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High pressure nervous syndrome: psychometric and clinico-electrophysiological correlations

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The high pressure nervous syndrome (h.p.n.s.) was studied in man from clinical, electrophysiological and psychometric viewpoints during a variety of simulated dives to depths deeper than 300 m (between 300 and 610 m), which used different modes of compression and different gas mixtures (Heliox, Trimix). In particular we studied tremor, myoclonia, changes in electroencephalogram and psychometric performance. Three points stemmed from these results.

(1) Some h.p.n.s. signs are present whichever technique is used, while others depend on the technique, both in intensity and in quality; so there is a syndrome due to compression, whose effects diminish, and a pressure syndrome, which persists at depth.

(2) There are differences between the susceptibility of different individuals, not only concerning h.p.n.s. as a whole, but also each symptom and its evolution at a given constant depth.

(3) There are no close correlations between the different symptoms observed.

Introduction

The high pressure nervous syndrome (h.p.n.s.) in man, as described by Brauer *et al.* (1969), after several dives made to more than 300 m with a helium–oxygen mixture (Heliox) includes a whole group of clinical and electroencephalographic (e.e.g.) signs.

The principal clinical symptoms are: tremor with rapid frequency (8–12 Hz), dysmetria, fasciculations and myoclonia (which occur without any e.e.g. modifications) and daytime drowsiness.

The principal e.e.g. symptoms are: the appearance of slow waves in bursts (most often θ-frequency; they especially occupy the anterior regions of the scalp), a reduction in the amplitude of the posterior α-rhythm and the occurrence of microsleep accompanying the decrease in the level of vigilance noted in the clinical observations.

Complementary symptoms have subsequently been added, in particular the possibility of dizziness and nausea, a relative reduction of the psychomotor performance (Bennett & Towse 1971; Hugon *et al.* 1983; Hugon & Fagni 1981) and a lightening of night-time sleep (Rostain & Lyagoubi 1971; Serbanescu *et al.* 1969; Rostain *et al.* 1973; Bennett *et al.* 1975; Rostain 1980).

Epileptic seizures, preceded by myoclonia and accompanied by e.e.g. paroxysmal discharges, are not found in h.p.n.s. in man, whereas they are one of the characteristics of the h.p.n.s. in the sub-human mammal (Rostain 1973). The fact that man has not yet had any epileptic seizures in deep dives can certainly be explained in part by the fact that man has been submitted to lesser depths than animals.

In 1969, when h.p.n.s. was first described, the various symptoms were thought to be due

to the pressure, without taking into account the role of other parameters such as the composition of the gas mixture, or the compression speed and profile.

It was even thought that man could not go beyond depths of 365 m without suffering damage. Thanks to research done with sub-human mammals and in man, in different hyperbaric centres in France, in England and the U.S.A., it has been demonstrated that this limit could be extended and it is now known that man can work in the sea without too much difficulty at a depth of 500 m (French experiment in the Mediterranean in 1978) and work and live safely in a chamber under pressure beyond 600 m (610 m in France, the Physalie VI experiment in 1972, and the Sagittaire IV experiment in 1974 at the Comex in Marseilles (Rostain & Naquet 1974, 1978); and deeper in the U.S.A. and U.K. during experiments reported in this symposium).

The data presented in this paper are based on 20 experimental dives, made at either Comex in Marseilles, or at the French naval station in Toulon. The gas mixture was helium–oxygen in 13 dives (33 subjects) and helium–nitrogen–oxygen in 7 others (30 subjects). Only the experimental dives in which subjects reached or went below 300 m are taken into account (63 subjects, 300 m; 38, 400 m; 24, 450 m; 8, 500 m; 4, 610 m) (Rostain & Naquet 1974, 1978; Fructus *et al.* 1976; Rostain *et al.* 1980; Naquet 1982).

These experiments have shown that the intensity and the type of symptoms vary according to the experimental conditions and the subjects tested, and they have made it possible to establish several general rules.

Rate and compression mode effects

The compression curves without intermediate stages are less favourable than those interrupted by stages. When stages exist, the compression curves are more favourable when they are slow and exponential than when they are linear. For equivalent compression speeds, and especially at high ones, the effects increase at greater depths (Corriol *et al.* 1973; Hunter & Bennett 1974; Rostain & Naquet 1974).

The following examples, with Heliox, illustrate these points. During the Physalie VI and Sagittaire IV experiments (Rostain & Naquet 1978) the compression speeds were identical up to 550 m and the e.e.g. modifications in the different subjects were similar from one experiment to another. Between 550 and 610 m, the compression speed was three times faster and the e.e.g. changes five times greater during the Sagittaire IV experiment.

During the Physalie V experiment, compression was much faster between 350 and 400 m and between 460 and 490 m than between 400 and 460 m and 490 and 518 m. Up to 460 m, tremor did not increase more than 200% for the two divers during compression and at the stages. Between 460 and 490 m, both divers showed a very marked increase in tremor, which exceeded 600% for one diver (Rostain & Lemaire 1973).

In contrast, during the Physalie VI experiment, where the compression was slower (610 m was reached in 231 h) and where linear compressions were suppressed, tremor, which appeared between 200 and 300 m, did not increase more than 200% up to 610 m.

Also, depending on compression speed, the clinical and e.e.g. symptoms appeared at different depths. The variation was about 100 m for tremor, and 200 m for myoclonia, drowsiness, θ-activities and depression of α-rhythm and microsleep.

Gas mixture type effects

Lever *et al.* (1971) and Miller *et al.* (1973) demonstrated that there is an antagonism between the narcotic agent and the pressure, nitrogen being one of the narcotic agents, and the addition of a certain amount of nitrogen to the helium–oxygen mixture (Trimix) was proposed to avoid the inconveniences of rapid compression in animals (Brauer *et al.* 1974; Miller 1972) and in man (Bennett *et al.* 1974). Although the addition of nitrogen does not abolish the h.p.n.s., as was thought by Bennett *et al.* (1974), the addition of a given quantity of nitrogen to the helium–oxygen mixture modifies the electroclinical symptomatology of the h.p.n.s.

With a mixture containing a sufficient percentage of nitrogen (9% (by volume)) tremor disappears. However, upon arrival at 300 m for rapid compression, behavioural symptoms (euphoria) and increased fatigue occur, the e.e.g. changes are greater than in a Heliox mixture at the same depth, and the power spectra of the slow waves and also of the fast activities are greater than at the surface. Daytime drowsiness is very marked. However, even when the subject remains at a constant depth, the clinical and e.e.g. symptomatology is more transitory than in a Heliox mixture; in general the clinical symptoms disappear in 24 h (Rostain *et al.* 1980).

With a mixture containing a lower percentage of nitrogen (4–5%) and with the same compression curve, the effects of this gas are still noticeable, but the side effects (euphoria, fatigue) are less pronounced (Naquet *et al.* 1975, 1980; Rostain *et al.* 1976, 1980).

A series of experiments was made with this lower percentage of nitrogen in baboons, and a new method of compression and nitrogen introduction was devised (Rostain *et al.* 1978, 1979; Gardette & Rostain 1981). This technique of compression was then used in man in three experimental dives (Operation D.R.E.T. 79/131, ENTEX 5 and 8) up to 450 m, reached in 38 h. The results obtained with 16 subjects showed that clinical signs are minor upon arrival at depth and that e.e.g. modifications are not more important than those recorded during slower compression with a helium–oxygen mixture at the same depth.

The results of psychomotor performance were of particular interest. Some points were already known.

(1) Decrements in performance during the very deep dives to 610 m with a breathing mixture of Heliox were as pronounced as −14% for manual dexterity, −30% for vigilance (visual choice reaction time), −48% for an intellectual test (number ordination) (Lemaire & Murphy 1976).

(2) From a study of the effects at 300 m the best percentage of nitrogen was 4.5%, compared to 0% and 9%, from a psychomotor performance point of view (Charpy *et al.* 1976).

(3) The breathing mixture (pressure of N_2 = 160 kPa) used during the Janus 4 experiment allowed a relatively slight decrement in performance (8 subjects; manual dexterity, −11%; visual choice reaction time, −12%; number ordination, −10%).

After these experiments, a series of 3 dives to 450 m with a 38 h compression was undertaken (see above). The tests in use for the 16 subjects were 2 sensorimotor tests (manual dexterity and visual choice reaction time) and 2 intellectual tests (number ordination and double figure barring, or letter recognition). The tests were always made in the morning, twice during the pre-dive at 10 m and several times at 450 m. The results show an increase in performance between the two series at 10 m. Upon arrival at 450 m, a mean decrement is present for all the tests compared to the last series at 10 m (manual dexterity, −10%; visual choice reaction time, −10%; number ordination, −16%; letter recognition, −22.5%).

Recovery is evident 24 h after the end of the compression, for example, during ENTEX 8, the difference in performance between the two first days is: manual dexterity, +4%; visual choice reaction time, +8%; number ordination, +11%; letter recognition, +12%. Nevertheless, the results obtained for manual dexterity during the pre-dive tests are never reached during the course of the dive, while the pre-dive results for the intellectual tests are reached only at the end of the 12 d sojourn.

These results confirmed that with a relatively slow compression and a helium–nitrogen–oxygen breathing mixture (Trimix), the divers have a slight decrement in psychomotor performance upon arrival at depth. The performance 24 h later is better and proper operational work can be performed.

Susceptibility of different individuals

For a given mode of compression, the symptoms are not reproducible, with the same intensity, from one subject to another. This difference in sensitivity was noted not only with Heliox mixture, but also during the dives with Trimix.

The difference may be very important. For example, some divers may show almost no e.e.g. modifications, at a certain depth, some others may show an increase of the power spectra of the slow waves that may reach 1000%. There are also differences for tremor and psychomotor performance, but they are less pronounced, particularly for the latter.

A tentative study was made of the classification of subjects, based on the e.e.g. data obtained during very fast compression at 180 m and on e.e.g. symptoms found at depths beyond 300 m. The results of this study showed that it is possible to correlate e.e.g. modifications induced by a fast compression at 180 m to the e.e.g. modifications found with a slower compression at 450 m. But no correlation exists between the importance of e.e.g. modifications at 180 m and the psychomotor performance at 180 m, and between importance of e.e.g modifications or tremor and decrease in performance at 450 m. For example, during the three experimental dives at 450 m, upon arrival at the bottom, in certain subjects, there were very marked e.e.g. modifications and few changes in the sensorimotor performance, while in others, the e.e.g. records were very slightly modified and there was a marked deficiency in the psychomotor tests.

The different symptoms of H.P.N.S. are not governed by the same laws

In a given subject, the symptoms do not all occur simultaneously. First, symptoms do not all occur at the same depth for one type of compression; for example, tremor appears between 200 and 300 m, θ-activities between 200 and 400 m, myoclonia, daytime drowsiness and microsleep between 300 and 500 m. Secondly, even for a given depth, symptoms do not occur simultaneously. This is especially true when compression is very rapid. For example, it has been shown that for a compression to 180 m in 15 min, tremor appears immediately, reaches its maximum suddenly, and eventually diminishes over several hours. The e.e.g. modifications appear slowly and may not reach their maximum until 7 h after the arrival at the bottom, while the other symptoms have already begun to diminish (Rostain *et al.* 1980).

If the subject stays at a given depth for a long time, symptoms may vary differently.

(1) Tremor, e.e.g. slow waves, decrease in psychomotor performance, developed during the compression or upon arrival at depth, may diminish during the stay without reappearing during the sojourn. This is particularly true for the psychomotor performance and with the Trimix mixture.

(2) On the contrary, tremor and e.e.g. may vary during the stay at depth: tremor shows circadian variation, more pronounced in the morning than in the evening (Rostain *et al.* 1982, 1983).

(3) E.e.g. and tremor may show variations of a different type. The symptoms may first decrease upon arrival at depth and then increase progressively, or they may show slow variations, accentuation and diminution appearing with a period varying between 4 and 6 d. This is particularly noticeable for the variations of the power spectra of the slow waves.

Conclusions

The h.p.n.s. as it was described by Brauer *et al.* (1969), while remaining valid, must be slightly revised. It seems that some of the symptoms described as characteristic of the h.p.n.s. are more likely to be the consequence of the mode of compression than of the pressure alone, at least for analogous depths. Also, the variability of the symptoms according to the subject and to the mixture used suggests that this should not be considered as a single entity, but as the association of multiple symptoms of different origins.

An analytical description of the evolution of each of the symptoms in relation to the experimental condition (gas mixture, pressure, compression profile) would perhaps contribute to a better understanding of the origin, the significance and the value of each of them. As was demonstrated in animals for some of the symptoms (Fagni *et al.* 1982), it seems too that one cannot consider that the disappearance of a given symptom, owing to the modification of one or several parameters of the compression, necessarily signifies the disappearance of the h.p.n.s.

A very clear demonstration of this fact was shown by the comparison, in different subjects, of the intensity of different symptoms by using a new technique of compression, and a special Trimix mixture. In one subject, e.e.g. and tremor may stay within the limits of normality, and the quality of his psychometric performance may be very affected ($-20\,\%$) and on the contrary, in another subject, the psychometric performance may not be affected very much ($-7\,\%$) while his e.e.g. is very disturbed ($+1300\,\%$ augmentation of power spectra of θ-waves).

At a given depth the difference of evolution of the different symptoms raised the problem of the possibility of acclimatization of one subject to the hyperbaric environment. It seems that, if with Trimix mixture the amelioration of the psychometric performance is faster (4 h for the series of experiments at 300 m) and better than with Heliox, it is not the same, as a rule, for the e.e.g. and the tremor. These latter symptoms may show different patterns of evolution (as was seen for the series of experiments at 450 m), which are not explained at the moment.

If one considers the symptoms induced by the compression and the symptoms at depth, one must admit that many questions have not yet received any answer. Experiments are still necessary to evaluate not only the most significant warning signals for each type of compression used, but also to evaluate the duration at depth that an individual can tolerate. Attempts to select divers, who may work without any problem at great depth, based on e.e.g., have only indicated one warning symptom, which is the appearance of e.e.g. modifications particularly

modifications of the slow waves. It was demonstrated that it is possible to predict only the e.e.g. reactivity of a subject at depth, the correlation with the other symptoms being too variable. It will also be important to know what the best warning symptom is (e.e.g., tremor, decrease in psychomotor performance, or a non-neurological change) if one wants to work at greater and greater depths without any problems.

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Discussion

A. ANGEL (*Department of Physiology, The University of Sheffield, U.K.*). As an invited discussant, I thought that I would save all my questions on today's presentations until now and then be deliberately provocative.

One of the problems I have always associated with the physicochemical theories of anaesthesia is that they imply that anaesthetics work as membrane stabilizers and exert a more, or less, global effect. This is in contrast to the actual effect of anaesthetics upon central nervous cells where they can have an inhibitory or excitatory effect, or indeed exert no effect at all. One other factor that is becoming clearer is that anaesthetics may act in one of two ways, either as anaesthetics *per se* or in a way analogous to the action of the major tranquillizers.

When drawing distinctions upon the effect of pressure on various levels of central nervous system organization, it is perhaps as well to bear in mind that the effector organs are also different, for instance, coelenterate muscle is not capable of giving a twitch-like response and hence these animals could not convulse.

Next, one word has been used repeatedly throughout the day and that is 'convulsion'. There are at least three ways that an animal may convulse; either by cortical cell discharge, or by a brain-stem mechanism, or via a spinal mechanism. These cannot be distinguished by eyeball. So when titrating pressure against a convulsion, such as occurs in h.p.n.s., it seems to me to be mandatory that the right end point be used. This may be important if the effects of high pressure are to be ameliorated chemically. Perhaps an analogous situation would occur if you were titrating a weak acid against a tribasic salt with three different indicators but all showing the same colour change!

Lastly, we come to the subject of the electroencephalogram. This is useful as a tool to show something has changed, but it lacks the ability to say what has changed. The other observation I can make about the e.e.g. is that it is perfectly possible to obtain an animal preparation with

an 'asleep' e.e.g., but for it to be behaviourally awake, and vice-versa an 'awake' e.e.g., but deeply anaesthetized. Perhaps more specific information would be forthcoming if cerebral evoked responses were to be examined.

R. NAQUET. I was very interested by Professor Angel's discussion, which he considers 'deliberately provocative'. But, as you will see, if I am in accord with him in some aspects of his discussion, I am obliged to consider that some of his conclusions seem, to me, contradictory.

I fully agree with Professor Angel that 'there are at least three ways that an animal may convulse' and that it is difficult to distinguish by eyeball the origin of the convulsions. The best way to distinguish between a seizure that starts at the cortical level and those starting at the level of the brain stem or at spinal level is the registration of the electrical activity at the level of these different areas. The e.e.g. registration is also necessary to differentiate an epileptic convulsive seizure (generally starting at the cortical level, neo- or archi-cortex) from a convulsive, non-epileptic seizure (corresponding to a syncopa and accompanied during the convulsion by an electrical silence at the cortical level and a paroxysmal discharge at the level of the brain stem). It is very important that we all agree on what we call a convulsion if we want to progress in the understanding of the effects of hyperbaric pressure, gas mixture, etc., in the nervous system.

Concerning the value of the e.e.g., the example that Professor Angel gives about sleep is true, only if it is separated from a polygraphic study. In fact, we have been learning during the last twenty years that the association of the record of the e.e.g with eye movements, electromyogram, makes it possible without any doubt to differentiate, from the electrical point of view alone, the stage of vigilance of a man or an animal. It is possible to characterize the state of arousal of the subject (agitated or calm, eyes open or closed), the stage of sleep of the same subject (light sleep, deep sleep or paradoxical sleep).

Considering h.p.n.s. again, the e.e.g. has also shown its value. In animals, it helps to distinguish the type of seizure that the animal is having (epileptic or not; if epileptic, focalized or generalized). In man no seizure seems to have been induced, but in the early days of the experiments with high pressure, some inadequate curves of compression were sometimes used and it has been reported that some subjects almost fell into a transitory coma. Here also the correlations between the e.e.g. and the clinical data were very close and the records, from almost normal when the subjects were conscious, became very slow (diffuse θ- and δ-waves) when they were in a state close to coma.

Returning to the data presented in our paper, I consider that it was very important to take into account the appearance of bursts of slow waves (generally in the θ-band, but also in the δ-band) in the frontal region, during compression. I still do not know the origin of these slow waves, but I learnt that they were the consequence of the hyperbaric experiment, because they were particular in shape and localization, and because they were not found in the same subject in normal conditions, at atmospheric pressure, in the same state of vigilance. I also learnt that some subjects were more likely than others to present these e.e.g. modifications during compression, and that for a given subject with the same compression profile and with the same gas mixture, these slow waves reappeared at the same depth.

I am still hoping that it will be possible one day to understand the significance of these particular slow waves, and to appreciate their value as an alarm symptom or not. But in any case their appearance is part of the symptomatology of the h.p.n.s. and cannot be forgotten.