Undersea Biomedical Research, Vol. 1, No. 3, September 1974

Suppression of the high pressure nervous syndrome in human deep dives by $He\text{-}N_2\text{-}O_2$

P. B. BENNETT, G. D. BLENKARN, J. ROBY, and D. YOUNGBLOOD

Department of Anesthesiology and Biomedical Engineering, Duke Medical Center, North Carolina; Harbor Branch Foundation, Florida

Bennett, P. B., G. D. Blenkarn, J. Roby, and D. Youngblood. 1974. Suppression of the high pressure nervous syndrome in human deep divers by $He\text{-}N_2\text{-}O_2$. Undersea Biomed. Res. 1(3):221-237.–Four subjects were compressed to 720 fsw (23 ATA) in 20 min for 1 hour breathing 5.6 N_2-16.9 He ATA with 0.5 ATA O_2 (i.e. N_2 = 25%) and the result compared with exposures to 22.5 He-0.5 O_2 ATA or 7 ATA (200 fsw) compressed air (5.6 ATA N_2). Measurements were made of EEG, tremor, psychomotor and intellectual performance, subjective appreciation, and pulmonary function. Decompression using 0.8 ATA O_2 required 3 days. The same men were also compressed in 33 min to 1000 fsw (31 ATA) breathing N_2-He-O_2 (5.6 ATA N_2 = 18%) or He-O_2 or air at 200 fsw (7 ATA). Decompression took 4 days. At both depths with the trimix, N_2 suppressed completely the tremors noted when diving with He-O_2 alone. Psychomotor tests improved markedly and the nausea and dizziness associated with HPNS did not occur. Some decrement in intellectual function remained. The EEG results showed little change. Subjectively two subjects were HPNS-sensitive and preferred He-N_2-O_2; the other two found that nitrogen narcosis reduced their efficiency. Symptoms of pulmonary oxygen toxicity occurred during the first 24 hours of decompression but disappeared 24 hours later. There was a mean -4.62% reduction in forced vital capacity and +7.4 torr alveolar-arterial gradient post 1000 fsw dive. It is concluded that nitrogen will suppress HPNS but the present partial pressure was too high, causing narcosis and, therefore, needs to be reduced.

HPNS	performance	oxygen toxicity
helium	trimix	deep diving
hydrostatic pressure	nitrogen narcosis	tremor
	anesthesia mechanisms	

When man is exposed to pressures greater than some 16 atmospheres absolute (ATA), such as when breathing oxygen-helium at 500 fsw (16 ATA) and deeper, signs and symptoms of the high pressure nervous syndrome (HPNS) start to appear. These become progressively more severe with increasing depth, particularly as compression rate increases, and are primarily characterized by disorientation, nausea, dizziness, tremors of the hands and arms, an increase in slow wave electrical activity (4-6 Hz) of the brain, and depression of other EEG activity. In man these lead to lapses of consciousness termed microsleep and in animals, convulsions. The etiology of this syndrome has been reviewed recently elsewhere (Bachrach and Bennett 1973; Hunter and Bennett 1974).

In 1961, Zaltsman (1968) noted that these effects with helium at high pressures were considerably different from the narcotic effects of nitrogen and the noble gas series (Bennett 1966; 1969) and, in the course of a protracted series of investigations, seems to be the first to have studied physiological function in men exposed to He-N_2-O_2 mixtures to depths as great as 400 fsw (13 ATA). The characteristic trembling was not observed at shallower depths and only briefly sensed by the subjects starting at a helium partial pressure of 11 ATA. The helium, it was noted, did not intensify the narcotic effects of nitrogen. Experiments continued with air and helium with a maximum nitrogen partial pressure of 4.5 ATA. Under such conditions, at 527 fsw (17 ATA), heavy work between 221-580 kg · m/min was possible with little or no tremors and no thermal-balance or voice-distortion problems.

More recently Brauer and his colleagues (Brauer, Way, Jordan, and Parrish 1971; Brauer 1972; Brauer, Goldman, Beaver, and Sheehan 1974) reported that narcotic gases added to the breathing mixture of animals significantly raises the convulsion-threshold pressure, although they are less effective in regard to the tremor threshold, which seems only half as susceptible to such protection.

The early work of Zaltsman to reduce the narcotic effects of nitrogen by addition of helium was further extended by Smolin, Rappoport, and Kuchuk (1968) who exposed 4 men to mixtures of nitrogen, argon, and helium. Psychological tests and electroencephalogram (EEG) measurements were made with an exposure time of 30-40 min at maximum depth. With an argon-helium mixture (argon 3.5 atm) at 16 atm (530 fsw) difficulty was experienced with the tests due to narcosis but tremors were not observed. The same effect was found at 17.5 atm with an air-helium (nitrogen 5 atm) mixture and this corresponded only to the narcotic action of the 5 atm nitrogen present.

In preliminary studies Vigreux (1970) examined a mixture of 18% O_2, 42% N_2, 40% He, but, although the mixture was useful, it was found to cause respiratory embarrassment during moderate work at about 400 fsw (13 ATA). Accordingly, modifications were made so that at 400 fsw (13 ATA) the mixture was composed of 12% O_2, 12% N_2, and 76% He. This was satisfactory with effective pulmonary ventilation under moderate work and no narcosis.

Unfortunately, these and many of the previous studies give little or no quantitative data. Further, at 400 fsw (13 ATA) HPNS, if present, is only of a very mild nature indeed. At depths greater than 600 fsw (19 ATA) HPNS is more severe and at 800 fsw (25 ATA) and deeper (Bennett 1967; Hunter and Bennett 1974) it can become a serious hazard to the safety of divers operating from oil-drilling rigs or escaping from submarines where fast rates of compression are required so as not to court long decompression procedures.

There are good basic reasons why a narcotic may negate the effects of hydrostatic pressure (HPNS). Bennett, Papahadjopoulos, and Bangham (1967) have shown that increased pressures of nitrogen, oxygen, argon, and carbon dioxide are adsorped by a monolayer of egg-phospholipid. The resulting decrease in surface tension indicates, by application of Regular Solution Theory (Bennett, Simon, and Katz 1974), that a synonomous increase occurs in the membrane volume. Conversely, helium at increased pressures does not adsorp but causes an increase in surface tension and thus a decrease in the volume of the membrane. This is in keeping with contemporary concepts of anesthesia mechanisms (Clements and Wilson 1962; Bangham, Standish, and Miller 1965; Bennett and Hayward 1967; Sears and Fuller 1968; Bennett and Dossett 1970; Miller 1972; Miller, Paton, Smith, and Smith 1973; Bennett, Simon, and Katz 1974). If such theories are correct, then the right amounts of helium (hydrostatic pressure) and nitrogen should result in no change in surface tension or membrane volume and thus neither narcosis nor HPNS.

Pressure reversal of anesthesia has been known for sometime–since the early work with tadpoles of Johnson and Flagler (1950); it has been shown by a number of others in the isolated nerve (Spyropoulos 1957) and in newts and mice (Miller et al. 1973).

In the present study the amount of narcotic, namely nitrogen, to be added to the helium-oxygen was calculated on the basis of the surface-tension measurements described earlier. This suggested that the correct partial pressure of nitrogen required was 5.6 ATA.

The present investigations were made, therefore, to study the protective effects of a narcotic additive such as nitrogen to men breathing oxygen-helium to depths as great as 1000 fsw (31 ATA) and with rapid rates of compression. Further, the experiments were planned to provide a direct comparison of the same subjects both with and without the narcotic additive while a quantitative investigation was made of the signs and symptoms of HPNS.

METHODS

Four young men carried out all of the simulated dives. One (D.Y.) was one of the two clinicians who was responsible for the health and safety of the subjects while they were under pressure. He and the other two Harbor Branch subjects (C.S.; J.P.), had not previously dived greater than 200 fsw. The fourth subject (E.G.) was an experienced commercial diver of Oceaneering Inc., well used to deep oxygen-helium diving as deep as 500-600 fsw (16-19 ATA).

A 20-min test battery was evolved which would detect changes in intellectual function due to narcosis (arithmetic and visual analogy) or psychomotor performance due to HPNS (ball bearing and Purdue Pegboard), together with other measurements of tremor and electroencephalogram (EEG) activity. The subjects were tested extensively prior to the dives so that performance was stable and they were on their learning plateaux.

TEST BATTERY

Tests compatible with earlier work during deep dives to study HPNS (Bennett and Towse 1971a; 1971b) and inert gas narcosis (Bennett 1966) were selected. Thus the arithmetic and visual analogy tests, as indicators of short-term memory and intellectual function, would be likely to be more sensitive to nitrogen narcosis than HPNS. Conversely, due to the hand tremors, psychomotor tests such as the ball bearing and Purdue Pegboard would likely be more sensitive to HPNS rather than nitrogen narcosis.

PERFORMANCE TESTS

1. *Arithmetic.* The subjects were presented a sheet of 40 multiplication problems (e.g. 68 × 9 =) and required to answer correctly as many as possible in 1 min (Bennett and Towse 1971a).

2. *Visual Analogy* (Wechsler Bellevue Digit Symbol Test). The subjects were required to relate symbols to a set of numbers from 1 to 9 given in a key. The score was the number correct in 1 min (Bennett and Towse 1971a).

3. *Ball-Bearing Test.* A subject was required to pick up ball bearings with tweezers and place them, one at a time, in a tube of almost the same diameter. Time for the test was 1 min and the score, the number of balls in the tube (Bennett and Towse 1971a).

4. *Purdue Pegboard.* In 1 minute as many pegs and washers as possible must be assembled correctly on a board. Score was the number of parts assembled, there being 4 parts to each unit (i.e. 1 peg, a flat washer, a thick washer (¼ inch), and another flat washer).

TREMOR

1. *Postural Tremor.* A Grass SPA Tremor Transducer was attached to the middle finger of a subject by a rubber band. The output of this accelerometer was fed to a Grass 6-channel EEG and displayed. In addition it was recorded on tape with a Narco Physiotape recorder No. CDR411 for subsequent further power spectrum analysis.

2. *Intention Tremor.* An instrument constructed at the U.S. Naval Medical Research Institute, Behavioral Sciences Department, was utilized. This requires the subject to hold his finger against a transducer and exert a load of 500 g, guided by red and green lights as to whether too much load or too little is being exerted. The output of the transducer was fed to a tape recorder for subsequent frequency analysis.

ELECTROENCEPHALOGRAM

Spontaneous EEG

Electrodes were attached to the head by collodion after the scalp had been shaved and cleaned with alcohol. They were attached at the vertex and left occipital areas with a ground behind the ear. The output from the electrodes was fed to a Brush 6-channel polygraph and also to an Ampex ½-inch tape recorder. Further, the electrode output was fed to a Nihon Kohden EEG Frequency Analyzer MAF 5 and the analyzed output displayed on the polygraph recording on-line in the activity bands, delta (2-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta 1 (13-20 Hz), and beta 2 (20-30 Hz). Measurements were made for 1 min with eyes open and 1 min with eyes closed.

Visual evoked potentials

Flash stimuli were applied to the darkened pressure chamber through a port by means of a Grass Photostimulator. The resulting evoked cortical potentials from 120 stimuli were averaged and displayed on a Technical Instruments CAT 1000 computer and recorded on an x-y plotter.

During the test battery, all the divers answered a questionnaire developed by Weybrew and Parker (1968) and kept a personal log of their signs and symptoms including the time of onset and site of any arthralgias.

The battery required 20 min to execute and was performed by the subjects immediately on arrival at depth and again 40 min after arrival, immediately prior to the start of decompression. A further control test was made, when possible, immediately on reaching the surface after decompression. During the trimix exposure to 1000 fsw (31 ATA), further tests were given on the change to oxygen-helium at 850 fsw (26.6 ATA) during the decompression.

DIVE PROFILES

Air controls

The subjects were compressed with air at 60 ft/min to 200 fsw (7 ATA) giving a nitrogen absolute partial pressure of 187 fsw (5.6 ATA); time at maximum depth was 30 min and decompression was by modified USN Tables. An air dive of this kind, during which the subjects completed one full test battery for comparison with predive controls, was made prior to each of the 720-fsw (23 ATA) and 1000-fsw (31 ATA) dives of this study.

720 fsw (23 ATA).

Two dives were made to 720 fsw with 60 min at maximum depth. In both cases compression was achieved in 17 min plus a 1-min stop at 50 fsw, 240 fsw, and 600 fsw (2.5, 8, and 19 ATA).

Trimix–In the first dive the subjects were compressed with trimix to give 0.5 ATA oxygen, 5.6 ATA nitrogen (25%), and 16.9 ATA helium. They were transferred, during decompression, into a chamber containing only He-O_2 with an O_2 of 0.8 ATA and decompressed over 77 hours using a modified Bühlmann et al. (1970) schedule with air from 60 fsw (2.8 ATA).

Helium-oxygen–In the second dive, 1 week later, the same subjects were compressed as previously to 720 fsw (23 ATA) breathing 0.5 ATA oxygen and helium throughout, with the decompression as before.

1000 fsw (31 ATA)

Two dives were made to 1000 fsw with 60 min at maximum depth. Compression in both cases was in 27 min plus 1-min stops at 50 fsw and 240 fsw (2.5 and 8 ATA) and 2-min stops at 600 fsw and 720 fsw (19 and 23 ATA).

Trimix–In this first exposure, the four subjects were compressed to give a mixture of 0.5 ATA oxygen and 5.6 ATA nitrogen (18%) and the remainder helium. They were decompressed using a modified Bühlmann et al. (1970) schedule in 97 hours. The subjects were decompressed to 850 fsw (26.6 ATA) breathing the trimix and then transferred to a larger chamber containing only helium-oxygen with the latter at 0.8 ATA. A change to air was made at 60 fsw (2.8 ATA).

Helium-oxygen–One week later the same subjects carried out a dive with only helium and oxygen (0.5 ATA) using the same compression and decompression profile as previously.

PULMONARY FUNCTION TESTS

Due to the high oxygen partial pressures during the decompression, full pulmonary function tests were made and arterial blood samples taken pre- and post- the 1000-fsw dives. Measurements included forced vital capacity, functional residual capacity, total lung capacity, 1-sec forced expiratory volume, maximal mid-expiratory flow rate, Pa_{CO_2}, Pa_{O_2}.

RESULTS

SUBJECTIVE SIGNS AND SYMPTOMS

Subjective signs and symptoms checked by the subjects on the forms supplied and described in their personal logs were analyzed and these are summarized in Fig. 1 on a shaded histogram scale of 0 to 4 as follows:

- 0 - no symptoms
- 1 - barely perceptible or minimal
- 2 - definitely present but mild
- 3 - moderately severe
- 4 - very severe and incapacitating

It may be seen that there was considerably more tremor, dizziness, and nausea in the pure helium-oxygen exposure and except for the most sensitive subject, C.S., none of these were

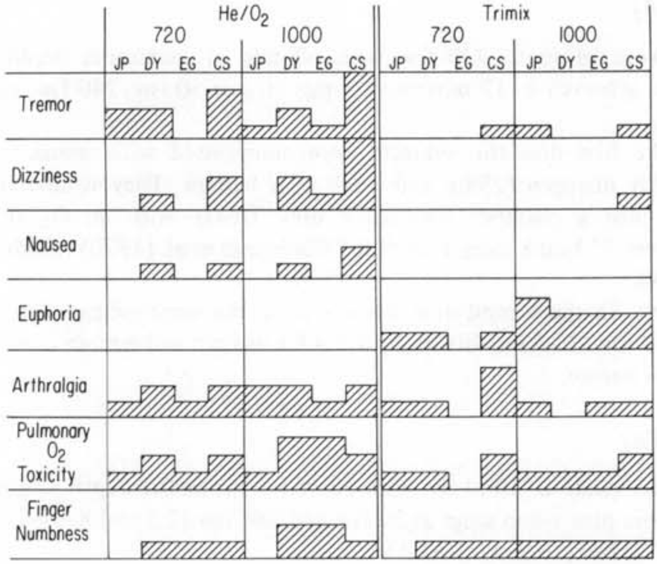

Fig. 1. Subjective experiences of the four subjects during exposure to $He\text{-}O_2$ or $He\text{-}N_2\text{-}O_2$ at 720 fsw (23 ATA) and 1000 fsw (31 ATA). At 720 fsw the N_2 was 25% and at 1000 fsw, 18%.

present with the trimix. On the other hand euphoria, a common symptom of compressed air narcosis, was not present with the helium-oxygen but was reported in subjects breathing trimix containing the narcotic nitrogen and in association with a sensation of "shimmering lights."

During otherwise uneventful decompressions, arthralgias and *popping* joints were slightly less with trimix as were symptoms of oxygen toxicity such as substernal pain on deep inspiration and numbness of the fingers.

The subjective signs and symptoms for trimix at 1000 fsw (31 ATA) compared with helium-oxygen exposure are similar to those at 720 fsw (23 ATA) (Fig. 1) except that the HPNS signs and symptoms were more severe at 1000 fsw (31 ATA) helium-oxygen. Two of the subjects (D.Y., C.S.) felt very nauseated and dizzy so that the dive was aborted 10 min prior to the 60 min planned. Indeed, it was only through considerable will power and cooperation of these two subjects that the dive was prolonged sufficiently to acquire the necessary data. With the 18% nitrogen in the trimix these two subjects felt no nausea and were able to tolerate the exposure comfortably. However, the other two men (J.P. and E.G.) remarked that the euphoria and narcosis from the nitrogen was subjectively higher than that experienced at 200 fsw (7 ATA) with some difference in sensations too. Time for each test seemed much prolonged. As with the 720 fsw (23 ATA) trimix, visual hallucinations of shimmering lights and halos around the chamber light bulbs were reported by J.P. and E.G. The general view was that there was less increase in efficiency with the trimix at 1000 fsw (31 ATA) compared to that noted with the 720 fsw (23 ATA), chiefly due to a more narcotic effect with the 1000 fsw (31 ATA) trimix.

Nevertheless, the divers stated that in spite of the narcosis problem, after such a fast compression they would only have been prepared to work underwater in a real situation outside a submersible chamber if the gas breathed was trimix.

When the change back to $He\text{-}O_2$ was made at 850 fsw (26.6 ATA) during the decompression from the trimix at 1000 fsw (31 ATA), the divers noted dizziness and tremors as the nitrogen came out of their bodies, leaving only helium-oxygen.

PERFORMANCE TESTS

The comparative results for the three subjects who carried out the performance tests are shown in Figs. 2 and 3 for subject C.S., Figs. 3 and 4 for subject J.P., and Figs. 6 and 7 for subject E.G. The odd-numbered figures refer to the dives during which only helium-oxygen was breathed and the even-numbered ones refer to dives where nitrogen was present. The presence of the nitrogen partial pressure in the trimix effectively reduced the marked psychomotor decrement and tremors of the hands found with helium-oxygen alone, as shown by the ball-bearing and pegboard tests. The associated reduction in tremors is discussed in more detail later and further emphasizes the relationship between decrement in tremors and reduction in efficiency with psychomotor tests such as the ball-bearing test.

The math test in general also showed a decrement, although with more variation of the test results. Subject C.S. (Fig. 2) showed a decrement during the breathing of trimix synonomous with that produced by the same partial of nitrogen at 200 fsw (7 ATA) of compressed air. Much the same decrement also was found with the pure helium-oxygen (Fig. 3). This was probably due to the marked HPNS with nausea and dizziness in C.S., who was the most sensitive of the four divers to this syndrome. Thus, for this subject, although the nitrogen did ameliorate the psychomotor decrement of HPNS as shown by the ball-bearing and pegboard tests, there was no similar improvement in intellectual function.

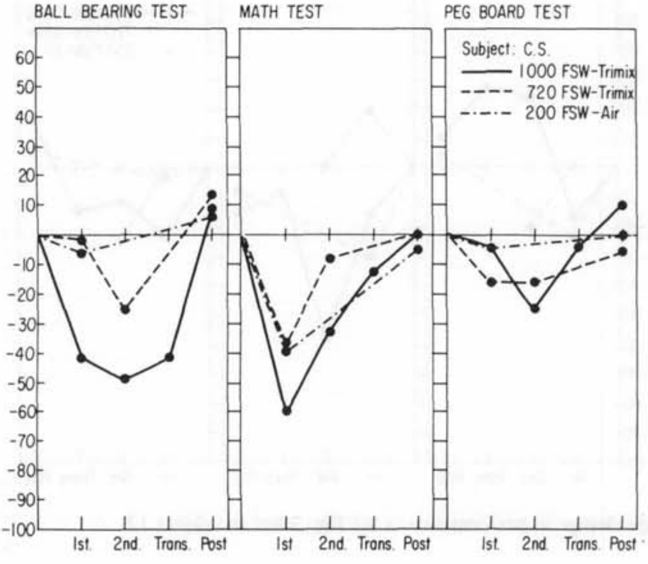

Fig. 2. Percentage changes in test performance of subject C.S. against predive controls during exposure to either air or trimix at 720 fsw (23 ATA) and 1000 fsw (31 ATA); 5.6 ATA N_2 was present in all experiments. The first measurements are on arrival at depth; the second, for the trimix dives only, is after 40 min at depth; and the third point, during the 1000 fsw exposure, is the result of transfer from trimix to helium-oxygen at 850 fsw. The final point is on return to the surface.

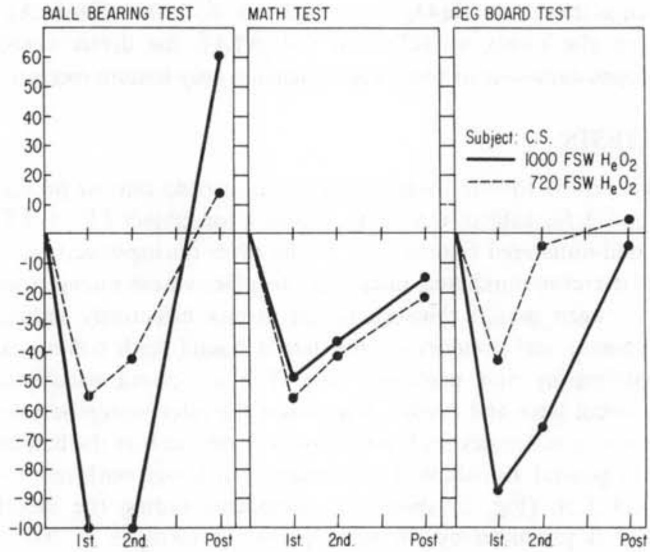

Fig. 3. Percentage change in test performance of subject C.S. during exposure to 720 fsw (23 ATA) and 1000 fsw (31 ATA) while breathing oxygen-helium. The first point is on arrival at depth, the second after 40 min at depth, and the final point on return to atmospheric pressure.

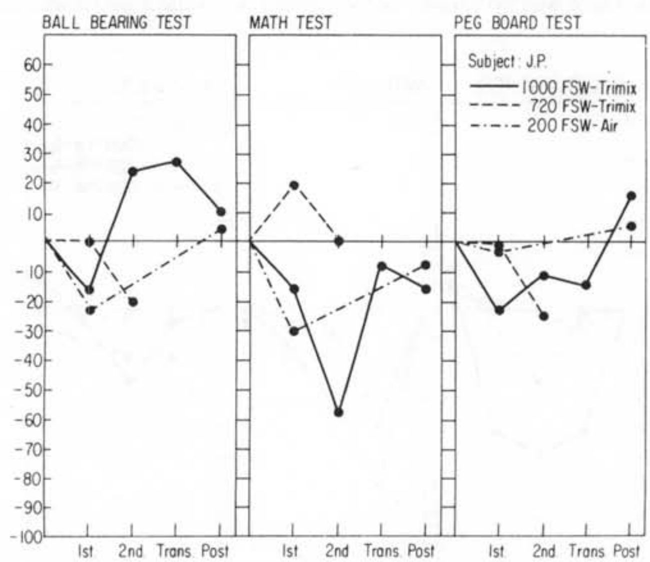

Fig. 4. Percentage change in performance as for Fig. 2 but in subject J.P.

The second subject, J.P., showed a similar result but to a lesser degree (Figs. 4 and 5). This individual showed more decrement in psychomotor performance during his exposure to helium-oxygen at 720 fsw (23 ATA) than at 1000 fsw (31 ATA), which was probably the result of apprehension to his first very deep dive beyond 200 fsw (7 ATA). With trimix, this decrement was reduced, especially in the sensitive ball-bearing test. The math test also reflected the variability of the results of this individual. At 720 fsw (23 ATA) the test was not affected by breathing trimix but at the deeper level of 1000 fsw (31 ATA) the nitrogen presence caused a much greater decrement compared to helium-oxygen alone.

Subject E.G., an experienced commercial deep diver (Figs. 6 and 7), was little affected by the rapid helium-oxygen compression (Fig. 7). He showed only small changes in the tests, except with the most sensitive, the ball-bearing test, on arrival at depth. This is a good example, as perhaps are the results discussed previously for subject J.P., of the value of

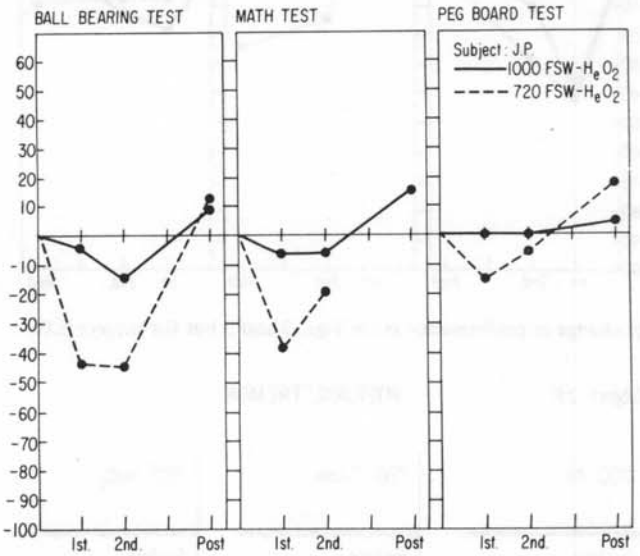

Fig. 5. Percentage change in performance as for Fig. 3 but in subject J.P.

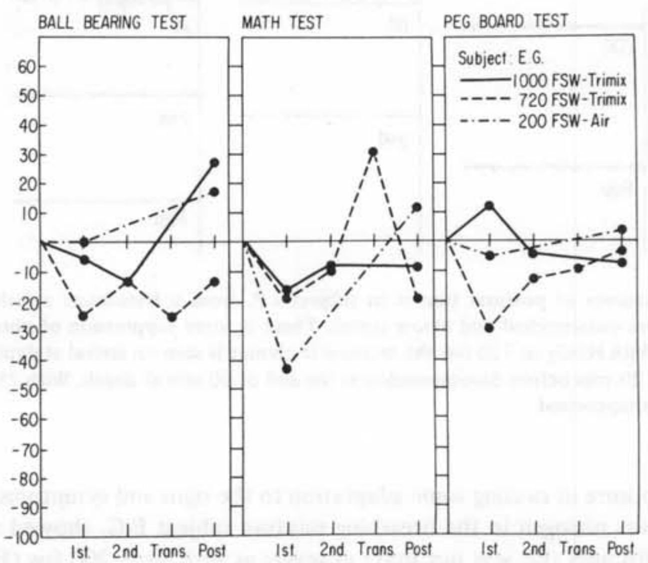

Fig. 6. Percentage change in performance as for Figs. 2 and 4 but for subject E.G.

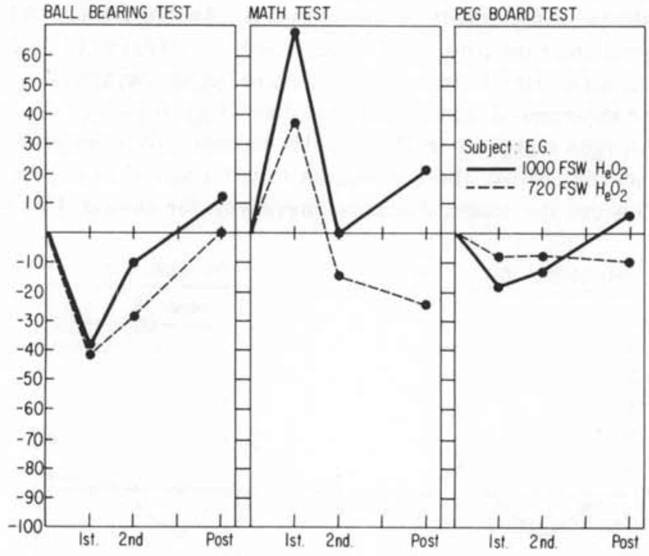

Fig. 7. Percentage change in performance as for Figs. 3 and 5 but for subject E.G.

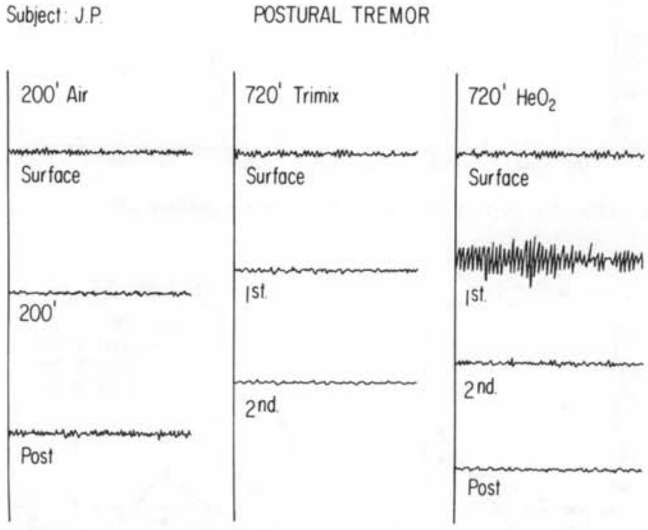

Fig. 8. Measurements of postural tremor in subject J.P. from a transducer attached to the middle finger with the hand outstretched and elbow rested. There is some suppression of normal resting tremor by air at 200 fsw. With $He\text{-}O_2$ at 720 fsw the increase in tremor is seen on arrival at depth with a return to normal during the 20 min before decompression at the end of 60 min at depth. With 25% N_2 (trimix) the increase in tremor is suppressed.

frequency of exposure in causing some adaptation to the signs and symptoms of HPNS.

When there was nitrogen in the breathing mixture subject E.G. showed a decrement on the math test, although this was not quite as severe as with air at 200 fsw (Fig. 6) and there was a minor improvement in the psychomotor tests. Thus, the nitrogen was of little value to this individual and in fact served to make his performance worse by virtue of introduction of nitrogen narcosis.

The visual analogy test indicated only minor variations from controls under the various experimental conditions.

In general the performance tests and subjective sensations indicated amelioration of HPNS psychomotor decrement by the presence of nitrogen but narcosis resulting from the latter resulted in decrement of intellectual function and euphoria.

POSTURAL TREMOR

The results of the output of the tremor transducer at 720 fsw (23 ATA) are illustrated in Fig. 8 for subject J.P., who was between the least affected (E.G.) and the most affected (C.S.) by tremors during the helium-oxygen compression. The characteristic tremor of the

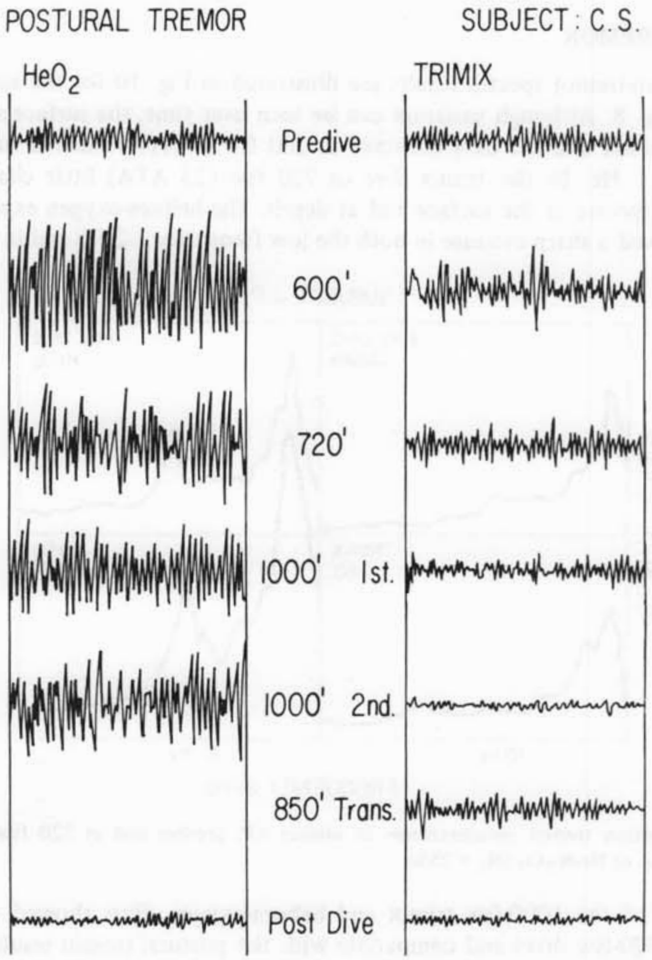

Fig. 9. Postural tremor measurements in subject C.S. during compression with oxygen-helium (He-O_2 or trimix [18% N_2]). Addition of nitrogen for the trimix was begun at 600 fsw. The comparative reduction of tremor is clearly seen. On return from trimix to oxygen-helium at 850 fsw, the tremor returns.

hands due to fast compression is illustrated as is the well-known adaptation during the 30-min break between measurements 1 and 2. Compressed air at 200 fsw (7 ATA) suppresses even the slight resting tremor and the 25% nitrogen in the trimix is very effective at suppression of the tremors elicited by compression to 720 fsw (23 ATA).

The comparative results of the changes in postural tremor during exposure to either helium-oxygen or trimix at 1000 fsw (31 ATA) are illustrated in Fig. 9 in subject C.S. With helium-oxygen there was a large increase in postural tremor as compression proceeded up to 600 fsw (19 ATA) and then was generally no worse from there to 1000 fsw (31 ATA). With trimix and the presence of 18% nitrogen the tremors were markedly suppressed, although there was still evidence of adaptation effects during periods 1 and 2 at 1000 fsw. During decompression on transfer from trimix to helium-oxygen at 850 fsw (26.6 ATA) the tremors returned. The other two subjects were not as severely affected but illustrated similar changes to varying degrees as next described for the intention tremor results.

INTENTION TREMOR

The intention-tremor spectra results are illustrated in Fig. 10 for the same subject, J.P., described in Fig. 8. Although variation can be seen over time, the surface sample taken just before compression and the data collected at 200 fsw (7 ATA) showed suppression of the peak around 11 Hz. In the trimix dive to 720 fsw (23 ATA) little change was seen in comparing the spectra at the surface and at depth. The helium-oxygen exposure to 720 fsw (23 ATA) showed a sharp increase in both the low frequency 1-2 Hz and in the 11-Hz range.

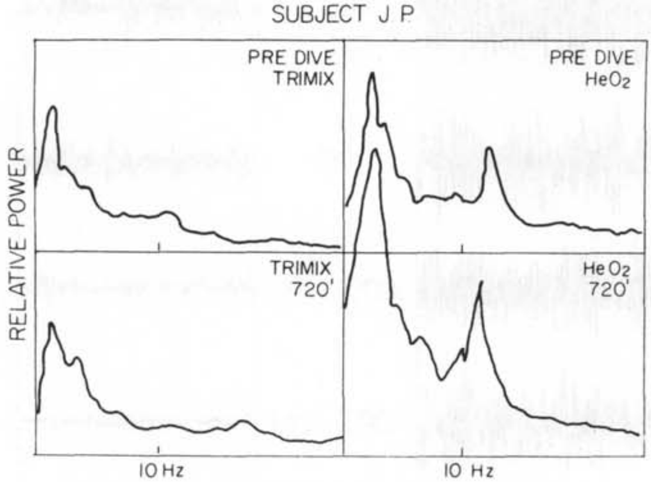

Fig. 10. Intention tremor measurements in subject J.P. predive and at 720 fsw (23 ATA) during exposure to $He\text{-}O_2$ or $He\text{-}N_2\text{-}O_2$ (N_2 = 25%).

The results of the 1000-fsw trimix and helium-oxygen dives showed results (Fig. 11) similar to the 720-fsw dives and compatible with the postural tremor results above. Subject E.G. exhibited little change on either dive. C.S.'s plots showed increases in tremor on both trimix and $He\text{-}O_2$ but a greater increase was seen with $He\text{-}O_2$. No changes were seen on subject J.P.'s spectra during the trimix dive, but increases in the 9-11 Hz area while on the $He\text{-}O_2$ dive were exhibited.

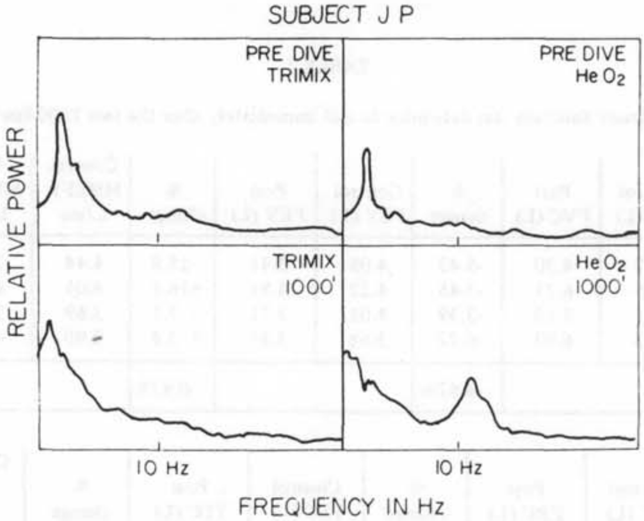

Fig. 11. Intention tremor measurements in subject J.P. predive and while breathing either trimix (18% N_2) or oxygen-helium at 1000 fsw.

ELECTROENCEPHALOGRAM

The EEG analysis showed little variation from normal with either He-O_2 or trimix at 720 fsw (23 ATA). In general the mean activity showed a slight rise, which is in keeping with earlier studies reported in man at 450 fsw and 600 fsw (14.5 and 19 ATA) (Bennett and Towse 1971b). The two deep dives often indicated different effects, however, from the air exposure to 200 fsw (7 ATA). With delta (2-4 Hz) and theta (4-8 Hz) activity, the air dive showed a rise of some 20% with eyes open whereas there was little change with the deep dives. Theta showed a similar rise with the trimix but not with the helium-oxygen. With alpha (8-13 Hz) and beta (13-20 Hz) activities, however, there was generally a rise in activity which was not seen with air at 200 fsw (7 ATA).

Visual evoked potentials were not affected in any significant manner during exposure to these pressures and there was not sufficient difference between the compressed air and results with trimix to enable any firm statements to be made.

With eyes open, the helium-oxygen at 1000 fsw (31 ATA) resulted in an average increase of 25% in all activities. This was less pronounced with trimix for the delta (2-4 Hz) and beta (13-30 Hz) activities and only alpha (8-13 Hz) and theta (4-8 Hz) showed such a rise.

With eyes closed, there was no significant change with trimix but with helium-oxygen there was a rise in alpha and beta activity and a depression of theta.

OXYGEN TOXICITY AND PULMONARY FUNCTION

During the first day of decompression with 0.8 ATA oxygen, the subjects experienced symptoms of oxygen toxicity such as substernal pain on deep inspiration and numbness of fingers and/or toes. However, the substernal pain was not of sufficient severity to concern the subjects unduly. By the second day the signs and symptoms were markedly ameliorated and graudally became less or nonexistent throughout the remainder of the 4 days of decompression.

TABLE 1

Pulmonary function test data prior to and immediately after the two 1000-fsw dives

Subject	Control FVC (L)	Post FVC (L)	% change	Control FEV (L)	Post FEV (L)	% change	Control MMEFR L/sec	Post MMEFR L/sec	% change
DY	4.97	4.70	-5.43	4.05	3.41	-15.8	4.44	2.47	-44.3
EG	6.95	6.71	-3.45	4.22	4.91	+16.4	4.04	4.66	+15.4
JP	5.31	5.13	-3.39	4.01	3.71	- 7.5	3.69	2.95	-20.1
CS	6.43	6.03	-6.22	3.68	3.81	+ 3.4	2.90	4.50	+55.2
Mean			-4.62%			-0.87%			+ 1.6%

Subject	Control FRC (L)	Post FRC (L)	% change	Control TLC (L)	Post TLC (L)	% change	Control A-a torr	Post A-a torr
DY	3.12	2.78	-10.9	6.13	5.73	-6.53	20.0	32.0
EG	4.10	3.98	-4.9	9.32	8.34	-10.5	25.5	36.0
JP	2.90	2.30	-20.7	6.77	6.34	-6.35	37.5	44.5
CS	3.97	3.80	-4.3	8.06	7.32	-9.19	29.5	29.5
Mean			-10.2%			-8.14%	28.1	35.5

The pulmonary function data are shown in Table 1. All subjects manifested small restrictive-type defects as supported by reductions in the forced vital capacity (4.62%), functional residual capacity (10.2%), and total lung capacity (8.14%). In addition to this evidence of restrictive defects, two subjects had evidence of small airway obstruction to expiration as supported by reductions in the 1-sec forced expiratory volumes (15.8% and 7.5%) and the maximal mid-expiratory flow rates (44.3% and 20.1%). The other two subjects evidenced less obstruction to air flow than in the control in predive measurements. Subject C.S. had mild bronchitis at the time of the initial pulmonary function tests. The existence of this condition at this time might explain why he had no increase in his alveolar-arterial (A-a) oxygen gradient following the 1000-fsw (31 ATA) dives. There was a significant and meaningful increase in the A-a gradient in the other three subjects relative to their control values.

DISCUSSION

It is clear from these results that trimix is effective in ameliorating signs and symptoms of HPNS as deep as 1000 fsw (31 ATA) although, in the present investigations, there is evidence that the inspired nitrogen partial pressure of 5.6 ATA in both trimix dives was too high and resulted in signs and symptoms of inert gas narcosis. These results are similar to those of an earlier study by Smolin et al. (1968) described in the introduction. Further, there was a significant interindividual variation in susceptibility to HPNS as has been reported during earlier studies (Bennett and Towse 1971b). Of the four subjects, two (E.G.

and J.P.) were not very sensitive to the high hydrostatic pressure and fast rates of compression with helium-oxygen and experienced only very mild HPNS signs and symptoms. These two subjects would have been capable of performing work at 1000 fsw (31 ATA) after only a surprisingly short compression compared with U.S. Navy practice and earlier deep dives summarized in the reviews by Bachrach and Bennett (1973) and Hunter and Bennett (1974). When breathing trimix, however, these two subjects appeared more sensitive to the nitrogen narcosis than the other two subjects.

Conversely, the other two men (C.S. and D.Y.) were highly sensitive to the HPNS, feeling dizzy, nauseated, and on the verge of vomiting. They were very pleased to have the ameliorating effects of the nitrogen in spite of the narcosis, especially as the compressed air narcosis was in general slightly less than that expected for compressed air at 200 fsw (7 ATA).

Recently, application of Regular Solution Theory to anesthesia mechanisms (Bennet et al. 1974) has emphasized that the *cohesive energy* of the anesthetic site δa is equal to 4.3 $(cal/cm^3)^2$. This is much more compatible with olive oil as a model system rather than egg phospholipid. If olive oil is used as the substrate, then it can be calculated that the correct proportion of nitrogen to helium should be 1:10 if there is to be no change in volume of the substrate. On this basis, it is not surprising that nitrogen narcosis occurred when the nitrogen percentage was 18% at 1000 fsw (31 ATA) and further experiments with only 10% nitrogen are likely to be more successful.

The expected antagonism of the narcosis by hydrostatic pressure also occurred only to a minor extent of that implied in the earlier work of Zaltsman (1968). That such pressure reversal of narcosis may well be possible in man is indicated, however, in experiments by Proctor, Carey, Lee, Schaefer, and van der Ende (1972). During decompression from a 1000-fsw (31 ATA) dive, the divers breathed 3.5 atm nitrogen, 1-1.5 atm oxygen, and the remainder helium for 10 min at 600 fsw, 400 fsw, 240 fsw and 200 fsw (19, 13, 11, and 7 ATA). At 19 ATA there were no signs or symptoms of narcosis but at pressures less than that nitrogen narcosis occurred. Perhaps at 19 ATA the pressure was sufficient to antagonize the action of the narcotic nitrogen but not at the lower pressures.

The evidence of this present study is that although there was some indication of pressure antagonism of the narcosis it was very little and much higher pressures are required to negate the narcosis due to 7-ATA compressed air.

The subjective phenomena of induced tolerance to high inspired tensions of oxygen after 24 to 36 hours of exposure is surprising. However, the early symptoms of pulmonary oxygen toxicity originate from the large airways and their abatement does not necessarily imply that tolerance and a reversal of known pathological change is occurring peripherally in noninervated lung units. It also is somewhat disconcerting to see small but significant and consistent impairment in pulmonary function and alveolar-arterial oxygen gradients at a time when all the subjects reported freedom from all respiratory symptoms.

In this respect it is interesting to note that subject J.P. emphatically denied the development of respiratory symptoms at any time during the last 1000-fsw helium control dive, yet he had the largest arterial-oxygen gradient postdive (arterial PO_2 was the lowest at 52 mmHg). He was also the only diver who complained of postdive chest tightness. Is this further evidence of the dissociation between symptoms and what is actually going on in the lung pathologically, or does it represent interindividual variability of pathophysiologic responses that were observed in the other phenomena such as HPNS and narcosis? This merely underlines the need for more studies and for the development and use of better ways to assess disturbed tissue and organ function during exposure to high oxygen pressures.

In connection with this subjective adaptation to pulmonary toxicity it is relevant that Bradley and Vorosmarti (1968) have reported that experienced divers were somehow hematologically less sensitive to hyperbaric oxygen through frequent exposure to compressed air. Again, in the Tektite II experiment (Miller, Vanderwalker, and Waller 1971) there was a 35% incidence of pulmonary oxygen toxicity with substernal pain in the chest during 20-hour decompression schedules in which 100% oxygen was breathed for 5½ hours. However, during a similar decompression in a Hydrolab study (Widell 1973) there was no symptomatology or changes in vital capacity. The only difference was that the latter study involved 7 days at depth with an increased oxygen partial pressure of 367 mm Hg before the decompression, while in TEKTITE the oxygen was 150 mm Hg. Perhaps this is further evidence of adaptation to high partial pressures of oxygen during saturation-type exposures, possibly due to changes in the blood morphology.

Finally, it is necessary to comment on the wide interindividual variability of the divers to HPNS effects. This was noted also in an early deep dive (Bennett and Towse 1971a, b). The reasons must await a better understanding of the mechanism of HPNS but it would seem advisable, on the basis of the information to date, that investigators involved in sending divers to depths in excess of 500 fsw (16 ATA) should select those who are least sensitive to the effects of pressure and rapid compression as well as incorporating a certain amount of nitrogen or other narcotic. However, if nitrogen is used, it should be less than 5.6 ATA and probably closer to 10% at 1000 fsw (31 ATA) than the 18% of the present study.

We would like to take this opportunity to thank the four subjects of these studies, Dave Youngblood, Erik Geerts, Jeff Prentice, and Chris Swann for their excellent support throughout this study, without which the work could not have been done.

Grateful appreciation is extended to the Harbor Branch Foundation who assisted the project to a major extent financially and also with staff; to Oceaneering International, Inc., for their support and to the technical staff of the Duke Hyperbaric Chamber Complex for the efficient and safe operation of the diving systems. The production of this paper and the research involved was supported in part also by Public Health Service Grant H107896-11 and by the Office of Naval Research Contract N00014-67-A-0251-0022 with funds provided by the Naval Bureau of Medicine and Surgery.

We would like also to thank Dr. A. J. Bachrach, Chairman, Behavioral Sciences Department, Naval Medical Research Institute, and his co-workers for the loan of the intention tremor apparatus and for subsequent analysis of the data tapes and production of Figs. 10 and 11.

Received for publication July 1974.

REFERENCES

Bachrach, A. J., and P. B. Bennett. 1973. Tremor in diving. Aerosp. Med. 44:613-623.

Bangham, A. D., M. D. Standish, and N. Miller. 1965. Cation permeability of phospholipid model membranes. Effects of narcotics. Nature 208:1295-1297.

Bennett, P. B. 1966. The aetiology of compressed air intoxication and inert gas narcosis. Pergamon, Oxford.

Bennett, P. B. 1967. Performance impairment in deep diving due to nitrogen, helium, neon, and oxygen. *In* C. J. Lambertsen, ed. Underwater physiology. Proceedings of the third symposium on underwater physiology. The Williams & Wilkins Co., Baltimore, Md.

Bennett, P. B. 1969. Inert gas narcosis. *In* P. B. Bennett and D. H. Elliott, eds. The physiology and medicine of diving and compressed air work. Bailliere, Tindall, and Cassell, London.

Bennett, P. B., and A. N. Dossett. 1970. Mechanism and prevention of inert gas narcosis. Nature 288:1317-1318.

Bennett, P. B., and A. J. Hayward. 1967. Electrolyte imbalance as the mechanism of inert gas narcosis and anesthesia. Nature 213:938-939.

Bennett, P. B., and E. J. Towse. 1971a. Performance efficiency of men breathing oxygen-helium at depths between 100 ft and 1500 ft. Aerosp. Med. 42:1147-1156.

Bennett, P. B., and E. J. Towse. 1971b. The high pressure nervous syndrome during a simulated oxygen-helium dive to 1500 ft. Electroencephalogr. Clin. Neurophysiol. 31:383-393.

Bennett, P. B., D. Papahadjopoulos, and A. D. Bangham. 1967. The effect of raised pressures of inert gases on phospholipid model membranes. Life Sciences 6:2527-2533.

Bennett, P. B., S. Simon, and Y. Katz. 1974. High pressures of inert gases and anesthesia mechanisms. Proceedings symposium: Molecular mechanisms of anesthesia, Raven Press, New York.

Bradley, M. E., and J. Vorosmarti. 1968. Hematological changes resulting from hyperbaric oxygenation in divers and non-divers. Aerosp. Med. 39:493-497.

Brauer, R. W. 1972. Studies concerning the high pressure hyperexcitability in the squirrel monkey. Final report on Contract N00014-69-C-0341. Wrightsville Marine Biomedical Laboratory, Wilmington, North Carolina.

Brauer, R. W., S. M. Goldman, R. W. Beaver, and M. E. Sheehan. 1974. N_2, H_2, and N_2O antagonism of high pressure neurological syndrome in mice. Undersea Biomed. Res. 1(1):59-72.

Brauer, R. W., R. O. Way, M. R. Jordan, and D. E. Parrish. 1971. Experimental studies on the high pressure hyperexcitability syndrome in various mammalian species. *In* C. J. Lambertsen, ed. Underwater physiology. Proceedings of the fourth symposium on underwater physiology. Academic Press, New York.

Bühlmann, A. A., H. Matthys, G. Overrath, P. B. Bennett, D. H. Elliott, and S. P. Gray. 1970. Saturation exposures of 31 ats in an oxygen-helium atmosphere with excursion to 36 ats. Aerosp. Med. 41:394-402.

Clements, J. A., and K. M. Wilson. 1962. The affinity of narcotic agents for interfacial films. Proc. U.S. Acad. Sci. 48:1008-1014.

Hunter, W. L., and P. B. Bennett. 1974. The causes, mechanisms, and prevention of the high pressure nervous syndrome. Undersea Biomed. Res. 1:1-28.

Johnson, F. H., and E. A. Flagler. 1950. Hydrostatic pressure reversal of narcosis in tadpoles. Science 112:91-92.

Miller, K. W. 1972. Inert gas narcosis and animals under high pressure. Sym. Soc. Exp. Biol. 26:363-378.

Miller, K. W., W. D. M. Paton, R. A. Smith, and E. B. Smith. 1973. The pressure reversal of general anesthesia and the critical volume hypothesis. Molec. Pharmacol. 9:131-143.

Miller, J. W., J. G. Vanderwalker, and R. A. Waller. 1971. Tektite II scientists in the sea. Special Report, U.S. Dept. of the Interior, Washington, D.C.

Proctor, L. D., C. R. Carey, R. M. Lee, K. E. Schaefer, and H. van der Ende. 1972. Electroencephalographic changes during saturation excursion dives to a simulated sea-water depth of 1000 ft. Aerosp. Med. 43: 867-877.

Sears, D. F., and E. L. Fuller. 1968. Volume changes of polar and non-polar liquid hydrocarbons exposed to pressures of gases. Respir. Physiol. 5:175-186.

Smolin, V. V., K. M. Rappoport, and G. A. Kuchuk. 1968. Combined effect of inert gases under pressure on man. Pages 178-185 *in* G. L. Zaltsman, ed. Sechenov Inst. Evolutionary Physiol. Biochem., U.S.S.R. Acad. of Sciences, Leningrad.

Spyropoulos, C. S. 1957. The effects of hydrostatic pressure upon the normal and narcotized nerve fiber. J. Gen. Physiol. 40:849-857.

Vigreux, J. 1970. Contribution to the study of the neurological and mental reactions of the organism of the higher mammal to gaseous mixtures under pressure. M.D. Thesis, Toulouse University, France.

Weybrew, B. B., and J. W. Parker. 1968. Performance effects of increased ambient pressure. 1. Helium-oxygen saturation and excursion dive to a simulated depth of 900 ft. Report 556, U.S. Naval Submarine Medical Center, New London, Conn.

Widell, P. J. 1973. Physiological responses of three subjects to a seven-day saturation dive to fifty feet of sea water breathing air. M.S. Thesis, University of Southern California.

Zaltsman, G. L. 1968. Hyperbaric epilepsy and narcosis [in Russian]. Sechenov Inst. Evolutionary Physiol. Biochem., U.S.S.R. Acad. of Sciences, Leningrad.