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The causes, mechanisms and prevention of the high pressure nervous syndrome

W. L. HUNTER, JR. and P. B. BENNETT

Medical Department, Submarine Development Group One, U.S. Navy, San Diego, California; and Department of Anesthesiology, Duke Medical Center, Durham, North Carolina 27710

Hunter, W. L., Jr., and P. B. Bennett. 1974. The causes, mechanisms, and prevention of the high pressure nervous syndrome. Undersea Biomed. Res. 1(1): 1-28.–The literature concerning the high pressure nervous syndrome is reviewed. The HPNS complex has the following characteristics in a variety of invertebrates and vertebrates, including man. It usually appears at depths somewhat greater than 500 fsw. Its symptoms involve primarily the central nervous system, being manifested as neuromuscular disturbances with incoordination, fasciculations and tremors or as disturbances of higher cerebral functions with disorientation, *microsleep*, and in animals, convulsions. These neurological aberrations can be correlated to some degree with changes in the electroencephalogram. The development and intensity of HPNS is augmented by rapid compression to depth. This symptom complex seems to be a manifestation of some aspect of hydrostatic pressure per se, rather than the result of other more indirect effects of increased ambient pressure. The use of excursion diving or anesthetic gases and anticonvulsants may offer some degree of *protection* against this phenomenon. Attention is called to the difference between the *compression syndrome* and the *hydrostatic pressure syndrome.*

review	tremor
helium	EEG
HPNS	performance
pressure	convulsions
compression rate	nervous system

In 1965 the Royal Naval Physiological Laboratory (RNPL) Alverstoke, Great Britain, was conducting a series of deep chamber dives to depths of 600 to 800 feet of sea water (fsw). During the course of these dives the subjects were noted to develop coarse tremors involving the extremities or even the whole body, accompanied by nausea, occasional vomiting, dizziness, and vertigo. This condition led to a severe decrement in psychomotor performance, especially in any task requiring manual dexterity, as well as documented decrements in cognitive function (Fig. 1). However, it was noted that after some 90 minutes at depth the subjects gradually returned to normal (Bennett 1965; Bennett and Dossett 1967). Subsequent experimental dives confirmed the existence of this entity (Bennett 1967; Hamilton et al. 1967; Zaltsman 1968) and noted a relationship of the symptoms with rate of compression. It was demonstrated that if compression rates were kept sufficiently slow, symptoms were kept to a minimum (Overfield et al. 1969).

In 1968 a French dive to 1189 fsw was aborted because of the development of electroencephalographic changes associated with somnolence and confusion (Fructus et al. 1971).

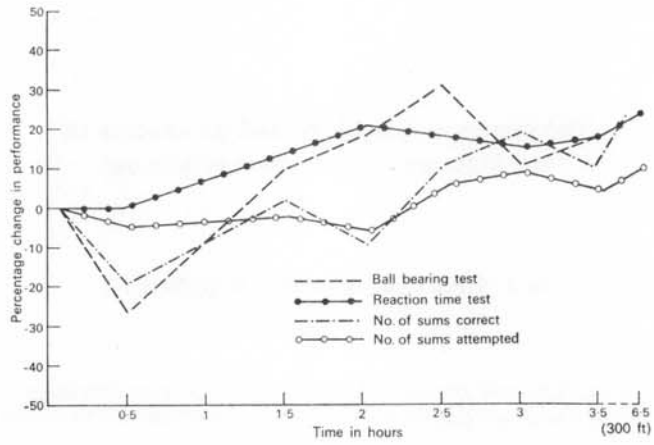

Fig. 1. Tests of performance efficiency on six men at 19.2 ATA (600 fsw) breathing 5:95% oxygen/helium with compression at 41 ft/min. There is a decrement on compression with recovery in 1-1½ hours (Bennett 1965, 1967).

Similar changes had been seen earlier in animal experiments as a prelude to the development of generalized seizures (Brauer et al. 1966). This complex of tremors, EEG changes, and somnolence was termed the High Pressure Nervous Syndrome (HPNS) (Brauer 1968). Since that time numerous deep dives, animal experiments, and pharmacological studies have been conducted in an attempt to elucidate the nature of this syndrome, its possible etiology, and possible methods to counteract it. The purpose of this paper is to summarize these studies, attempt to draw conclusions based on current knowledge, and point out specific problems that must be solved before man's diving capabilities can be extended to great depths.

ASPECTS OF THE HIGH PRESSURE NERVOUS SYNDROME IN HUMANS

Various general descriptions of HPNS have been published (Bennett and Towse 1971b; Fructus and Agarate 1971; Fructus et al. 1971; Fructus and Conti 1971; Fructus and Vigreux 1970). These descriptions are in agreement regarding the basic characteristics of this syndrome. Compression rate seems to affect when symptoms begin and their severity. When the French Physalie series of dives, for example, utilized a compression rate of approximately 8.25 ft/min without rest stops, the following pattern was seen. Tremors appeared at 21 ATA; electroencephalogram (EEG) changes began at 25 ATA; motor incoordination developed at 33 ATA. By 35 ATA the subjects were experiencing loss of alertness, and by 36 ATA they had developed extreme indifference and decreased comprehension (Fructus and Vigreux 1970). In general, symptoms have tended to rapidly abate with the beginning of decompression (Fructus et al. 1971), although EEG changes may persist for somewhat longer (Bennett and Towse 1971b). It has been the consensus of a number of authors that there are no residual effects. Personal observations by subjects have corroborated these patterns (Brauer 1968). Brauer describes the tremors precluding his note-taking at depth. In addition, he relates a certain degree of disorientation and confusion in reading dials. However there are no comments in relation to residual effects after dives.

Neuromuscular signs and symptoms tend to be the initial manifestations of HPNS. One group has described fine resting and intention tremors in a dive to 1000 fsw utilizing a

compression rate of 40 ft/hr (Summitt et al. 1969). Many authors have described gross resting and intention tremors of the limbs and body of varying severity (Bachrach et al.

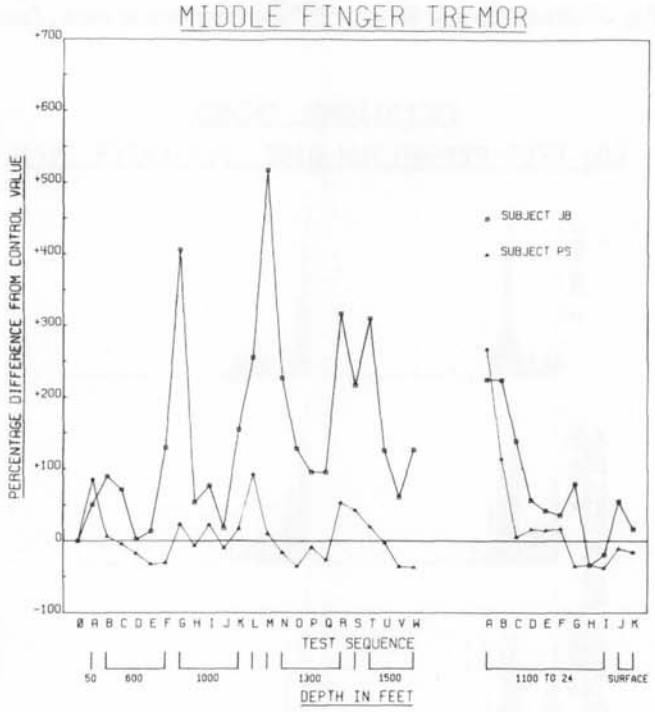

Fig. 2. Percentage change in postural tremor measurements during exposure of two subjects to 1500 fsw in stages with compression at 16-17 ft/min. At depths greater than 600 fsw each compression phase elicits in one subject (JB) a marked increase in tremor, which recovers with time at the stage, together with an overall increase in resting tremor, which does not improve with time. The other subject (PS) is unaffected (Bennett and Towse 1971a).

1971; Bennett 1971b; Bennett et al. 1970; Bennett and Towse 1971b; Brauer 1968; Buhlmann et al. 1970; Fructus and Agarate 1972; Fructus et al. 1971; Fructus and Vigreux 1970; Morrison et al. *in press*; Naquet and Rostain *in press*; Schaefer et al. 1970). Depth at onset and severity have been almost uniformly correlated with compression rate. Other experimenters have noted muscle fasciculations (Brauer 1968; Fructus and Agarate 1972) or myoclonic jerks and spastic movements (Brauer 1968). Loss of coordination has been noted (Fructus and Agarate 1972; Fructus and Vigreux 1970; Waldvogel and Buhlmann 1968), which may be on the basis of tremor. Various attempts have been made to measure or quantify these tremors. Early experiments utilized tests to quantitate manual dexterity, such as the ball-bearing test (Bennett 1965, 1967; Bennett and Towse 1971a). More recent attempts have used transducers attached to the subject's fingers (Bachrach and Bennett 1973b; Bachrach et al. 1971; Bennett and Towse 1971a) or a magnetic finger ring held over an induction coil. Such measurements have shown enhancement of tremors by compression (Fig. 2) with gradual return towards normal levels during rest periods (Bachrach and Bennett 1973b; Bennett and Towse 1971b). It has also been noted that there are consistent, idiosyncratic

differences in the tremor patterns of different individuals, leading to the concept of individual tremor *signatures* (Bachrach et al. 1971; Hamilton *in press*), which might conceivably be used as a monitoring standard. Tremor measurements have shown increases in tremor amplitudes in a wide range of frequencies (Hamilton *in press*) with special augmentation of the 6-10 Hz band (Fig. 3) (Bachrach and Bennett 1973b; Hamilton *in press*; Zaltsman 1961).

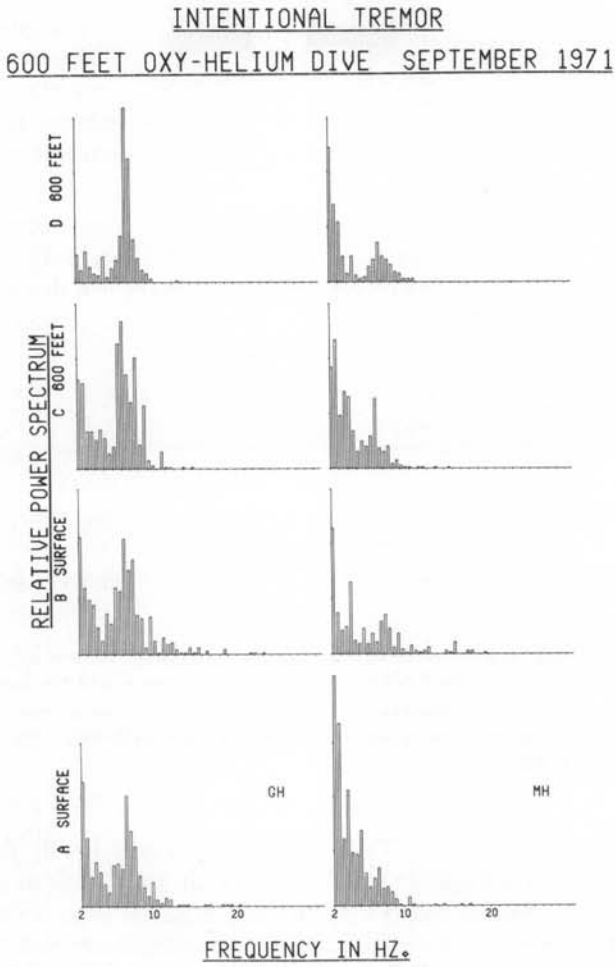

Fig. 3. Changes in the power spectrum of intention tremor during compression of two subjects to 600 fsw with oxygen-helium at 50 ft/min. Compression induces a rise in the 6-10 Hz bands as seen in GH.

All normal tremors, on frequency analysis, show a large frequency component between 8-12 Hz, whereas Parkinson's disease has a rest-peak frequency of 3-8 Hz as is also the case with cerebellar diseases. A postural tremor of 8-12 Hz is found in alcoholism and thyrotoxicosis and during the shivering of cold. Thus, the type of measurement and the frequency characteristics can be diagnostic. Bachrach and Bennett (1973b) have recently reviewed the neuroanatomical pathways involved in tremor.

It is necessary to be clear in describing a given technique for measurement of tremor and to amplify the physical characteristics quantified, the conditions which elicited them, and the type of tremor. A useful classification is that of Brumlik and Yap (1970) into *rest tremor, postural tremor,* and *intentional tremor*, which includes normal and abnormal expressions of these. Rest is defined as the state with no voluntary innervation of the muscles. Postural refers to when the part is voluntarily held still against the force of gravity—as when the arm is outstretched. Intentional tremor is that seen on purposeful movement.

It has been assumed that the tremors of HPNS represent an augmentation of normal resting tremor. However, there is good evidence that normal resting tremor is cardiovascular in origin (Brumlik 1962), which would imply totally different etiologies. One apparent difficulty in tremor measurements, especially in helium atmospheres, is isolating the effects of shivering (Bachrach et al. 1971). However, this can be overcome by close attention to chamber ambient temperatures.

In addition to neuromuscular disturbances, several authors have noted disturbances in the function of other specialized neurophysiological systems, specifically the special sensory organs. Nausea (Bennett 1965, 1967; Buhlmann et al. 1970) and dizziness with occasional vertigo (Buhlmann et al. 1970) have been reported. These symptoms, although temporarily troublesome, abate within several hours of arrival at depth.

It is apparent that at least two complex neurophysiological systems are functionally impaired by exposure to extreme depths. More generalized impairment can be seen in the effects of deep diving on higher cerebral function. Even in dives to moderate depths (23 ATA or 759 fsw) in which tremors are not seen, subjects may develop a loss of attentiveness (Waldvogel and Buhlmann 1968). In deeper dives, such as Sagittaire II (1640 fsw) and Physalie V (1706 fsw), loss of attentiveness was apparent on reaching depths of 1200 fsw (Fructus and Agarate 1971; Fructus et al. 1971; Fructus and Conti 1971). Because of considerable variation between subjects, Fructus and Charpy (1972) suggest that this may be related to basic intelligence of the subject. Other studies relate subjects having difficulty in reading dials and having a disturbance in right-left orientation (Brauer 1968). In both British and French dives, periods of microsleep have been observed at the depth extremes of the dives (Bennett and Towse 1971b; Brauer 1968; Fructus et al. 1971; Naquet and Rostain *in press*). This microsleep is characterized by brief bouts of somnolence from which the subject is easily aroused by external stimuli. The transition between wakefulness and sleep is almost instantaneous and imperceptible. Again in the Physalie series dives, extreme indifference and decreased comprehension were noted in some subjects at the extremes of depth (Fructus and Vigreux 1970).

Numerous efforts have been made to interpret these neuromuscular and neurophysiologic changes by the use of electroencephalography. However, measurement of the electroencephalogram without on-line frequency analysis (Fig. 4) may show little change on visual appraisal unless the HPNS is severe. Commonly reported is a decrease in mean frequency (Bennett and Towse 1971b; Proctor et al. 1972) with a decrease in the number of high-amplitude waves (Fig. 4). Often a decreased percentage of alpha waves (8-13 Hz) in the tracings occurs (Bennett et al. 1970; Bennett and Towse 1971b; Fructus et al. 1971; Morrison et al. *in press*; Proctor et al. 1972) which may even be seen at very shallow depths with compression rates of 100 ft/min (Bennett and Towse 1972). The most consistent EEG change is an increasing percentage of theta waves (5-8 Hz), which may occur at depths as shallow as 400-600 fsw (Fig. 5) (Bennett et al. 1970; Bennett and Towse 1971b; Fructus et al. 1971; Fructus and Vigreux 1970; Morrison et al. *in press*; Proctor et al. 1972). Theta

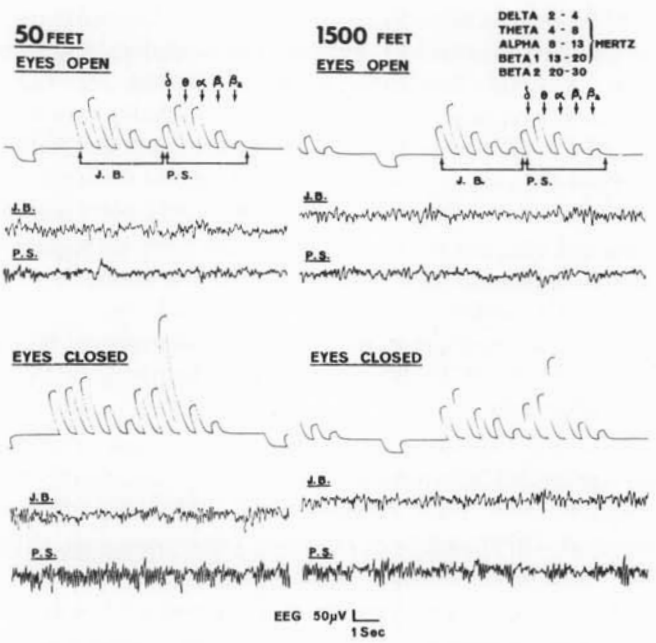

Fig. 4. Frequency analysis and electroencephalogram of two subjects breathing oxygen-helium at 50 fsw and 1500 fsw with eyes open and closed. At 1500 fsw, there is a reduction in EEG activity and an increase in theta activity (Bennett and Towse 1971b).

activity tends to begin as spurts in the temporo-occipital areas, which spread to involve anterior and middle regions of both hemispheres as compression progresses (Fructus and Vigreux 1970). There seems to be a tendency for suppression of this theta activity by keeping the eyes open, but if compression continues, the EEG is transformed first to a stage I sleep tracing, then to a stage II sleep tracing. Ultimately these effects are no longer reversed by opening the eyes or by external stimuli. EEG changes are elicited on compression, tend to be maximal immediately following compression, and revert towards baseline if pressure is held constant; they may not, however, return to baseline levels until well into decompression (Bennett et al. 1970; Bennett and Towse 1971b; Fructus et al. 1971; Morrison et al. *in press*; Proctor et al. 1972). Theta activity, once elicited, continues to rise for some 6 hours, regardless of the fact that compression has ceased. After the 6 hours, the theta falls to more normal values over a further 12 hours. Authors have not reported any residual problems. One report states that after a 7-ATA helium-oxygen exposure of 2 weeks duration, large amounts of spindle-stage activity and slow wave sleep patterns were seen. However, the subjects of this dive had experienced prior sleep deprivation, which may have led to the observed changes (Hock et al. 1966).

In addition to the EEG, evoked brain responses have been observed during deep dives. Investigators have found a progressive decline in the auditory evoked response (Bennett and Dossett 1972; Bennett et al. 1970; Bennett and Towse 1971b; Langley *in press*; Morrison et al. *in press*). This has attained as much as a 50% decrement in amplitude at 1500 fsw. Visual evoked responses have not yielded as consistent a decrement and sometimes there was no change (Kinney and McKay 1971; Kinney et al. 1972). Somatic evoked responses increased in amplitude, accompanied by an increase in threshold for sensory stimulation in studies by

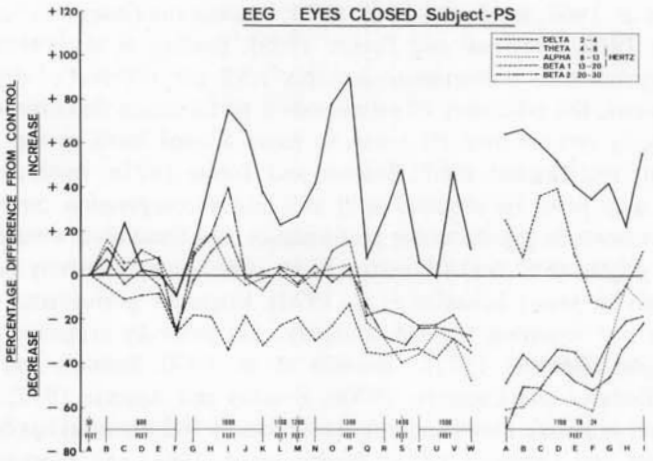

Fig. 5. Percentage change in the electroencephalogram (eyes closed) of a subject exposed in stages to 1500 fsw breathing oxygen-helium. On compression at depths greater than 600 fsw there is a rise in theta activity over 6 hours followed by a fall over a further 12 hours. At depths greater than 1300 fsw there is a reduction in overall activity (Bennett and Towse 1971b).

Langley *(in press)* who interpreted this finding as reflecting the microsleep phenomenon described previously.

Monitoring of brain biopotentials yields valuable information, but such information does not necessarily correlate well with the subject's ability to function normally. In order to assess function, some objective measure of functional impairment must be made. Performance on a variety of tasks has been utilized as such an index.

Several psychomotor tests involving manual dexterity have revealed performance decrements of as much as 50-60% (Fig. 6) (Bennett 1967; Bennett and Towse 1971a; Biersner

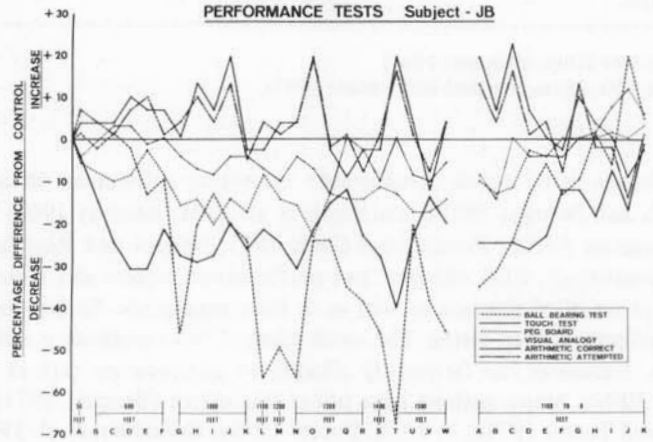

Fig. 6. Percentage change in performance of a subject exposed to 1500 fsw breathing oxygen-helium. Psychomotor tests indicate a marked decrement related in the most sensitive test (ball-bearing) to compression phases. Intellectual tests such as the arithmetic test show no change from predive controls (Bennett and Towse 1971a).

1971; Bradley et al. 1968; Buhlmann et al. 1970; Fructus and Charpy 1972; Morrison et al. *in press*; Parker 1969; Weybrew and Parker 1968). Bradley et al. (1968) state that the decrement in psychomotor performance averages 1.5% per 100 feet of depth. Correlating closely with tremors, the efficiency of psychomotor performance decreases during compression, then gradually returns over 1½ hours to more normal levels as the pressure is held constant (Bennett and Dossett 1967; Bennett and Towse 1971a; Buhlmann et al. 1970). However, levels may never be attained until well into decompression. Several studies have revealed no decrements in psychomotor performance, but these dives were characterized by either shallower depths (650 fsw) (Hamilton et al. 1966) or by relatively slow compression rates (Lambertsen *in press*; Schaefer et al. 1970). Cognitive performance or mental performance, when not requiring manual dexterity, has generally remained intact at depth without decrement (Bennett 1971b; Bennett et al. 1970; Bennett and Towse 1971b; Biersner 1971; Biersner and Cameron 1970b; Fructus and Agarate 1972; Hamilton et al. 1966; Lambertsen *in press*). However, long-term memory (60 minutes) has been observed to decrease (Biersner and Cameron 1970a; Bradley et al. 1968) and short-term memory (5 minutes) was unaffected. The authors reason that this memory decrement may have been due to psychological stress, pointing out the necessity for control of this variable. With very fast compressions, such as 100 ft/min, a decrement in mental performance has been noted (Bennett 1965; Bennett and Dossett 1967; Zaltsman 1968). This may occur without EEG changes but with dizziness, nausea, and possibly vomiting (Table 1).

TABLE 1

Mean psychomotor and cognitive decrement
during oxygen-helium exposures to 600 fsw and 800 fsw.

Depth	600 fsw* ($n = 6$)	800 fsw† ($n = 4$)
Sums correct	−18%	−42%
Sums attempted	−4%	−6%
Ball-bearing test	−25%	−53%

*Compression rate = 41 ft/min (Bennett 1965).
†Compression rate = 91 ft/min (Bennett and Dossett 1967).

Numerous studies have noted considerable individual differences in susceptibility to HPNS (Bachrach and Bennett 1973b; Bachrach et al. 1971; Bennett 1967; Bennett 1971a; Biersner and Cameron 1970b; Fructus and Conti 1971; Naquet and Rostain *in press*). This includes symptomatology, EEG changes, and performance indices and variability is seen in both the depth at onset of changes as well as in their magnitude. Some subjects seem more resistant to the effects of deep diving. The mechanism of this resistance is unknown.

The previous discussion has frequently alluded to compression rate as a factor in the development of HPNS. Many authors have noted this effect (Bennett 1971b; Bennett et al. 1970; Bennett and Towse 1971a, b, 1972; Brauer 1970a; Buhlmann et al. 1970; Fructus and Agarate 1971; Fructus and Conti 1971; Morrison et al. *in press*; Proctor et al. 1972). Generally, the more rapid the rate of compression, the shallower the depth at onset of HPNS and the more severe the changes and vice versa. This has led to the use of slower and slower rates of compression with increasing depth, resulting in a decrease in symptomatology.

Nearly all changes tend to revert towards baseline levels if pressure is held constant. This has led also to the development of staged compression in association with slow compression. However, changes that still occur may not revert to baseline levels until well after decompression is begun. It is important to note that several studies have shown persistent changes at depth involving symptoms, EEG changes, and performance decrements which did not reverse despite slow exponential compression with stops (Bennett and Dossett 1972; Bennett et al. 1970) and prolonged bottom times of as much as 100 hours (Fructus and Agarate 1972). This suggests the possibility that some of the changes may not be related to compression, but are due to some aspect of increased hydrostatic pressure.

THE HIGH PRESSURE NERVOUS SYNDROME IN ANIMAL EXPERIMENTS

Since HPNS is potentially dangerous to humans, a lot of experimental work with various animals has been conducted in order to clarify the full extent of this phenomenon. Many different strains and species have been used. Although there is some variability, the following general pattern has been observed in a variety of different animals (Bennett and Dossett 1972; Brauer 1972; Brauer et al. 1970; Chouteau et al. *in press*; Criscuoli and Albano 1972; Michaud et al. 1972; Parc et al. *in press*; Zaltsman 1968). The initial manifestations are usually tremors and *ratchety* movements. As compression continues the animals develop localized myoclonic episodes, which progress to generalized clonic seizures. If at this depth compression is halted, the animals will continue to manifest intermittent seizure activity for as long as 12 hours. Reduction of pressure will lead to cessation of the seizures. All manifestations are reversible to this point with no apparent permanent residual problems. If, however, compression is continued beyond this level, animals develop generalized tonic seizures which rapidly proceed to coma and death. Reduction of pressure during these stages may not affect survival. Therefore, at some depth the syndrome appears to become irreversible. At given compression rates, threshold pressures for tremors and for convulsions show strain and species variability (Brauer et al. 1971; Criscuoli and Albano 1972), but the overall pattern described above is remarkably constant. It appears, in comparing different species, that susceptibility to HPNS increases with increasing complexity and development of the nervous system (Brauer, Way, and Perry 1968). The question of possible adaptation to pressure effects is not settled. Operant-conditioned rats have been observed to manifest improvement in task performance at depth after frequent repeated exposures (Thomas et al. *in press*) but, apparently, convulsion threshold pressure is a constant characteristic in individual animals (Brauer 1972).

As in analysis of HPNS in humans, electroencephalographs have been extensively utilized in animal experiments. More positive correlations between observed symptomatology and EEG changes have been possible. One investigator found little change in EEG frequencies during the tremor-only phases (Wilcox 1973) but other work has shown the same depression of fast frequency (Fig. 7) activity (Bennett and Dossett 1972, 1973) previously described in human experiments (Criscuoli and Albano 1972; Zaltsman 1961). At greater depths polyphasic spikes appear with shifting focus, and synchronous and myoclonic activity (Brauer et al. 1971; Criscuoli and Albano 1972). Ultimately generalized seizure patterns develop which are synchronous with the animal's convulsive movements. As coma stages are reached, all frequencies progressively decrease in amplitude, culminating in cessation of cerebral activity when the animal dies.

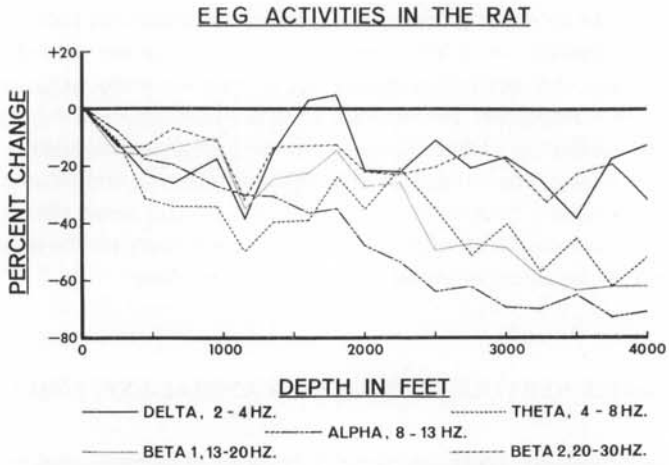

Fig. 7. Mean percentage change in frequency bands of the spontaneous electroencephalogram during compression of two rats with oxygen-helium at 10 ft/min to 4000 fsw (Bennett and Dossett 1973).

These changes are seen in cortical EEGs, but some remarkably different manifestations have been observed by using electrodes implanted in deeper structures of the brain. Using cats and rabbits in helium-oxygen atmospheres at 10 ATA, Chang-Chun (1960) found that initial changes occurred in the cerebellum and subcortical ganglia rather than in the cortex. Other investigators have confirmed this finding (Brauer 1972; Zaltsman 1968). Brauer states that minor changes in the hippocampus and more dramatic changes in the caudate nucleus (high-amplitude, high-frequency potentials) may precede cortical seizure activity by as much as 5 minutes. Zaltsman found that while cortical potentials were manifesting depression, nonspecific structures in the brainstem and thalamus were exhibiting increased activity. A pattern emerges revealing hyperexcitability of the more *primitive* areas of the nervous system accompanied by a simultaneous depression of activity in the neocortex. Thus, EEGs in animals subjected to high pressures confirm the activity seen in man as well as reveal patterns not yet observed.

Another factor seen in human deep dives that has been confirmed in animal studies is the importance of the rate at which pressure is applied. Several investigators have documented increase in tremor threshold pressures by slowing compression rates (Brauer 1972; Brauer et al. 1969; Brauer et al. 1971; Dossett and Hempleman 1972; Lever, Miller, Paton, Street, and Street 1971). As an example, Dossett and Hempleman (1972) observed that rats compressed at a rate of 3 atm/min developed tremors at a depth of 37-43 atm (1200-1400 fsw). However, if the compression rate was slowed to 0.3 atm/min, tremors did not begin until a depth of 107 atm (3500 fsw) was attained. Convulsion threshold pressures were similarly increased by slowing compression rates (Brauer 1971; Dossett and Hempleman 1972) although perhaps not to such a marked extent. Brauer notes that convulsion threshold pressure seems to rise linearly with decreasing logarithm of compression rate. Such a beneficial effect of slowed compression has been questioned with respect to EEG changes. Apparently neural biopotential alterations at depth are relatively independent of compression rate (Bennett and Dossett 1972).

There are thus some real advantages of slow compression rates. Some question exists as to whether this should be accomplished by using a slow linear compression, an exponential, or

by using staged compression. In mice, staging of compression offers no advantage over continuous compression, but in higher animals the recovery periods offered by staged compression tend to yield superior results (Parc et al. *in press*).

If data from animal experimentation is to be of practical value, correlations must be sought with human data and disparities resolved. First of all, there is an apparent paradox in EEG findings. Humans display depression and microsleep while animals exhibit hyperexcitability and seizures. However, upon closer inspection the paradox is resolved. Cortical tracings in animals under pressure do show the alpha and theta wave alterations seen in humans; it is the deeper, more primitive areas of the brain that manifest hyperexcitability. To date only cortical EEGs have been monitored in humans. No human subjects have developed the seizures seen in animals, but neither have they been exposed to such extreme pressures. It seems reasonable to postulate that a similar augmentation of deep brain activity may be occurring in human subjects, which we have been unable to measure.

It also seems reasonable to believe that if human subjects are exposed to ever-increasing pressures, they, too, will develop pressure-induced seizures. Data from primates, when extrapolated to man, suggests that the mean convulsion pressure for humans compressed at a rate of 1 atm/hr would fall near 84 ATA (2805 fsw) (Brauer 1972). Data from other species has been used similarly, with predicted mean convulsion pressures for humans always being calculated at somewhat greater than 67 ATA (2211 fsw) (Brauer 1972; Brauer, Way, and Perry 1968; Fructus et al. 1971). The deepest simulated dive to date has been to a depth just over 2000 fsw by the COMEX company at Marseille. It is apparent that human dives are approaching depths at which seizures may be anticipated.

ETIOLOGY OF THE HIGH PRESSURE NERVOUS SYNDROME

Many diverse factors have, at one time or another, been suggested as contributing to the genesis of HPNS. These factors may be conveniently divided into two categories, indirect and direct effects of increased ambient pressure. Indirect effects of depth include alterations in the partial pressure of oxygen and/or carbon dioxide, as well as alterations in temperature. More direct effects of exposure to depth would include osmotic gradients produced by dissolving of gases, possible toxicity of the diluent gas under pressure, changes induced by the increased mass of gas dissolved in tissues, and direct effects of hydrostatic pressure itself. This section will present the evidence both for and against the possible etiologic role of each of these factors and attempt to assess the likelihood that a given factor is responsible for the HPNS complex.

OXYGEN

Previous mention has been made that some symptoms of HPNS are found also in some pathological processes. Lucien and Barthelemy (1970) noted certain similarities with the symptoms of altitude hypoxia. They postulated that CNS hypoxia was present because of impaired oxygen diffusion secondary to increased gas density at depth. Chouteau et al. (1972) noted that some HPNS symptomatology in experimental animals could be reversed by increasing the inspired partial pressure of oxygen. Histoenzyme analyses in animals also exposed to a 29 ATA helium-oxygen atmosphere containing 1.6% oxygen (0.46 ATA) for up to 4 hours revealed changes suggestive of histotoxic anoxia (Michaud et al. 1972). In this experiment, however, the animals died during the pressure exposure, so that the observed changes could have taken place during the immediate post-mortem period. Conversely, Over-

field et al. (1969) found that in human subjects exposed to 31.3 ATA (1000 fsw) on a helium-oxygen mixture containing 0.9% oxygen (0.28 ATA) respiratory gas exchange remained normal. Arterial P_{O_2} values were consistently within normal limits, even though this gas mixture had four times the density of air at sea level. Additionally, using various mammalian species, other investigators found convulsion threshold pressures to be independent of P_{O_2} in the oxygen ranges of 0.4 to 2.0 ATA (Brauer et al. 1971; Brauer, Way, and Perry 1968).

The similarity between the generalized seizures seen in HPNS and those occurring because of CNS oxygen toxicity would suggest that excess oxygen might be implicated. The study by Overfield et al. (1969) previously cited demonstrated a lack of such excesses. The studies by Brauer and his coworkers (Brauer et al. 1971) did show that with a P_{O_2} of 2.4 ATA or greater, convulsion threshold pressures were decreased, but this level of oxygen is much higher than those generally utilized. They also discovered significant differences between susceptibility to HPNS convulsions and susceptibility to oxygen convulsions in various species (Brauer et al. 1972). Additionally, gamma aminobutyric acid (GABA) has been shown to decrease in cases of CNS oxygen toxicity (Wood 1969). However, in mice exposed to a normoxic helium atmosphere for 24 hours at 20, 40, or 60 atm, analysis of brain tissue after decompression revealed a linear increase of GABA with pressure (Ritter et al. 1969). The exact role of GABA in oxygen toxicity is not completely clear, but such opposite findings, combined with the other studies cited, would imply that in normoxic helium atmospheres, oxygen probably plays no more than a minor role in the etiology of HPNS.

CARBON DIOXIDE

In addition to changes in oxygen levels, an increase in carbon dioxide level was suggested as a possible etiologic factor in genesis of HPNS (Bennett 1967) when HPNS was first noted. Several authors have noted increased alveolar P_{CO_2} during deep dives, especially during exercise (Jarrett 1966; Salzano et al. 1970; Schaefer et al. 1968). This has been attributed to decreased alveolar ventilation secondary to gas density, but Schaefer et al. (1968) noted that experienced divers tended to retain carbon dioxide during dives even while at rest. This was explained on the basis of a characteristic breathing pattern seen in trained divers that led to increases in alveolar P_{CO_2}, mixed expired P_{CO_2}, and urine CO_2 excretion. Arterial levels of carbon dioxide were not stated. Conversely, Overfield et al. (1969) in the dives cited previously, found an absence of CO_2 retention in trained divers, with arterial partial pressures of carbon dioxide ranging from 30.5 to 42 mm Hg. Using mice pretreated by intraperitoneal injection of either saline or THAM buffer as a control, Brauer (1972) and Brauer et al. (1970) found that there was no significant difference in convulsion threshold pressures of the two groups. Additionally, it was noted that HPNS symptoms will develop even in CO_2-free atmospheres (Brauer 1970a). It should be noted that the characteristic response to increased carbon dioxide tensions in the absence of hypoxia bears little resemblance to the symptomatology of HPNS. This fact, when combined with the variable carbon dioxide levels that have been observed without corresponding variability in the HPNS manifestations and with the lack of effect of buffers, leads to the conclusion that carbon dioxide retention, like variations in oxygen levels, probably plays no causative role in HPNS.

TEMPERATURE

The third indirect effect that has been suggested as playing a role in HPNS is variation in temperature. Although lowered ambient temperatures may induce shivering in helium atmospheres, several authors have demonstrated in animals that lowering core temperatures has no

effect on tremor or convulsion threshold pressures (Brauer, Way, and Perry 1968; Leon and Cook 1960; Zaltsman 1961). Liquid-breathing mice have developed convulsions at lower pressures when rectal temperatures were greatly lowered (Kylstra et al. 1967; Ornhagen and Lundgren *in press*), but this was a greatly altered environment with many added variables. Zaltsman (1968) states that temperature increases of 7 to 15°C during compression to depth increases the risk of both tremors and convulsions. Conversely, Brauer, Way, and Perry (1968) exposed various series of 10 mice to pressurization with chamber temperatures rigidly controlled at levels from 18 to 35°C and neither tremor threshold pressures nor convulsion threshold pressures were affected by changes in temperature although shivering appeared below 25°C. The ambient chamber temperatures reported in most dives are well within this range. Thus it appears that, even though increased temperatures may accelerate the development of HPNS, if chamber temperature fluctuations are kept in the ranges that are comfortable for the divers, onset of HPNS will be unaffected by this variable.

GAS-INDUCED OSMOSIS

These previously mentioned indirect effects of increasing ambient pressure can perhaps affect the appearance of HPNS. However, even though increased temperatures may accelerate its development, none of these factors seem to be primarily responsible. One of the more direct effects, gas-induced osmosis, has been suggested as a cause. Osmosis generated by dissolving inert gases was first demonstrated by Kylstra et al. (1968). Such osmotic pressures may lead to fluid shifts between the various body compartments. Hills (1971) has implicated this phenomenon in the development of arthralgia and vestibular disturbances during compression as well as in the development of aseptic osteonecrosis in divers. Others have extended these concepts to include the manifestations of HPNS (Fructus et al. *in press*; Fructus and Conti 1971). It is reasoned that onset of symptoms during rapid compression results from fluid shifts generated by saturation gradients of inert gas between hydrophilic *rapid tissues* (such as blood) and hydrophobic *slow tissues* (such as the CNS). Similarly, equilibration of these gradients would account for the decrease in symptoms after some period at stable pressure. However, the osmotic pressures generated in Kylstra's experiment were very short-lived—no longer than 20 minutes. As has been previously noted, HPNS symptoms may require 12 to 18 hours to abate after reaching stable pressure. Even then, baseline levels may not be reached. Ornhagen and Lundgren (*in press*) found that in liquid-breathing mice where there was no gas phase and hence no increase in gas partial pressures, rapid compression rates generated convulsions at lower pressures. Obviously, saturation gradients of the type described above could not be causing this lowering of convulsion threshold pressure. Additionally, the persistence of certain of the features of HPNS, despite bottom times of 100 hours or more, would suggest that although gas-induced osmosis may be playing some role, it is certainly not the only etiologic factor. Any saturation gradients that might be operative would almost surely reach equilibrium during such a prolonged period at depth.

DILUENT GAS

Saturation gradients could be produced by any inert gas. However, the diluent gas could conceivably be producing some direct effect itself, by virtue of its own molecular properties. A number of studies have shown that helium and neon possess no narcotic properties of the nitrogen type (Bennett 1964; Bennett 1971b; Bennett et al. 1967; Biersner 1971; Biersner and Cameron 1970b; Brauer, Jordan, and Way 1968; Brauer et al. 1971; Hamilton *in press*;

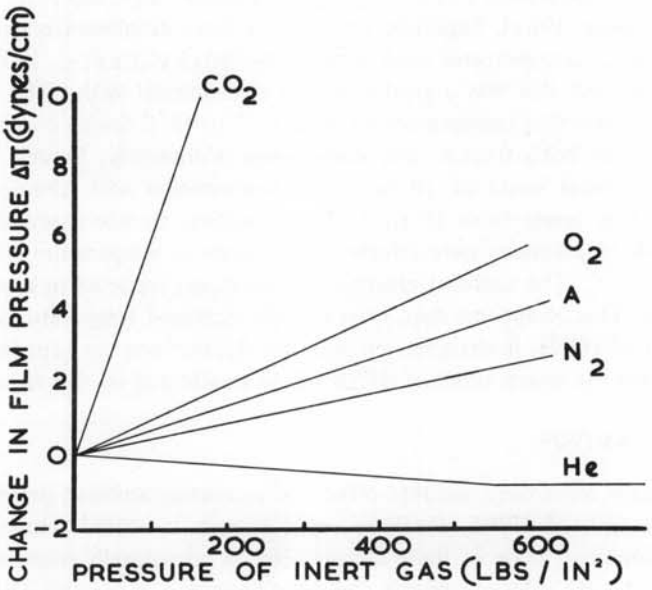

Fig. 8. Penetration of a lipid monolayer of egg phospholipid by inert gases, oxygen, and carbon dioxide at increased pressures. An increase in film pressure represents a comparable fall in surface tension. All the gases except helium adsorb to the model membrane. (Bennett et al. 1967).

MacInnis et al. 1967; Parker 1969; Roger et al. 1955). Helium and neon do not appear to penetrate phospholipid membranes (Fig. 8), so that this lack of narcotic potency would be expected (Bennett et al. 1967).

If HPNS were a manifestation of helium narcosis, one would expect changes in the symptom complex if the diluent gas were abruptly switched at depth. Hamilton (*in press*) has shown that such changes do not occur. Cognitive performance, memory, and learning ability—factors markedly affected by increased partial pressures of nitrogen—show no decrement at increased partial pressure of helium (Biersner 1971; Biersner and Cameron 1970b; Parker 1969).

If inert gas narcosis cannot be implicated, could helium produce some metabolic or toxic effects leading to HPNS? Helium, possessing a thermal conductivity approximately six times that of air, increases basal metabolic rate in response to heat loss. The magnitude of this response is proportional to the thermal gradient between the organism and the environment (Leon and Cook 1960). However, if ambient temperature is kept stable and near body temperature, this response can be eliminated. Even more basic metabolic alterations have been observed. South and Cook (1953) demonstrated that substitution of a normoxic helium atmosphere for air at 1 ATA resulted in changes in both aerobic and anaerobic glycolysis of mouse liver slices. Featherstone et al. (1971) suggest that inert gas molecules may be altering protein function by *binding* at critical sites. Other investigators have observed that the growth rate of certain bacteria and fungi is altered by changing the diluent gas in the atmosphere (Doebbler et al. 1967; Fenn 1967; Schreiner et al. 1962).

Apparent toxic effects have been observed in skeletal muscle (Hawkins 1973) and cardiac mitochondria (Hawkins 1972) of mice maintained in a normoxic helium atmosphere at 1 ATA for 90 days. The author of these studies notes that these effects could have been the

result of nitrogen washout, rather than of helium exposure. An identical atmosphere, also at 1 ATA, produced human EEG changes, such as increased theta and delta waves and decreased alpha waves and distinct *helium tremors* after an exposure of 4 hours (Hu and Russo 1972). Although the other effects cited above cannot be readily correlated with HPNS, the distinct similarities found in this latter study must be considered, for it seems that the term *inert gas* may prove to be inaccurate when applied to gases of the helium group.

INCREASED MASS OF DISSOLVED GAS

There are, however, other actions of inert gases under pressure that would not necessarily imply metabolic alteration. One study has suggested that the increased mass of gas dissolved at high pressures may impair the function of the cardiorespiratory system in eels (Barthelemy et al. 1971). What bearing this finding may have on the function of the nervous system is not clear. However, HPNS can be produced either by increasing partial pressure of the atmospheric gases or by increasing pressure hydraulically in the absence of a gas phase. In newts, effects are seen at comparable absolute pressures by either method (Lever, Miller, Paton, and Smith 1971; Miller et al. 1967). Mice breathing oxygenated fluorocarbon liquids also develop symptoms of HPNS at hydraulic pressures comparable to the helium pressures producing HPNS in gas-breathing animals (Kylstra et al. 1967; Ornhagen and Lundgren *in press*). These findings would imply that some aspect of hydrostatic pressure itself is a major factor, rather than the concentration of dissolved gas molecules.

DIRECT EFFECTS OF HYDROSTATIC PRESSURE

Such a suggestion is not at all unreasonable, for hydrostatic pressure is known to have ubiquitous effects in physical, chemical, and biological systems (Zimmerman 1970, 1971). For example, classical gas laws do not hold true at extreme depths; dissolved gases may behave differently under such conditions (Enns et al. 1965) and liquids, usually thought of as being incompressible, display volume decreases with concomitant increase in viscosity (Fenn 1969). Under extreme pressures, gases may form solid hydrates and clathrates and cause increased ordering of water molecules (Doebbler et al. 1967; Featherstone et al. 1971). Since ionization of a solution leads to a decrease in volume (charged particles attract water molecules, producing electrostriction; the greater the number of charged particles, the greater this effect and the less the volume), pressures tend to favor ionization (Johnson and Eyring 1970; Podolsky 1956) and alter pH (Fenn 1969; Morita and Becker 1970). Molecular volumes can be altered by pressure (Johnson and Eyring 1970; Morita and Becker 1970). This may cause marked structural changes in complex molecules, leading to such effects as protein denaturation (Featherstone et al. 1971; Suzuki and Taniguchi 1972).

Biological proteins and enzymes are very large and complex molecules. Because of this, molar volume changes associated with enzyme activation and substrate reactions are sometimes quite large. As Landau (1970) observes, in any enzyme-substrate reaction involving an increase in volume, hydrostatic pressure would be inhibitory. If such a reaction resulted in volume decrease, the result would be stimulation; if no volume change occurred, hydrostatic pressure would have no effect on the reaction. This relationship has held true for numerous bioenzyme systems. Aggregation of a variety of enzymes with their substrates results in an increase in molecular volume, and hydrostatic pressures inhibit such aggregation.

Among these enzymes are included sickle-cell hemoglobin (Murayama 1966), ribonuclease S_1 (Morita and Becker 1970), fibrin (Murayama and Hasegawa 1970), myosin (Josephs

and Harrington 1968), flagellin (Gerber and Noguchi 1967; Zobell and Kim 1972), and beta-galactosidase (Landau 1971). Adenosine triphosphatase also appears to be pressure-sensitive (Gottlieb et al. *in press*; Laidler and Beardell 1955). Glycolysis is inhibited, since this reaction involves a volume increase of 24 ml/mole (Fenn 1967, 1969). Gel-sol transformations, which involve volume changes, are altered by pressure (Fenn 1967; Landau 1970; Marsland 1958). Johnson and Eyring (1970) reason that probably all biological processes have an optimum pressure, just as they have an optimum temperature. What influence changes in enzyme systems may have on the development of HPNS is unknown, but the possibility of some such relationship cannot be dismissed.

Hydrostatic pressure also affects more complex systems such as isolated biological tissues. Erythrocytes lose their biconcave shape and become spherocytic at high pressures (Fenn 1969). Isolated muscle preparations display enhancement of tension development (Fenn 1969; Lever, Miller, Paton, Street, and Street 1971; Podolsky 1956), and at extremely high pressures they become rigid. The frog-skin preparation undergoes a pressure-related increase in membrane permeability to sodium ions with increased membrane potential (Brauer et al. 1971). Nervous tissue also shows pressure-related changes. Isolated frog nerves display increased excitability, increased action potential amplitude, and increased conduction velocity under increased hydrostatic pressure. These changes are reversible upon lowering the pressure (Grundfest 1935; Spyropoulos 1957b). Similar pressure exposures utilizing the giant axon of the squid yield similar results with only minor differences (Spyropoulos 1957a). This *hyperexcitability* of isolated nervous tissue may have some bearing on the hyperexcitability phase of HPNS in animals described earlier.

Intact organisms, like isolated tissues, are susceptible to hydrostatic pressure. Some bacteria show inhibition of growth under pressure (Fenn 1967, 1969). In others, pressure increases resistance to high temperatures. Probably because of effects on gel-sol transformations, ameboid movement and pinocytosis in amebas are inhibited by pressure, and the organism will eventually become spherical (Fenn 1969; Marsland 1958). Marine organisms are likewise affected by hydrostatic pressure. Shallow-water amphipods and crustaceans display increased locomotor activity up to pressures of 100 to 150 ATA. At greater than 200 to 270 ATA locomotor activity is completely inhibited. These changes are completely reversed within 2 minutes at 1 ATA (MacDonald *in press*, 1972). Some fish may display cardiorespiratory inhibition if taken to depths greatly beyond those to which they are accustomed (Barthelemy et al. 1971). Amphibians, such as newts, lose their righting reflex between 100 and 200 ATA when compressed hydraulically (Lever, Miller, Paton, and Smith 1971). Application of hydrostatic pressure to liquid-breathing mice (no gas phase, hence no increase in gas partial pressures) leads to the development of tremors, incoordination, and seizures indistinguishable from the HPNS complex seen in gas breathing mice (Kylstra et al. 1967; Ornhagen and Lundgren *in press*).

It can readily be seen that hydrostatic pressure causes many alterations in biological systems. It is important to know the site where pressure acts to cause HPNS in divers. Good indications are given by the results of some further animal experiments. Pithed frogs develop twitching of their toes when subjected to high hydrostatic pressures (Fenn 1967). However, isolated hind limbs do not contract at all, even at 200 ATA (Klystra et al. 1967). Additionally, if the spinal cord of a liquid-breathing mouse is sectioned and the animal is then pressurized, muscles distal to the section remain flaccid and develop none of the signs of HPNS. Those muscle groups supplied by cord tissue proximal to the section will develop such signs.

These findings indicate that HPNS is correctly termed a *nervous syndrome*, for it seems that the symptoms and signs are originating in the central nervous system. Chouteau et al. (*in press*) concluded from their experiments with baboons that the basic function of the neuromuscular system was unaffected in HPNS. Rather, they suggested that spinal and supraspinal neuromotor regulatory centers were altered. Bachrach and Bennett (1973b) have recently reviewed the pathways and centers involved in tremor. Prominent in these pathways are midbrain centers, the ascending reticular system, the basal ganglia, and portions of the thalamus. It is proposed that these areas are activated by increased ambient pressures (Bennett 1971b). This is in agreement with the findings of Zaltsman and Brauer, previously cited. Further, Brauer (1972) has demonstrated that cerebellar ablation sensitizes an animal to HPNS convulsions. Helium-oxygen atmospheres under pressure seem to facilitate impulse spread in the CNS (Brauer, Jordan, and Way 1968). Increased conduction velocity in isolated nerves compressed hydraulically has been previously discussed. Brauer states that his data suggest that development of HPNS involves pathways originating largely in the brainstem and impinging on the midbrain and limbic system. These pathways probably involve monoamine transmitters. Current work seems to indicate that serotonin may play an important role. Obviously, too little is known at present to make definitive statements regarding the exact mechanism by which pressure affects the central nervous system. It seems that its effects are certainly profound, and that hydrostatic pressure is probably of primary importance in the development of HPNS. It may be necessary in the future to consider the effects of hydrostatic pressure as *drug effects.*

PHARMACOLOGY OF THE HIGH PRESSURE NERVOUS SYNDROME

Many years ago it was noted that the inhibition by chloroform of bacterial luminescense could be overcome by the application of hydrostatic pressure (Fenn 1969). Additionally, the narcotizing effects of ethanol on isolated nerves were shown to be reversed by pressure (Spyropoulos 1957a). A similar effect has been more recently demonstrated in newts. Narcosis produced in these animals by several gaseous and intravenous anesthetics can be rapidly reversed by application of hydrostatic pressures of 100 to 200 ATA (Lever, Miller, Paton, and Smith 1971; Lever, Miller, Paton, Street, and Street 1971). These findings have been reproduced in mice (Miller et al. 1972). Such information has led Miller and his associates to formulate the *critical volume hypothesis* regarding the mechanism of action of anesthetic agents (Miller 1972; Miller et al. 1972; Miller et al. 1973). They relate the anesthetic potency of an agent to the ability of its molecules to modify the dimensions of lipid phases, possibly those in cell membranes. It is theorized that anesthesia occurs when the volume of some hydrophobic region is caused to expand beyond some critical volume by adsorption of molecules of the anesthetic agent. This hypothesis accounts for the pressure reversal of anesthesia. It is argued that hydrostatic pressure opposes the *lipid-layer swelling* caused by anesthetic agents, resulting in the reversal of the anesthetized state. It should be noted that this hypothesis seems to correlate more closely with observed facts than do previous explanations of anesthetic action.

If pressure can reverse the action of anesthetics, it seems possible that anesthetics might reverse some of the effects of pressure. This might be the opposite effect of the pressure reversal of anesthesia. If symptoms and signs of HPNS are caused by a compression of lipid layers by hydrostatic pressure, then adsorption of molecules of the anesthetic agent into such lipid layers might reexpand them to their original dimensions.

Whether or not this is the mechanism of such an effect is unknown. However, this effect has been observed in animals (Brauer 1970b, 1972; Brauer et al. 1966, 1969, 1970, 1972; Brauer, Way, and Perry 1958). When added to the breathing mixture, narcotically effective gases significantly raise convulsion threshold pressures. Brauer (1972) noted that the ability of a gaseous anesthetic to prevent high-pressure convulsions is proportional to its relative narcotic potency. Anesthetic gases have even greater effects on tremor threshold pressures, at least in monkeys. Using this concept, one group has exposed mice to pressures to 270 ATA (8900 fsw) without loss of righting reflexes or convulsions. Some animals died during decompression, but survivors had no apparent residual difficulties. This amazing feat was accomplished by adding nitrous oxide to the breathing medium (Halsey et al. *in press*).

Since gaseous anesthetics are more effective against tremor than against convulsions, classical anticonvulsant agents might complement their effects. This has been attempted with several barbiturate derivatives and found to be true (Brauer 1971, 1972; Brauer et al. 1972; Lever, Miller, Paton, Street, and Street 1971). Pretreatment of an animal with barbiturates alone may raise the convulsion threshold pressure by as much as 50% (Brauer 1972). Combinations of anesthetic gases and anticonvulsants may yield synergistic effects, with significant elevation of both tremor threshold pressures and convulsion threshold pressures (Brauer et al. 1972).

POSTPONING THE HIGH PRESSURE NERVOUS SYNDROME

The concepts discussed in the previous section have obvious implications for human diving. Postponing or prevention of HPNS symptomatology has been accomplished in a variety of animals by the use of anesthetic gases and/or anticonvulsant agents (Brauer 1970b, 1972; Brauer et al. 1966, 1969, 1970, 1972; Brauer, Way, and Perry 1968; Halsey et al. *in press*). The relatively constant nature of the response of these different animals to such agents is striking. Additionally, the symptoms of HPNS are remarkably similar in a host of different animals, including man. The major difference seems to be that susceptibility to HPNS increases with increasing complexity of the central nervous system (Brauer, Way, and Perry 1968). (Susceptibility to HPNS can be expressed either by depth at onset of symptoms at a given compression rate or by maximum tolerable compression rate to a given depth without development of symptoms.) The fact that HPNS is quite similar in animals and humans (disregarding differences in susceptibility) and the fact that various different animals can be *protected* from HPNS by pharmacologic agents implies that such agents may very well also protect against HPNS in humans.

Vigreux (1970) examined such nitrogen-helium-oxygen mixtures in man with almost equal parts of nitrogen and helium (O_2 18%, N_2 42%, He 40%). This produced a reduction in the cost of the dive, increased thermal comfort, and improved the distortion of speech due to helium.

At depths to 262 fsw Vigreux reported the results were good, but at 394 fsw a mixture of O_2 13%, N_2 43%, and He 44% caused breathlessness and narcosis during moderate work. In an effort to reduce this problem, density equivalents (ED) in relation to air were calculated. Thus, the 262-fsw mixed-gas dive corresponds to an air dive of 174 fsw and the 394-fsw dive to an air dive of 246 fsw. With this method it was found that a 50% oxygen and 50% nitrogen mixture has an acceptable ED for dives not exceeding 1 hour and, therefore, four mixtures were prepared as shown in Table 2. These mixtures proved effective with satisfactory pulmonary ventilation under moderate work and no narcosis. However, there is little indication by Vigreux of scientific measurements to support his statements.

TABLE 2

Oxygen-nitrogen-helium mixtures for deep diving*

Depth msw	Mixture O_2 : N_2 : He	ED† msw
60	23 : 23 : 52	31
80	18 : 18 : 64	35
100	14 : 14 : 72	38
120	12 : 12 : 76	42

*Data evolved by Vigreux (1970)
†Density equivalent in relation to air

As early as 1961 Zaltsman (1961) reported an *antagonism* of the narcotic action of nitrogen in the presence of helium and investigated the use of nitrogen-helium-oxygen mixtures. For simplicity, Zaltsman used air-helium mixtures of 50% volume of helium at depths from 197-328 fsw and 67% volume of helium from 331-527 fsw. This gave a maximum nitrogen partial pressure of 4.5 ATA and the oxygen did not exceed 2 ATA.

Using such mixtures (Table 3) at 527 fsw, heavy work between 221-580 kg/m/min was possible with little or no tremors or signs of HPNS and apparently no thermal-balance or voice-distortion problems. However, again there is little quantitative data in support.

A further possibility with the use of such a 'trimix' is that the high hydrostatic pressure at some 1000 fsw or 30 ATA will nullify any narcotic effect of the nitrogen present in the mixture.

Some quantitative indication of such a pressure antagonism was found by Proctor et al. (1972) without realizing it. During decompression from the 1000 fsw, the divers breathed a gas mixture of 3.5 atm N_2, 1.0-1.5 atm O_2, and the balance helium for 10 minutes at 600, 400, 240, and 200 fsw (19, 13, 11, and 7 ATA). At 600 fsw there were no narcotic effects or performance deterioration but at the shallower depths the high nitrogen mixture caused narcosis. Presumably at 600 fsw the narcotic effect of the nitrogen was effectively balanced by the hydrostatic pressure. However, at the shallower depths the hydrostatic pressure was insufficient and nitrogen narcosis occurred.

TABLE 3

Characteristics of air-helium mixtures composed for humans in conditions of high pressures*

Total pressure (m H_2O)	Mixture ratio %		Partial pressure of gases ATA			Decrease in thermal conductivity of medium as compared to helium-oxygen (*number of times*)	Increase in density of medium as compared to helium-oxygen (*number of times*)
	air	oxygen	oxygen	nitrogen	helium		
From 60 to 100	50	10.4	0.7-1.1	2.8-4.4	3.5-5.5	2.0	2.1
from to 160	33	6.9	0.76-1.13	2.94-4.53	7.4-11.3	1.65-1.9	1.75-2

*Data from Zaltsman (1961).

Recently the value of 'trimix' in deep diving has been confirmed during dives to 720 fsw at Duke University. Compression to 720 fsw in 20 minutes induced signs and symptoms of marked HPNS when using oxygen-helium alone, including the appearance of marked tremor, nausea, dizziness, and performance decrement. However, when 25% nitrogen was added to the oxygen-helium, then compression in 20 minutes did not cause tremor or other HPNS signs or symptoms (Fig. 9). Indeed, even rest tremors at atmospheric pressure prior to the dive were less at 720 fsw. These experiments are continuing with further studies at 1000 fsw.

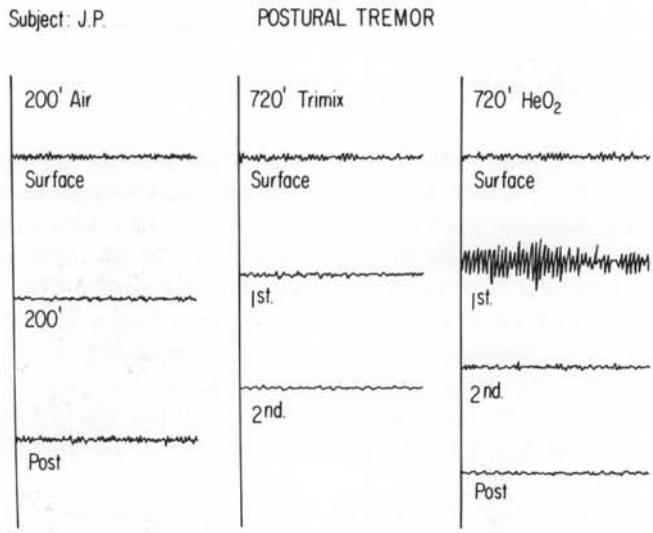

Fig. 9. Postural tremor measurements from a Grass SPA transducer on the index finger in a subject exposed to either air at 200 fsw, 25% N_2:75% He:0.5 ATA O_2('trimix') or helium-oxygen (0.5 ATA). The compression rate was 60 ft/min with 1-minute stops at 50 fsw, 240 fsw, and 600 fsw. The nitrogen suppresses the resting tremor during the air dive and prevents the increase in tremor seen during the helium-oxygen dive by virtue of its presence in the 'trimix' (25%) (Duke University Experiments, August 1973).

Other methods of postponing the development of HPNS are already in widespread use. There is no question that rapid compression rates not only generate the HPNS complex at shallower depths, but also augment the intensity of the symptomatology (Dossett and Hempleman 1972; Lever, Miller, Paton, Street, and Street 1971; Ornhagen and Lundgren *in press*). Conversely, slowing of compression rates has been shown to have opposite effects (Brauer 1972; Dossett and Hempleman 1972; Parker 1969; Summit et al. 1969). Additionally, Bennett and Towse (1971a, b) have suggested that staged compression offers definite advantages over continuous compression. In their experience rest stops during which the CNS might *accommodate* to pressure have led to decreased symptomatology. To date the choice of any particular rate of compression has been empirical or arbitrary. However, based on Kylstra's concepts of osmotic gradients caused by dissolving gases, Fructus et al. (*in press*) have devised a method of calculating optimum compression rates.

$$\frac{dP}{dt} = \frac{\text{Log } 2xG}{T(1 - G')} \tag{1}$$

where P = depth, T = tissue half time, G(P) = proposed gradient function, and $G' = dg/dP$. Their method takes into account the necessity of maintaining a given gradient of dissolved gas tension between the fastest and slowest tissues of the body, the gradient being a function of depth.

A further method of ameliorating or preventing HPNS is to use excursion diving from a saturated depth. It has been observed that decompression from excursion dives permits quite large excursions without the need for stops (Bornmann 1971). In the same way, excursion dives appear to provide one way to dive deep with fast compressions but without undue HPNS (Bachrach and Bennett 1973a). The technique involves compression to a saturation depth, as described previously, followed some hours later by a fast compression to a work depth 150 fsw or so deeper, at rates which would not be possible from the surface. With such techniques it may be possible, for example, to make no-decompression excursions to 1400 fsw from 1000 fsw. However, it has not yet been ascertained whether or not HPNS would result with standard rates of compression of 60 ft/min.

It is known that rates of 100 ft/min to 300 fsw do not elicit HPNS (Bennett and Towse 1972) and that rates of 50 ft/min to 600 fsw will cause the syndrome (Bachrach and Bennett 1973b) as will 16.7 ft/min to 600 fsw and from 600 fsw to 1000 fsw and also from surface to 1000 fsw (Bennett and Towse 1971a, 1971b). Indeed, even rates as slow as 3.4 ft/min to 800 fsw, as used in the New London experiment, elicited the classic EEG changes of HPNS (Proctor et al. 1972). With such a slow speed, computer analysis showed EEG changes at 400 fsw and deeper.

During the latter experiment, excursions were made at 27 and 28 ft/min from 800 to 1112 fsw, and 800 fsw to 1050 fsw which resulted in weakness and slight tremors. A slower rate of 17 ft/min a day later did not produce tremor. Neither did the very similar rate of 16.7 ft/min used by Buhlmann et al. (1969) in excursions from 1000 fsw to 1150 fsw. However tremor, as shown by a decrement in the ball bearing test, was seen on compression from the surface to 1000 fsw. The results of the RNPL dive (Bennett and Towse 1971a, b) suggest that in some individuals, at least, a rate of 16.7 ft/min from 1000 fsw to 1100 fsw and 1300 fsw to 1400 fsw will cause EEG changes and tremor.

Recently at Duke University an experiment known as Deep Work 1000 (Bachrach and Bennett 1973a) involved the compression of six men to 870 fsw over 2 days with four stages and three rates of compression of 25 ft/min (0-450 fsw), 10 ft/min (450-600 fsw) and 2 ft/min (600-870 fsw). During the 4 days at 870 fsw three of the subjects together made excursions to 1000 fsw on different days at 16.7 ft/min, 50 ft/min, and 100 ft/min. Of the 2 hours at depth, during the first 20 minutes, measurements were made of postural and intention tremor, EEG, and performance at the ball bearing test, Wechsler Bellevue Digit Symbol Test, Purdue Peg Board, and arithmetic. One of the subjects then carried out various tasks and postural-tremor tests underwater. A further test battery was applied at the end of the 2 hours. There was no significant increase in tremor and this was substantiated by no significant psychomotor decrement (Table 4), regardless of the rate of compression. The EEG showed no evidence of a compression-induced rise in theta activity (4-6 Hz) but there was a reduction in the overall EEG energy, which was more evident in the alpha and beta frequencies than delta and theta.

This is interpreted as showing that such excursions do not elicit the signs of HPNS induced by over-rapid compression but that the depression of the EEG due to hydrostatic pressure is present. Further it was concluded that a standard excursion compression rate of 60 ft/min from 870 fsw would be unlikely to precipitate serious HPNS. Additional study is needed before this may be extrapolated to depths beyond 1,000 fsw for it would seem that

TABLE 4

Performance efficiency during excursion from saturation at 870 fsw to 1000 fsw at 100 ft/min

Test		Predive test 4	870 fsw (Pre-excursion)	Arrival at 1000 fsw 100 ft/min	1¾ hrs at 1000 fsw 100 ft/min
Ball-bearing	Mean	15.67	19.00	18.33	18.33
	SD	±3.79	±2.08	±2.08	±2.08
Pegboard	Mean	28.67	32.67	31.33	30.00
	SD	±3.26	±4.73	±4.51	±1.00
Visual analogy	Mean	47.00	49.33	51.00	48.33
	SD	±6.25	±5.51	±7.00	±2.31
Arithmetic Correct	Mean	11.00	8.00	9.00	13.33
	SD	±5.57	±8.89	±7.81	±8.08

the deeper the saturation depth, the slower must be the rate of compression to excursion depth and the greater the excursion depth from the saturation depth, the slower must be the rate of compression.

For example, in the 1500-fsw RNPL dive, confusion and a sense of impending loss of consciousness were experienced by one subject at 1535 fsw (Bennett and Towse 1971a, b) during a recompression from 1170 fsw to relieve vestibular decompression sickness in another subject. The pressure was increased in a series of short compressions and stages over 8½ hours. However, only 10 hours were spent at 1500 fsw and the 20-hour cycle of EEG change was continuing during the decompression, which may have been partially responsible for the effects. Nevertheless, even though 3 days had been spent deeper than 1000 fsw, the subject was unable to tolerate, even with such a slow rate of compression, a 365-fsw excursion from 1170 fsw.

Clearly much more research is required in this critical area, with careful measurement of HPNS to identify the operationally optimum rates of compression both for deep-saturation and excursion dives.

SUMMARY

In summary, then, the high pressure nervous syndrome has the following characteristics in a variety of invertebrates and vertebrates, including man. It usually appears at depths somewhat greater than 500 fsw. Involving primarily the central nervous system, its symptoms are manifested as neuromuscular disturbances (incoordination, fasciculations, tremors) or as disturbances of higher cerebral function (disorientation, microsleep, convulsions [in animals]). These neurological aberrations can be correlated to some degree with changes in the electroencephalogram. The development and intensity of HPNS is augmented by rapid compression to depth. This entity seems to be a manifestation of some aspect of hydrostatic pressure per se, rather than the result of other more indirect effects of increased ambient pressure. The use of anesthetic gases and anticonvulsants may offer some degree of *protection* against this phenomenon. HPNS is a serious factor that must be considered in human diving to great depths.

To the authors it appears that what has been called high pressure nervous syndrome may be in reality two (or more) different processes producing a single clinical picture. The signs and symptoms described are not specific but are, rather, a general indication of excitation of the central nervous system. It becomes obvious that rapid compression to depth can produce or augment this clinical picture. Osmotic gradients created by dissolving gases offer one plausible explanation for this *compression syndrome*. However, osmotic gradients equilibrate, and the persistence of symptoms, signs, and EEG alterations after very prolonged times at depth cannot be satisfactorily explained on the basis of such a phenomenon, which would be expected to be transient. This stable picture seen after prolonged times under pressure might be termed the *hydrostatic pressure syndrome* to distinguish it from the effects of compression. This latter phenomenon is most probably caused by some action of hydrostatic pressure per se, although the exact mechanism of this action is not fully understood. The distinction seems appropriate, for manipulation of compression rates will affect only the compression syndrome, while pharmacologic agents might be expected to have their greatest usefulness in ameliorating the hydrostatic pressure syndrome.

Lambertsen (1973) has demonstrated that gas density will probably not be the limiting factor in deep diving. Simulation of the density equivalent of helium-oxygen atmospheres at 5000 fsw has been accomplished in humans. These subjects were able to function despite the burden placed on their respiratory and cardiovascular systems. Thus the high pressure nervous syndrome would seem to be the factor that will set the ultimate depth limit for human divers. Even so, that limit becomes increasingly hard to predict with the advent of advancing knowledge of HPNS and the means to ameliorate or prevent it. Further, and perhaps of even greater importance, is the fact that this knowledge can be used to develop safer techniques for shallower diving by using such concepts as mixed gas with three or more gases and excursions.

Such a mixed gas system should be much safer for short-duration shallow and deep diving, permit fast compression times, be less expensive than pure helium dives, and, in addition, help to overcome the problems of voice distortion and the necessity of supplying heat due to the intrinsic thermal conductivity problems of helium alone. Decompressions should also be rapid for short deep-dives (Workman 1963). Here, then, may be the solution to many of the problems which have limited diving safety and depth in the past decade and should be an area of increasing research interest in the years ahead.

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