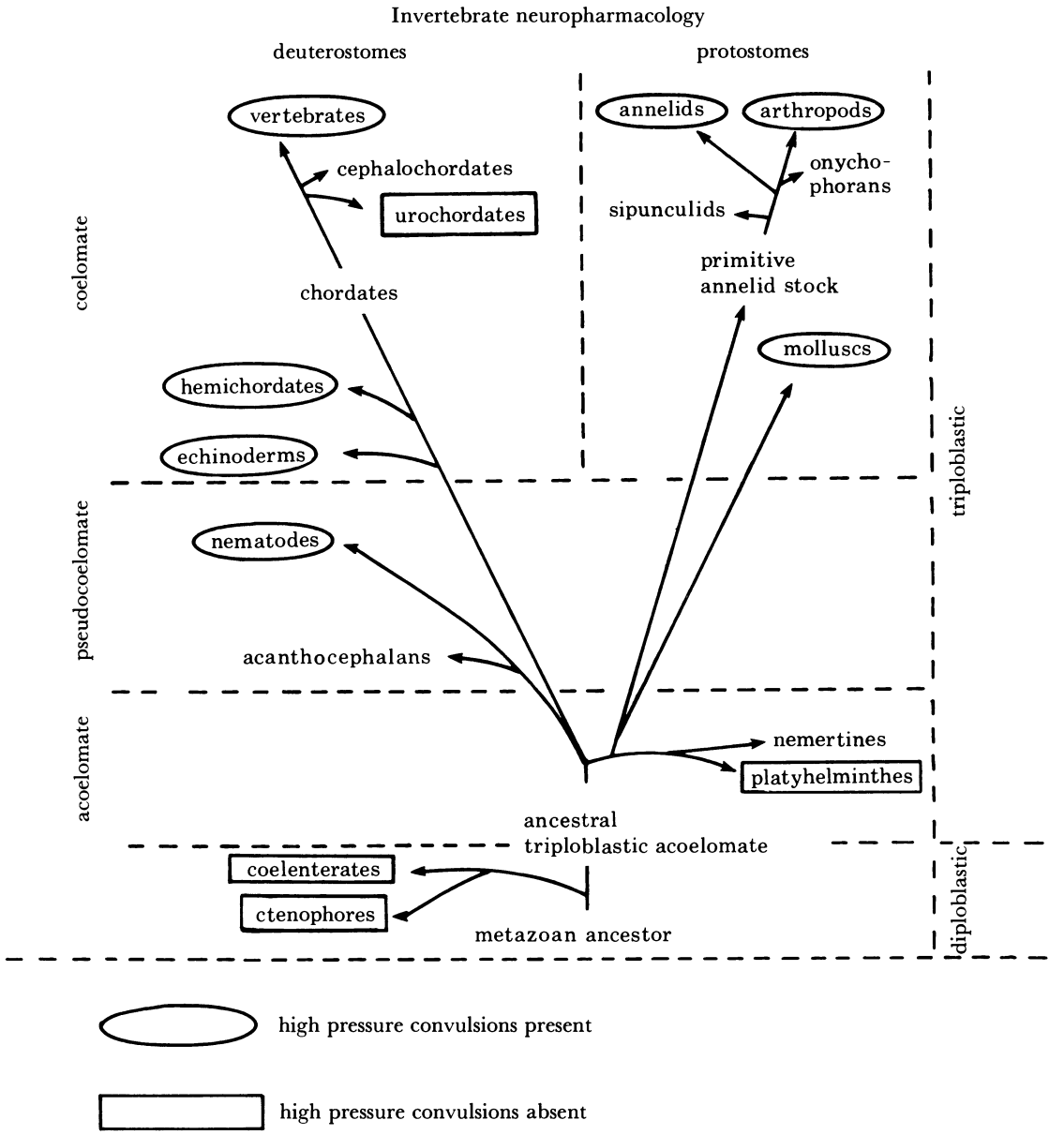

FIGURE 1. Distribution of susceptibility to high pressure convulsions among different phyla (from Brauer *et al.* 1981).

of 100 atm (absolute) (Brauer *et al.* 1980), are marked. To all intents and purposes, such pressure effects have been observed in all taxa with central nervous organization at least as complex as that of the flatworms; as far as we know, this effect is absent in still simpler forms such as coelenterates. It is a reasonable, but not fully proven, inference that this pattern implies that the pressure effects of interest here require not merely the properties of simple neurons, but rather some factor inherent in nervous structures able to perform to a substantial degree integrative functions. Taxa devoid of this particular effect, such as coelenterates, typically show no recognizable effects of hydrostatic pressure upon their behaviour or the survival until they become paralysed at pressures several times higher than those necessary to elicit seizures in the

higher taxa. We may take this as an illustration of the remark made above that on the whole it would appear that the central nervous system is substantially more pressure sensitive than any other tissue.

Pressure tolerance: acclimation and adaptation phenomena

Most of the pressure sensitive invertebrate animal species living at or near the surface of the world ocean undergo substantial changes in behaviour at pressures between 30 and 150 atm (absolute), corresponding to depths in water between 300 and 1500 m. Similarly, for vertebrate species ranging from eels to baboons, convulsion threshold pressures under a particular set of compression conditions range from 60 to 80 atm (absolute) (Brauer *et al.* 1974).

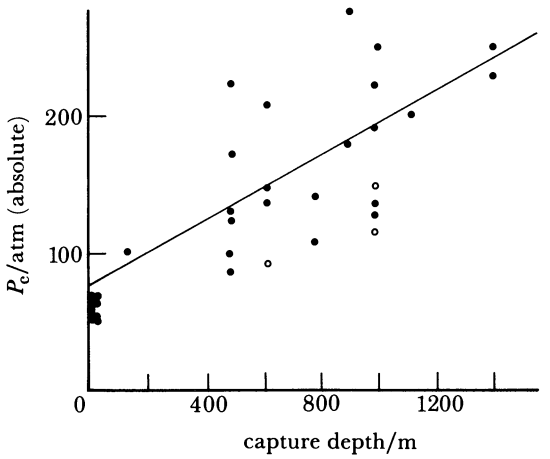

Figure 2. Pressure tolerance of Baikalian cottoid fishes. Correlation diagram showing convulsion threshold pressure P_c as a function of capture depth. The line is a least-square regression of P_c on capture depth. The cluster of points on and near the ordinate represents shallow water cottids. The other solid points represent abyssocottids. Open circles indicate *B. nikolskii* (from Brauer *et al.* 1983*b*).

With this information in mind, one might properly consider how it is possible that animals should be able to populate the deepest waters of the ocean. Clearly, to do so must entail a considerable degree of acclimation or adaptation to high pressure. As an illustration of what is involved, consider some data we recently obtained during an expedition to the world's deepest lake, Lake Baikal, in central Siberia (Brauer *et al.* 1983*b*). Because of its geologic history, this lake has been a major evolutionary laboratory, comparable in many respects to an inverted version of the Galapagos Islands. Among other taxa, a group of swimbladderless fish has been present in this lake for a very long time and developed an extraordinary wealth of closely related species, most of which are benthic and can be conveniently divided into a family preferring shallow water, Cottidae, and a family preferring deep water, Abyssocottidae (Sidelyova 1982). For a number of these cottoid fish species, we found a well defined relation between the depth of water they inhabit and the hydrostatic pressure at which they undergo high pressure convulsions (figure 2). As one progresses from shallow to increasingly deeper water animals, on average the convulsion threshold pressures increase by an amount that is only a little larger than the corresponding increase in habitat pressure (1.3 atm (absolute)/10 m). To a reasonable degree of approximation, one can describe these data by stating that all of these fish undergo

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high pressure convulsions when hydrostatic pressures exceed habitat pressures by just over 100 atm. While in principle this could reflect either acclimation or adaptation, the Baikalian fauna has provided what we term 'cross-over species', i.e. a few members of the shallow water cottids that have come to adopt a deep water mode of existence, and conversely one or two members of the abyssocottids that live in shallow waters. These are relatively rare species, and up to now we have only limited information on the first of these groups, (open circles in figure 2) represented by the deep water cottid *Batrachocottus nikolskii*. Unlike the remaining cottoids, convulsion threshold pressures for this species were a mere 40–45 atm greater than their habitat pressure, which strongly suggests that at least in this case the animals may have taken the genetic make-up of their shallow water forebearers into the depths and increased their limited inherited pressure tolerance by acclimation; the contrast between this and the much higher pressure tolerance of the abyssocottids, then, would be a reflection of the importance of genetic, and hence presumably adaptational, factors in providing for the overall pressure tolerance that enables animals to survive in these deep waters. If these indications are strengthened by similarly aberrant but opposite characteristics of shallow water abyssocottids, then this unique biological system will, for the first time, have furnished definitive evidence that genetically conditioned adaptation to high pressure does exist, and that, consequently, hydrostatic pressure can constitute a significant selection factor affecting the evolution of deep water animals.

While these considerations apply primarily to aquatic animals, which under natural circumstances may be exposed to high pressures, the basic mechanisms are present as well in terrestrial animals, and in particular in mammals. Thus, by using susceptibility to one of the components of the h.p.n.s. as the index of pressure tolerance, we have shown that among mice there is a considerable degree of genetic control over this factor; indeed, it has been possible to unravel the genetic mechanism involved and to show that these are surprisingly simple in that convulsion resistance appears to be determined largely by one major and two minor loci, the position of which in the mouse genome (McCall & Frierson 1981) is well defined.

Acclimation of individual mice to high pressure environments has also been demonstrated (figure 3) (Hinson & Brauer; unpublished work). Acclimation of these mice to 80 atm (absolute) resulted in an increase in convulsion threshold pressure by 35 atm, a ratio of 0.44 atm/atm (absolute), which is almost the same as the ratio 0.40 atm/atm (absolute) for the 35 atm increase in mean convulsion threshold pressure shown by *B. nikolskii* from 870 m mean habitat depth relative to the rest of the cottids from 0–75 m depth.

Pressure acclimation of this type requires about two weeks to go to completion. Such a timescale points to substantial changes in tissue composition, for example, changes in the lipid make-up of the excitable membranes of neurons, and probably precludes the hypothesis that the acclimation reflects no more than a mere accommodation of the ionic skeleton. On the other hand, loss of the extra pressure tolerance in acclimated mice on return to 1 atm (absolute) occurs quite rapidly, which suggests that whatever changes in tissue composition underlie the acclimation, they cannot be the only factor responsible for the observed changes in pressure tolerance.

The several sets of data described so far allow us to define more sharply the precipitating factor giving rise to neurologic effects of high pressure exposures. The key parameter would appear to be not pressure as an absolute thermodynamic quantity, but rather the difference between the pressure to which the animals are exposed during the test and the pressure to which they were previously acclimated or adapted.

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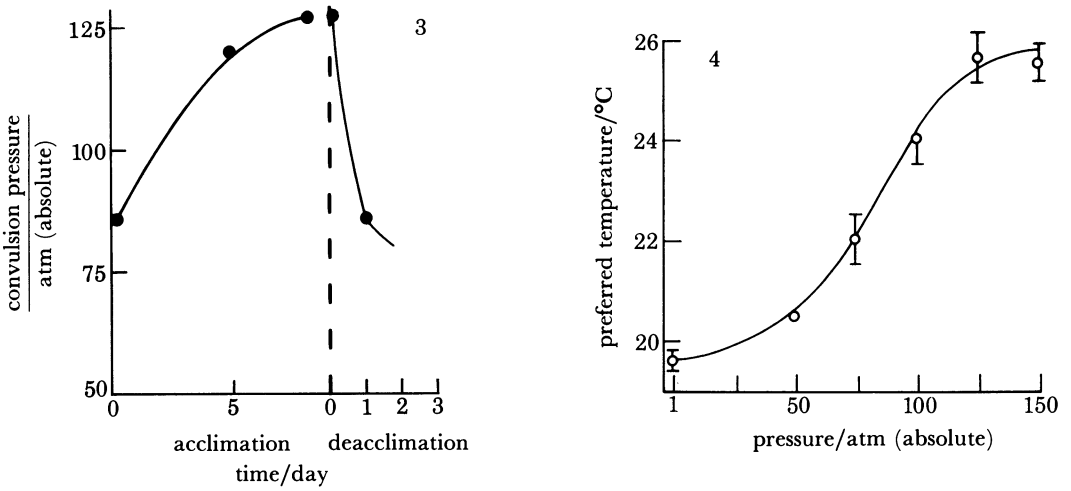

FIGURE 3. Change in convulsion threshold pressure of CD-1 mice (P_c) as a result of exposure for up to two weeks to 80 atm (absolute) in He–O_2 (to left of broken line) and of subsequent duration of stay in air at 1 atm (absolute) (to right of broken line) (Hinson & Brauer; unpublished work).

FIGURE 4. Variation of mean modal sojourn temperature of the euryhaline gammarid *Parhyale hawaiiensis* in a linear temperature gradient as a function of hydrostatic pressure (from Kinney *et al.* 1981).

PRESSURE–TEMPERATURE RELATIONS

In relatively simple reaction systems, there is a measure of equivalence between temperature and pressure effects such that appropriate temperature displacements can reverse the effects of hydrostatic pressure changes. Thus, for instance, changes in biomembrane fluidity can be brought about by manipulating either of these parameters, and the available data suggest that, for this example, a temperature increase by 2.7 °C is capable of reversing effects of a pressure increase by 100 atm (deSmedt *et al.* 1979). In a more complex system, a somewhat similar effect can be observed. If one examines the preferred temperature selected by certain crustaceans in a pressure gradient, pressure increases are found to elicit corresponding increases in the preferred temperature (figure 4) (Kinney *et al.* 1981). Although this relation is not as simple and linear as that for membrane fluidity, on the average it yields a pressure–temperature ratio not unlike that for the membrane model; for a pressure increase by 100 atm, the preferred temperature increased by approximately 4 °C.

Against this background, it seems highly significant to note that a similar correspondence between temperature and pressure has not been demonstrated for high pressure convulsions. Two examples may illustrate this point. First, in mice, 5 °C temperature displacement does not result in a recognizable change in convulsion threshold pressure (Brauer *et al.* 1977). If temperatures are manipulated over a still wider range, convulsion threshold pressures increase slightly at very low temperatures and decrease slightly at very high temperatures, the opposite of what would have been predicted from the temperature preference and membrane fluidity data. Second, in various ectotherm vertebrates we have explored temperature effects on convulsion threshold pressures and on the whole found these to be negligible in magnitude and inconsistent in sign (Beaver & Brauer 1981). In this case, it was possible to explore a 10 °C temperature range. Results for swimbladderless fish (figure 5) illustrate not only the lack of effect of manipulation of *test* temperature, but also the presence of a very significant effect due

to manipulation of the *acclimation* temperature. Thus, there would appear to be some degree of interaction between temperature acclimation and pressure tolerance. The patterns of that interaction, however, vary from species to species, and at this point are not understood.

Taken together, then, these several data indicate that, unlike many other pressure effects, effects giving rise to the h.p.n.s. – or at the very least to the convulsion stage thereof – have a net temperature coefficient near zero. This is certainly one of the constraints that will need to be taken into account in the future by those who would propose molecular models for events leading to the h.p.n.s.

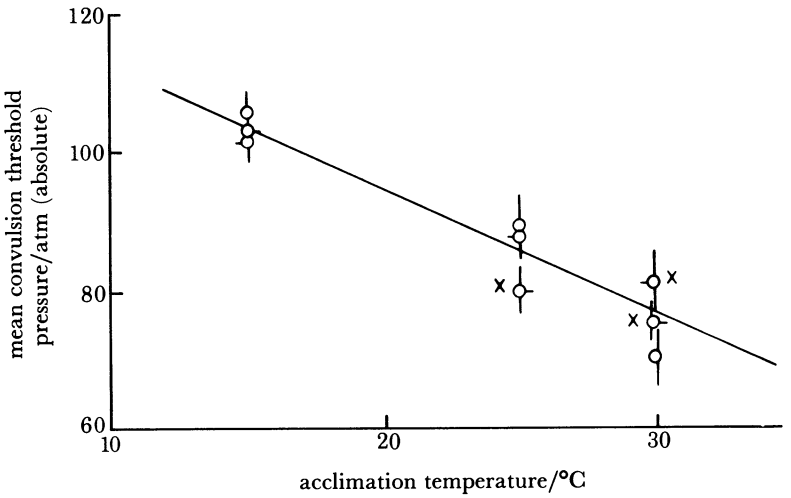

FIGURE 5. Mean convulsion threshold pressures of the flatfish *Symphurus plagiusa* as a function of acclin temperature. Test temperatures are varied with respect to acclimation temperature: ○, test temperatures, T_t = acclimation temperature T_a; -○ T_t was 5°C below T_a; ○- T_t was 5°C above acclimation temperature (statistically significant deviations from results for $T_t - T_a$ are indicated by × ($P < 0.005$)). $\dot{P}$ = 1000 atm/h; P_c = 132–1.84 T_a; $r = -0.72$.

COMPRESSION RATE EFFECTS AND OPTIMAL COMPRESSION PROFILES

I should now like to return to the question as to the nature of the stimulus giving rise to the high pressure effects under discussion. In many, but not all, vertebrates the critical pressure at which a given symptom is elicited during compression varies with the rate at which the pressure is increased, in such fashion that the critical threshold pressure decreases with increasing compression rate (Brauer *et al.* 1975). Of the several possible explanations for this behaviour, the one I judge most likely is that it reflects the interaction of two sets of effects: rate independent effects attributable to the hydrostatic pressure change as such, and time dependent reversal of, or compensation for, these pressure-induced effects. Rate dependence of the overall effect produced would be accounted for by assuming that the compensatory reactions are relatively slow, and that they are triggered by the primary pressure-induced changes. Two sets of observations underlie this position. In the first place, the severity of h.p.n.s. symptoms at any given pressure typically tends to be greatest when the challenging pressure is first attained and to decrease with increasing time spent at that constant pressure. In the second place, it has proved possible to separate the effects due to compression rate, as such, from those due to total time spent at pressure, by manipulating the compression profile. For

this purpose, we have used compression profiles involving an initial compression at 1000 atm/h to some intermediate pressure, followed by a stay at the pressure lasting from a few minutes to 24 h, and finally a second compression step, again at 1000 atm/h, to determine the resultant convulsion threshold pressure (Brauer *et al.* 1977). Such interrupted compression profiles yield convulsion threshold pressures close to those for compression experiments in which the same critical pressure was attained after same total time, but at a single continuous compression rate, which of necessity is very much smaller than the 1000 atm/h used in the step procedure. So, total duration of compression, rather than the rate at which the critical pressure is actually approached just before the seizure, appears to be the factor that primarily affects convulsion threshold pressure.

More detailed analysis of such experiments showed that the hypothetical recovery process is nonlinear, and that its initial rate is directly proportional to the pressure applied to the animal (Brauer *et al.* 1977). This led us to suggest that the optimal compression profile to reach the greatest depth in a minimum of time with freedom from serious h.p.n.s. symptoms should be one that proceeded as rapidly as possible to the greatest depth attainable without severe h.p.n.s. symptoms, and then followed a compression profile adapted to the recovery rate, so that depth was increased in proportion so the recovery reaction could progress. This yields a pseudo-exponential profile very similar to those that, as will be seen in subsequent papers, since the late 1970s have come to be widely adopted by those seeking to attain great depths in human dives.

The animal experiments further suggest that manipulation of compression profiles to control the h.p.n.s. has its limits. There appears to be a rather definite limiting value, at least of the convulsion threshold pressure, beyond which further progress becomes very slow, and the distinction between 'recovery' (or accommodation) and acclimation becomes rather hazy.

The rates at which recovery occurs for different h.p.n.s. symptoms may vary substantially; thus, compression rate dependence varies widely for different components of the h.p.n.s., as illustrated by changes in the threshold pressures of two different components of the convulsion stage with changing compression rate (Brauer *et al.* 1979). With regard to the nature of the hypothesized recovery processes, little is known at present. In at least one species, it has been shown that they can be blocked effectively by agents that interfere with storage or release of two or more of the three principal monoamine neurotransmitters (Brauer *et al.* 1976).

Antagonism of pressure and inert gas effects on the h.p.n.s.

Some of the earliest observations that called attention to the effects of hydrostatic pressures on the vertebrate central nervous system arose out of pharmacological studies, which showed that animals could be aroused from anaesthesia by high hydrostatic pressures (Johnson & Flagler 1952). A number of other high pressure effects have since been shown to be subject to apparent reversal in the presence of adequate concentrations of general anaesthetic agents (Brauer & Sheehan 1974; Miller 1974); this motivated a considerable volume of research concerning the nature of high pressure effects and their interaction with general anaesthetics. The general picture resulting from this work is now fairly clear: there exists a series of quantifiable pressure effects that are either antagonistic to or can be antagonized by metabolically inert general anaesthetics. The most completely studied examples of these are shown in table 1 (Brauer *et al.* 1983 *a*). The intrinsic potencies with which various agents of this

type antagonize the several pressure effects show the same rank order and on the whole similar numerical relations for each of the several responses of this type. It has been customary to analyse and interpret these data on the assumption that the observed antagonism of pressure and inert gas must be exerted at a common site in each cause, and that therefore, by manipulating the two types of agents, one should be able to provide some degree of description of the presumptive chemical nature of the site thus affected (see, for example, Miller 1974).

TABLE 1. SUMMARY OF RELATIVE INTRINSIC POTENCIES $N_{2,r,i}$ FOR INERT GAS–HIGH PRESSURE INTERACTIONS CHARACTERIZING VARIOUS GROUP A RESPONSES

	anaesthesia and high pressure reversal (a) $N_{2,r,i}$	high pressure convulsions (c) $N_{2,r,i}$	high pressure bradycardia (b) $N_{2,r,i}$	fluidity of liposomes (f) $N_{2,r,i}$	phase transformation of liposomes (p) $N_{2,r,i}$	neutral gas†
high pressure	−0.2	−0.6	−0.7	−0.70	−1.6	
He	0.07	0.00	0.17	0.12	0.2	
Ne	0.18	—	0.33	—	—	
						←a
H_2	0.39	0.34	—	0.25	—	
						←c, f
						←b
N_2	1.00	1.00	1.00	1.00	1.0	
						←p
N_2O	22.6	42	22	26	38	

† The arrows mark the approximate position of the neutral gas for each response.

The most popular versions of this hypothesis infer that the site involved needs to be a lipophilic component of the cell membrane and that the effect of pressure and of anaesthetic agent is to modify in opposite directions either the fluidity of the lipophilic layers of some key biomembranes, or the interaction of these membrane components with the protein constituents responsible for ion channeling properties.

While this form of theorizing seems to provide quite adequately for the interaction between pressure and this class of pharmacological agents, with respect to certain simple model systems and with respect to anaesthesia, I am far less certain that it is adequate to account for the apparent antagonism between inert gas anaesthetics and hydrostatic pressure, in regard to the h.p.n.s. Two lines of evidence give reasons to be cautious.

First, it is very clear that the hypothesis that the h.p.n.s. represents a single continuum of symptoms of progressively increasing severity is unsatisfactory. We have already encountered substantial differences in compression rate dependence between even such apparently closely linked events as the two successive types of h.p.n.s. seizures. Indeed, this particular differentiation is supported by evidence from genetic, electrophysiological, pharmacological, and neuroanatomical studies (Brauer *et al.* 1979*a*, 1981). With this in mind, it is hardly surprising that, in regard to the total sequence of events making up the h.p.n.s., experimental study has shown that the relations between the hydrostatic pressures needed to elicit a particular symptom and the concentrations of general anaesthetics required to antagonize that effect bore substantially different relations for no less than five components (Smith & Miller 1978). One way to reconcile these findings with the direct antagonism hypothesis was to postulate five

biochemically different interaction sites; it seems to me, however, that the complexity of hypothesis that this entails casts some doubt upon the applicability of the original hypothesis.

Second, the critical volume hypothesis needs must postulate linear relations between effective pressure and anaesthetic concentrations (Brauer *et al.* 1983*a*). While these do prevail to a reasonable extent in experiments in which the onset of anaesthesia is used as an end point, they do not always prevail, even to an approximate extent for high pressure convulsions, the one component of the h.p.n.s. for which adequate quantitative data are available. So, for example, the formulation underlying the critical volume hypothesis would predict that in an experiment like that illustrated in figure 6 (Brauer *et al.* 1983*a*), curves relating He and N_2 partial pressures at convulsion onsets for each mouse strain ought to have been straight lines. Clearly they are not. Furthermore, the slope of the lines should provide a measure of the ratio of effective anti-convulsant potency between helium and nitrogen. Here again, there are very large differences, both between species, and between inbred strains within a single species, which are hard to explain. While it does not appear altogether impossible to remodify the already modified critical volume theory to provide a place for this type of deviation from its original postulates also, it seems to me that such compounded modification becomes increasingly less plausible and more vulnerable to the application of 'Occeghem's razor'.

Application to diving practice: trimix and the 'neutral' gas

This question as to the nature of the high pressure–inert gas antagonism is not devoid of practical significance. Since the original discovery of the inert gas–high pressure antagonism with regard to h.p.n.s. effects, many experimenters have explored the possibility of using these phenomena to mitigate potentially deleterious effects of high pressures upon safety and work performance of divers working in very deep water. At an early stage of this development, it was hoped that by the use of a gas mixture based on these considerations, a so-called 'helium–nitrogen–oxygen Trimix', one might 'effectively eliminate the problem of the h.p.n.s.'. Such statements were justifiable only as long as one could assume that it would be possible to prepare a diving gas mixture of such composition that over the entire course of pressures attained during a given diving profile, the effects of the increasing partial pressures of the pharmacologically active gas component would just counter-balance the effects of the increasing hydrostatic pressure. This implies acceptance of three hypotheses with regard to inert gas–hydrostatic pressure antagonism: (*a*) the effect of the two agents on any given h.p.n.s. component is indeed exerted at a common site, so that the two could be said in truth to neutralize each other; (*b*) the quantitative relations between inert gas and pressure effects are the same for all components of the h.p.n.s.; (*c*) that the ratio between the two is constant over the range of pressures at issue. It is now clear that at least the second and third hypotheses do not, in fact, apply. With respect to (*b*), both dose–response studies during compression of mice in series of mixtures of helium with one of the more anaesthetically potent gases, and the results of comparisons of the effects of compression atmospheres consisting of different principal compression gases upon several different test objects (cf. table 1), indicate that effective potencies for pressure–inert gas antagonism vary with respect to different responses over a rather wide range. So for the pure gas experiments summarized in table 1, the 'neutral' gas (i.e. the gas for which $N_{2,r,p} = N_{2,r,i}$ in the terms of table 1) would have to have molecular properties rather similar to those of neon for the case of pressure reversal of anaesthesia, while for the phase

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transition in liposome models, at the other extreme of the scale, the 'neutral' gas would have to have properties intermediate between nitrogen and nitrous oxide. With respect to (*c*), figure 6 showed that the slope of the dose–response curves for onset of high pressure convulsions in a helium–nitrogen diagram is not, in general, constant, but rather varies continuously and may vary from −0.5 to 3 or from 1 to −0.6 over the course of a single compression series. Since these slopes represent the ratio of effective anti-h.p.n.s. convulsant potency of the gas under test to that of helium (Brauer *et al.* 1983*a*), these data clearly are incompatible with hypothesis (*c*). With regard to the more general hypothesis (*a*), i.e. the hypothesis of interaction at a common site, we have already examined the evidence that leads one to question the applicability of this hypothesis to some of the key phenomena in the development of the h.p.n.s.

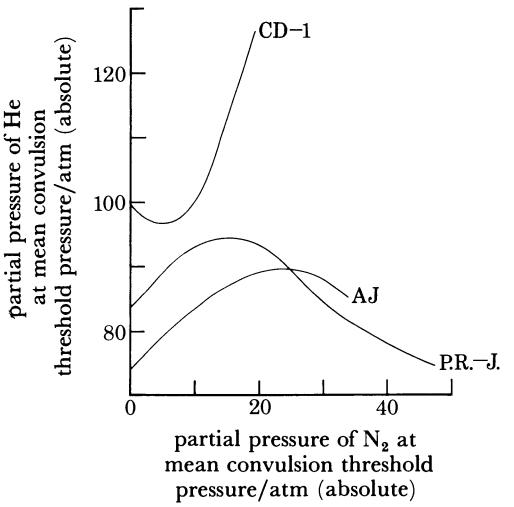

FIGURE 6. Test of linearity hypothesis for h.p.n.s. convulsion threshold pressures of three strains of mice in He–N_2 mixtures of varying composition: ordinate, partial pressure (He_{P_c}) of He at mean convulsion threshold pressure; abscissa, partial pressure (N_{P_c}) of N_2 at same point (see Brauer *et al.* 1983*a* for details) (from Brauer *et al.* 1983*a*).

If this reasoning is correct, it might lead one to change one's point of view with regard to the true significance of the observed remedial effect of helium–nitrogen Trimix upon development of the h.p.n.s. symptoms: instead of viewing the lessened severity of symptoms at any given pressure as a manifestation of reversal of hydrostatic pressure effects by the inert gas, one could have to consider the possibility that the observed effects merely represent suppression of the manifestation of such high pressure effects, by some pharmacological effect (such as narcosis) exerted by the nitrogen or other pharmacologically active component of the compression mixture. Such a hypothesis would yield the same rank and numerical order of anti-h.p.n.s. potencies for the several gases compared in table 1, since the new criterion of relative potency would be 'net anaesthetic potency'. From an operational point of view, the difference might seem of little importance as long as the modified compression procedure permitted a man to perform his job effectively at depths that he could not have reached on a simple helium–oxygen mixture. However, the implications of the divergent interpretations from the point of view of health and safety of the diver are substantially different. It is at least conceivable that in such a situation the nitrogen – which on the newer hypothesis would be assumed not to reverse the primary pressure effects – by masking their clinical manifestation,

might allow pressure-related pathological processes to go on unrecognized, and hence entail the possibility of exposing the divers to the danger of organic damage, which might not be negligible and could be long lasting.

Pressure effects that do not conform to the pattern of inert gas–high pressure antagonism

A number of clearly pressure-related effects altogether fail to conform to the pattern of pressure–inert gas antagonism outlined in connection with table 1. At present, knowledge of such deviant effects is limited largely to observations in single-celled animals or in tissue culture systems (Brauer *et al.* 1983*a*; table 7). Furthermore, the patterns of deviation among them differ from one to the next, so that we were constrained to summarize these effects under the somewhat lame negative term 'non-group A' responses to distinguish them from group A responses conforming to the pattern of table 1. In a number of the instances, the pressures employed to elicit the 'non-A' effects were rather higher than those discussed so far, extending from 200 to 500 atm (absolute). However, a considerable number of group 'non-A' effects can be elicited at pressures in the 50–150 atm (absolute) range. The fact that they fail to conform to the lipophilic pattern of the 'group A' reactions, suggests that reactions of the second type involve pressure-effects on systems that differ from the membrane model system, and may be exemplified by protein structural changes such as those affecting polymerization reactions like those of the actin–myosin or of the tubulin assembly systems (Salmon 1975). Cell pathology, cell replication, and information transfer within the cell are among the commonest biological responses in which such systems are involved. While we have focused on the effects of high pressures on the central nervous system, which are rooted in the behaviour of the excitable membranes, one can not assume that as one goes to higher and higher pressures these will be the only manifestations of compression effects in animals or in human subjects.

General conclusions: the question of residual effects

While we have learned a great deal about avoiding deleterious consequences of the h.p.n.s., there is reason to suspect that as our means to do so have increased in efficiency they have exposed us increasingly to new dangers. One of these was illustrated earlier: recovery rates for the two types of high pressure seizures are very different; if one uses excessively slow compression rates, one may risk that instead of the relatively innocuous type I seizure, the first critical event to occur may be a seizure of the second type, which, in animals at least, often entails mortality. Again, if by manipulating compression schedules one delays the onset of high pressure convulsions in baboons to a sufficient degree, there is risk of encountering a new set of symptoms bespeaking a type of brain damage different in kind from that hitherto associated with the h.p.n.s. (Rostain *et al.* 1982). A third illustration is the one discussed in the previous section, which suggests that if one relies to a large extent upon anaesthetic additions to the compression atmosphere to suppress h.p.n.s. manifestations, one may be running the risk of symptom-free development of pressure-associated tissue injury, which holds at least some possibility of converting what we have hitherto thought of as an essentially reversible phenomenon into one causing longer term injury that is not negligible.

As early as 15 years ago, this possibility was in our minds when we planned, together with

X. Fructus and R. Naquet, to undertake the first human compression experiments deliberately seeking to evoke the h.p.n.s. (Brauer *et al.* 1969). Before undertaking that study, we did replicate exposures to high pressure convulsions in squirrel monkeys that showed that, if one allowed at least four months recovery time between first and second compressions, the convulsion threshold pressures, both for individual animals and for the animals as a group, showed no recognizable systematic change as a result of an exposure to the point of high pressure convulsions (Brauer *et al.* 1974). Now, with considerations such as those just presented in mind, we have resumed studies of this. To date, the data indicate in mice, a small, marginally significant, increase of convulsion threshold pressure two weeks after one or even two exposures to high pressure convulsions in a heliox atmosphere, at most. The effect is substantially larger when one uses compression mixtures containing 12% (by volume) nitrogen and amounts to an increase in mean convulsion threshold pressure per exposure by just over 10% (Hinson & Brauer; unpublished work). For squirrel monkeys, after three compression exposures, convulsion threshold pressures in animals challenged in a Heliox atmosphere are very significantly elevated over what they were during the original Heliox compression; because of the structure of these experiments, however, we are not yet in a position to associate this effect with any particular component of the compression atmosphere. For mice, it is worth noting that present indications are that the displacement of convulsion thresholds as a result of repetitive exposures is dissipated in a matter of four weeks or so after the last pre-exposure.

So, at present, there is equivocal evidence of residual injury after Heliox exposures, there is unequivocal evidence that residual injury is present and enhanced when the compression is made to comparatively severe h.p.n.s. in the presence of nitrogen, but there is at present no evidence that would justify one's inferring from the animal experiments that there is long lasting or irreversible injury.

Significance of high pressure effects on the central nervous system

In closing, we will recapitulate my general assessment of the importance of the group of subjects briefly touched upon. From a broad biological point of view, I have tried to present evidence to bring into focus the significance of hydrostatic pressure as one of the environmental constraints in our biosphere, which has had substantial impact upon evolution of a wide variety of aquatic organisms. From the point of view of applied physiology, I have tried to present results of a variety of approaches to the experimental study of the series of pressure-determined physiological changes that affect the ability of men to work in deep water, and the degree of safety with which they may make such dives, as well as point to the risks and advantages of several strategies that may be adopted in trying to cope with this condition. I have touched only lightly in this discussion upon a third aspect of the subject, which nonetheless seems to me to hold substantial promise, namely the use of hydrostatic pressure-induced changes in central nervous system function as a tool to produce disease models to explore certain types of brain dysfunction. In view of our ability to manipulate with great precision, and the fact that many of the pressure-related central nervous system changes that have been observed appear to be readily reversible, this approach is singularly attractive.

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Discussion

Z. Török (*A.M.T.E. Physiological Laboratory, Gosport, U.K.*). It must be emphasized that hyperbaric convulsions are unknown in man. Some other h.p.n.s. features common between rodents and man on hyperbaric exposure may well be analogous. To expect seizure in man by this analogy is, however, an instance of extrapolation. Man tends to become drowsy when subject to h.p.n.s. Severe head injury is much less likely to lead to acute convulsions than it is for rodents. There may be some important species specific differences here.

R. W. Brauer. I would be surprised if the evolutionary continuity stopped at the baboon. Among primates, *Macaca mulatta* (rhesus monkey), *Saimiri sciureus* (squirrel monkey), and *Papio papio* (baboon), all undergo high pressure convulsions, as shown by Rostain (1981) and by us.

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