The Predictive Studies Series: Correlation of physiologic responses to extreme environmental stresses.

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INTRODUCTION

Periodically over the past four decades, investigators at the Institute for Environmental Medicine have carried out correlated physiologic experiments programs that were from the outset designated individually and collectively as 'Predictive Studies.' Because of my long and close association, I have been invited to summarize the scope of these studies designed to identify and quantitatively measure in human subjects the physiologic and pathophysiologic effects of extreme respiratory gas and ambient pressure environments that could limit or aid man's ability to live or work in those environments. Each of these eight broad studies was conceived, designed, and led by C. J. Lambertsen, and joined by selected collaborating participants from military, university, or corporate backgrounds. In most cases, the Predictive Studies employed a "dose-response" design, in which human subjects were exposed to a range of respiratory gases and pressures for durations that approached the limits of tolerance at both rest and during physical work. By measuring physiologic and/or toxic responses to each pressure-duration dose and then interpolating between doses, the intent was to "predict" responses to pressure-duration combinations over the ranges of stresses studied.

C.J. Lambertsen's earliest physiologic study of oxygen involved microtonometry to determine in-vivo relationships of PO_2, PCO_2, and hemoglobin O_2 saturation in the arterial blood of human subjects exposed to increasingly severe degrees of hypoxia (1). Ensuing analyses of arterial and brain venous blood at 3.5 ATA-inspired O_2, beyond full saturation of hemoglobin, demonstrated that human subjects are functional without the benefit of hemoglobin for O_2 transport to the brain or CO_2 transport from it (2). These early observations, superimposed on extreme personal exposures to hyperoxia and oxygen poisoning in development of practical self-contained diving (3, 4), led to seminal investigations of human respiration and brain circulation functions in hyperoxic states (5-7). Subsequently, the focus which emerged was on relations of evolving undersea and aerospace activity, in which Lambertsen played a special role as Chairman of the Man in Space Committee, Space Science Board, established by the National

Academy of Sciences-National Research Council. He served concurrently as Chairman of the National Research Council Panel on Underwater Swimmer Technology. These joint roles influenced the beginnings and evolution of the Predictive Studies Series, most of which have blended research in undersea, aerospace, and therapeutic aspects of unusual and useful atmospheric exposures, with an early emphasis on the expanding roles of diving.

Classical military and civilian diving operations were initially characterized by non-saturated, limited-duration diving from the surface, followed by decompression and a gradual return to normal ambient pressure. As the depth and duration of working dives increased, with increasing limitations by decompression requirements, the concept of inert gas 'saturation' diving was first proposed by Behnke (8) and later demonstrated to be practical in the Conshelf, Man-In-Sea, and Sealab programs (9). Such saturation exposures used helium. Whether they continued for one or many days, approximately one day of decompression was required for every 100 feet of depth. This led to the expansion of saturation-excursion diving, which involved prolonged exposure at one depth, with excursions to a greater depth followed by a no-decompression return to the saturation depth.

The prominent narcotic effects of nitrogen at shallow to intermediate depths necessitated the use of helium as the inert diluent gas at extreme depths. The absence of narcotic influences and relatively low respired gas density associated with helium diving allowed penetration to greater depths, but the adverse effects of compression and hydrostatic pressure *per se* became limiting (10-13). The evolutions of technical advances in diving exposed the diver to larger physiological stresses. These included decompression, oxygen toxicity, inert gas narcosis, hypothermia, increased work of breathing, and the adverse neurological effects of compression to extreme hydrostatic pressures. The Predictive Studies were designed to determine the limitations imposed individually and collectively by one or more of these stresses.

PREDICTIVE STUDIES OF TOLERANCE TO COMPRESSION AND INERT GAS ATMOSPHERES

The scope of the Predictive Studies to date is summarized in Table 1 (14). Available sources of additional details are cited in the text.

Table 1
THE PREDICTIVE STUDIES SERIES
DIVING, DECOMPRESSION, HYPEROXIA, HYPOXIA
Studies related to predictions of limiting physiologic effects in man of gases and pressure

PREDICTIVE STUDIES I (1969): TEKTITE I
A 60-day, open-sea exposure to normoxic N_2 at 43 FSW (2.3 ATA).
Collaborating sponsors: ONR, NASA, U. Penn, GE, Department of the Interior

PREDICTIVE STUDIES II (1970-1971)
A 14-day, continuous dry-chamber exposure to normoxic N_2 at 100 FSW (4 ATA).
Collaborating sponsors: U. Penn, NASA, Navy BUMED, ONR, NIH, Baylor U.

PREDICTIVE STUDIES III (1971-1973)
A 21-day, dry-chamber exposure to pressures ranging from 400 to 1200 FSW (12 - 37 ATA)
while breathing He-O_2, N_2-O_2, Ne-O_2 mixtures.
Collaborating sponsors: U. Penn, Navy BUMED, ONR, NASA, NIH, Union Carbide, Ocean Systems

PREDICTIVE STUDIES IV (1975)
Saturation - excursion series in phases of 0, 400, 800, 1200, and 1600 FSW. Exposure to normoxic He.
Physiologic studies and underwater work performance on oil wellhead.
Collaborating sponsors: U. Penn, Navy Medical R&D, ONR, NIH, NASA, Industry (offshore oil, gas, diving)

PREDICTIVE STUDIES V (1982-1987)
Definition of organ system O_2 tolerance - in relation to undersea activity, manned EVA, hyperoxic therapy,
and therapy of undersea and aerospace decompression accidents.
Collaborating sponsors: U. Penn, Navy Medical R&D, NOAA, NASA, Industry (offshore oil, gas)

PREDICTIVE STUDIES VI (1988-1992)
Extension of organ tolerance at normal and increased ambient pressure. Optimized intermittency.
Planning based on PS V - in relation to all oxygen uses.
Collaborating sponsors: U. Penn, Navy Medical R&D, NASA

PREDICTIVE STUDIES VII (1992-1997)
Interactions of hyperoxia, exercise, immersion, and CO_2 on brain oxygenation
and neurological O_2 tolerance.
Collaborating sponsors: U. Penn, ONR

PREDICTIVE STUDIES VIII (1992-1997)
Influences of CO_2 on brain O_2 flow and respiratory control during hypoxia in work and at rest.
Collaborating sponsors: U. Penn, Navy Medical R&D, NASA

Predictive Studies I

Predictive Studies I, also called Tektite I, symbolic of a meteorite fallen to the ocean, was a 60-day, open-sea, collaborative saturation exposure to normoxic nitrogen in an underwater habitat at an effective depth of 38 feet, or about 2.2 ATA (15-17). Collaborating sponsors included U.S. Navy, NASA, U.S. Department of the Interior, General Electric Corporation, and the University of Pennsylvania. This investigation was done in relation to NASA interest in exploring nitrogen saturation diving as a study of prolonged physiologic entrapment. The subjects were marine scientists who did practical technical work during the long exposure underwater. Pulmonary function evaluations showed that inspiratory and expiratory maximal flow rates decreased significantly during exposure, and post-exposure results were consistent with an increased strength of respiratory muscles in response to the sustained increase in inspired gas density and work of breathing (17). A discrete event was the observation, post-decompression, of a gas bubble in the aqueous humor of the eye in one subject (Figure 1) (15,16). No limiting effects were found, but the experience gained was used in the design of subsequent exposures to higher pressures and gas densities.

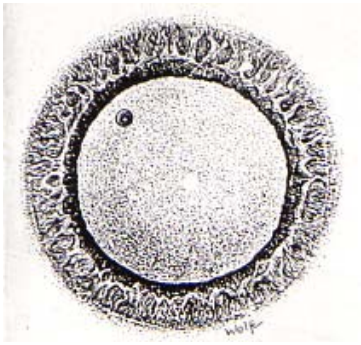

Fig. 1. Artist's drawing of a bubble in the aqueous humor of the eye as seen with an ophthalmoscope in a subject from Tektite I (15,16).

Predictive Studies II

Predictive Studies II, a 14-day, dry-chamber, continuous exposure to normoxic nitrogen at 100 fsw, or 4 ATA (18-25), was the first study to be done in a new environmental chamber system of the present Institute for Environmental Medicine at the University of Pennsylvania (18). The study was stimulated by the recognition that the potential benefits of manned undersea activity would be greatly enhanced by an ability to remain for extended periods at shallow and moderate depths, where much of the useful undersea work is performed. Areas of investigation considered likely to identify physiological responses or mechanisms that could potentially limit human tolerance or adaptation to increased atmospheric pressures included:

- Combined effects of increased work of breathing and nitrogen narcosis on respiratory control and pulmonary gas exchange.
- Effects of acute and sustained exposure to increased breathing resistance on pulmonary mechanical and other functions.
- Rates of adaptation to stresses imposed on pulmonary function and respiratory control, as well as rates of deterioration at rest and during exercise in the event that adaptations fail.
- Quantitative decrements, adaptations, and deteriorations in specific aspects of mental performance during acute and chronic exposure to nitrogen narcosis.
- Nitrogen influences on formation and destruction of blood cellular constituents.
- Patterns of chemical, endocrine, and metabolic adaptations during prolonged exposures to increased nitrogen pressure.

No serious, acute or chronic, toxic or nitrogen narcotic limiting effects developed during the 14-day exposure. Adaptation of respiratory control was manifested by a decreased ventilatory response to carbon dioxide, which did not interfere significantly with pulmonary gas exchange or progress with time (21). The respiratory muscles compensated for an increased work of breathing, thereby allowing exercise tolerance to remain high with adequate gas exchange. Cognitive function and technical competence remained more than adequate for the detailed experimental procedures carried out by and with the subjects. Quantitative measurements of mental function did not detect progressive deteriorations or adaptations to nitrogen narcosis (25). There were no alterations in blood cell formation or aging (22), or any limiting chemical, metabolic, or endocrine dysfunction (23). Plasma volume decreased concurrently with an increased urine output, but these changes were not functionally significant (24).

Predictive Studies III

Predictive Studies III comprised a multi-week series of dry-chamber exposures to normoxic nitrogen at pressures equivalent to 100, 200, and 300 fsw, culminating in a 21-day continuous exposure to simulated depths ranging from 400 to 1,200 fsw (13-37 ATA) while breathing nitrogen-oxygen, helium-oxygen, nitrogen-helium-oxygen, or neon-helium-oxygen gas mixtures (26). The gas-and pressure-related stresses experienced by each of the four subjects were, therefore, grossly more extreme than those studied in Predictive Studies II. The

experimental design was influenced by the awareness that actual exposure to hydrostatic pressures, which approached the limits of human tolerance, might involve an unacceptable level of risk. The danger was imposed by the unavoidable requirement for a slow decompression from prolonged or saturation exposure, thereby preventing rapid escape from dysfunctional or possibly harmful effects. In order to avoid this risk, the denser gas nitrogen, at relatively low ambient pressures, and neon, at intermediate pressures, were used to simulate the conditions and study the effects of increased gas density and the respiratory work expected to be associated with breathing helium-oxygen at extreme depths. The inhalation of a neon-oxygen gas mixture made it possible to study the potential (predictive) respiratory effects of breathing helium-oxygen at gas density-equivalent depths to 5000 fsw while remaining at an ambient pressure of 1200 fsw (26). Effects of extreme inert gas pressures on selected components of physiological function, as defined in Predictive Studies III (26), include the following:

- *Pulmonary Function*: As the density of respired gas and resistance to airflow progressively increased, pulmonary function indices, such as maximum voluntary ventilation and maximum expiratory flow rates, were progressively reduced, as previously described (27). However, the slope of flow rate reduction with respect to gas density appeared to approach an asymptote as density became extreme, an unexpected observation. This important characteristic facilitated the performance of high levels of exercise at extreme gas densities without incapacitating degrees of CO_2 retention.
- *Respiratory Control*: The slope of the ventilatory response to rebreathing metabolically produced CO_2 decreased progressively with increasing gas density. The associated reduction in ventilation was found to correlate with increased gas density and respiratory work, rather than with narcotic properties of the inert vehicle gases.
- *Respiratory Gas Exchange*: Blood gas measurements in arterial or arterialized venous blood detected no interference with O_2 or CO_2 exchange at rest or during exercise with nitrogen to 400 fsw, helium to 1200 fsw, or neon to 900 fsw.
- *Exercise Tolerance*: Two of the four subjects performed four sequential, six-minute periods of uninterrupted, incremental exercise on a bicycle ergometer during exposure to a range of increased gas densities and inert gas pressures. The highest exercise level was equivalent to about eighty percent of subject maximum work capacity at 1.0 ATA. Failure to complete this work profile occurred once in each of only two conditions, and for different reasons. In both cases, failure occurred during the last two minutes of the highest workloads. One cause of failure, which occurred while breathing N_2-O_2 at 400 fsw, was a severe degree of mental confusion and muscular incoordination induced by nitrogen narcosis. The second failure, observed while breathing crude neon at a gas density equivalent of breathing He-O_2 at 5000 fsw, was caused by high gas density and was associated with alveolar (end-tidal) CO_2 pressures of about 60 mm Hg. At the two lower workloads (300 and 600 kpm/min), ventilation was not subjectively difficult. Alveolar PCO_2 levels remained below 50 mm Hg.
- *Neurophysiological Changes*: There were no evident manifestations of a high-pressure nervous syndrome that was previously described (10-13) in association with rapid compression to extreme depths. This was attributed to the fact that the maximum 1200 fsw depth equivalent was intentionally achieved by a stepwise and slow adaptation to compression over several days.
- *Mental Function*: No detectable cognitive decrements were found with either helium or crude neon breathing at 1200 fsw. As expected, nitrogen produced a progressive central

nervous system depression that became prominent at pressures equivalent to 300 and 400 fsw (Figure 2).

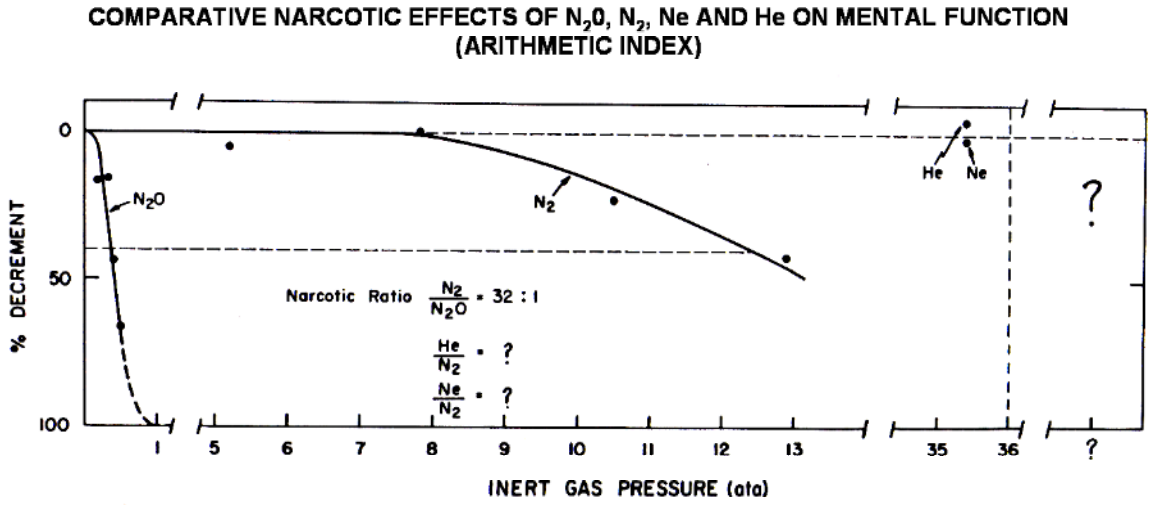

Fig. 2. Average decrements in paced arithmetic for two subjects during exposure to increased partial pressures of N_2, Ne, or He. Results are compared with average data from a previous study (28), in which eight subjects performed similar tests while breathing N_2O at inspired pressures to 0.5 ATA. Subjects remained extremely competent during N_2 breathing to nearly 8 ATA (about 230 fsw) and retained considerable mental function capacity to 13 ATA (500 fsw equivalent breathing air). The N_2:N_2O narcotic ratio was 32:1. Subjects were fully competent, without evident narcosis, during Ne or He breathing to 37 ATA (1200 fsw) (26).

- *Psychomotor Function*: Manual dexterity, coordination, and reaction time were impaired significantly only during nitrogen breathing at pressures equivalent to 300 fsw or greater.
- *Temperature Stress*: During exposure to helium at increased pressures, the subjects collectively negotiated a comfortable temperature. As helium density rose, the mean selected temperature was elevated with a narrowing of the comfort range.
- *Blood Chemical, Cellular, and Endocrine Characteristics*: With respect to pre-exposure controls, there were no physiologically important changes in blood electrolytes, blood cellular composition, catecholamine, or adrenal cortical hormone excretion.
- *Isobaric Inert Gas Counterdiffusion Syndrome*: An unexpected finding in Predictive Studies III was the occurrence of extreme pruritis, gas-filled skin lesions (Figure 3), and vestibular dysfunction when the subjects breathed N_2-O_2, N_2-He-O_2, or Ne-He-O_2 while their bodies were surrounded with He-O_2. Subsequent analyses and investigations of this phenomenon (29-31) led to its characterization as a new "gas lesion syndrome" (31), a gaseous supersaturation and venous gas embolism generated by unequal rates of inert gas counterdiffusion at stable (isobaric) ambient pressures (31). A resulting continuous evolution of subcutaneous and venous bubbles induced the potential of a possibly lethal embolization of gas from subcutaneous capillaries to the systemic circulation and heart (26, 29-31). As a possible cause of the vestibular symptoms, it was suggested that the inert gas counterdiffusion process might have occurred through the round window between the middle and inner ear, with the formation of bubbles in inner ear fluids (31). The detailed observations of isobaric inert gas counterdiffusion in Predictive Studies III,

Fig. 3. Gas-filled lesions in the skin of a subject breathing N_2-O_2 while his body is surrounded by He-O_2 at a pressure equivalent to 300 fsw (31).

and its studies in animals, provided the basis for its prevention in undersea operations and opened a new field of investigation that has been only partially exploited to date.

Predictive Studies IV

Predictive Studies IV was designed to investigate the physiological effects of staged rapid compressions in saturation-excursion diving on normoxic helium-oxygen to simulated depths of 400, 800, 1200, and 1600 fsw (32). There were two separate phases of investigation with four professional diver-subjects in each phase. Two divers participated in both phases. Phase One consisted of rapid compression to 800 fsw, a two-hour hold at that pressure, and subsequent rapid excursions to 1200 fsw while using 800 fsw as a saturation depth. Subjects were studied in pairs during the initial compression and successive excursions (Figures 4,5). Phase Two involved initial compression to 1200 fsw even more rapidly than before, a 22-hour hold at 1200 fsw, followed by repeated rapid and brief excursions to 1600 fsw with a return to saturation at 1200 fsw.

Fig. 4. Two diver-subjects after rapid compression to 800 fsw equivalent. Subject in foreground is having evaluation of bone conduction auditory thresholds. Subject in background is preparing to exercise on bicycle ergometer to measure ventilation and gas exchange (32).

Specific goals of Predictive Studies IV included the following:

- Determination of the character and time course of physiological and performance decrements during intentionally rapid compressions.
- Determination of rates of adaptation to compression effects upon reaching stable increased pressure.
- Develop markedly accelerated methods for decompression in deep saturation-excursion diving.
- Demonstrate work competence underwater at simulated depths of 1200 and 1600 fsw.

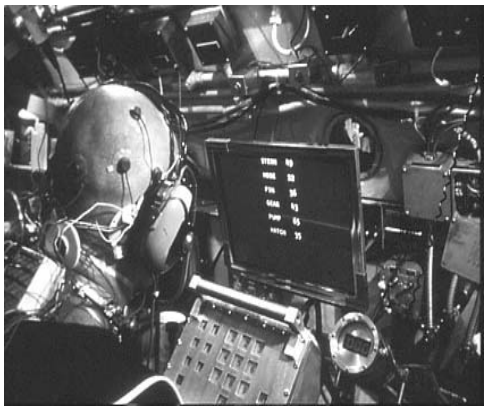

Fig 5. Resting subject station during computer-controlled and scored mental performance tests (32).

Previous investigators of high pressure nervous syndrome found that the rapid compression of human subjects to extreme pressures caused them to experience nausea, vomiting, dizziness, loss of alertness, indifference, disorientation, mental confusion, and somnolence (10-13, 33-35). Associated overt manifestations included coarse tremors, motor incoordination, impaired balance function, myofasciculations, and spasticity. Essentially all of the previously observed symptoms and overt

manifestations were also experienced by at least two of the diver-subjects at some time during the two phases of investigation. Detailed results of Predictive Studies IV are published in a comprehensive IFEM Report (32). Selected observations are summarized as follows:

- *Symptomatic and Overt Effects*: After rapid compression to 1200 fsw, symptoms were severe on arrival, with partial reversal over the next few hours. Only minor effects remained on the second day at 1200 fsw. Second-day excursions to 1600 fsw produced typical symptoms and signs, which were much less severe than on the previous day. Adverse effects continued to progressively ameliorate during successive daily excursions from 1200 to 1600 fsw. After the initial day of compression to 1200 fsw, subjects were capable of vigorous mental and physical activity, even at 1600 fsw, and skillfully performed precisely timed and coordinated technical maneuvers.
- *Vestibular Function and Balance*: The initial, rapid compression to 1200 fsw induced typical manifestations of vestibular dysfunction, such as dizziness, nausea, vomiting, and loss of alertness, usually accompanied by increased body sway. Eye muscle coordination was not affected, and there was no ocular dysmetria. Vestibular symptoms and signs decreased within one to two hours at 1200 fsw, were barely detectable by the morning of the second exposure day, and were absent by the third day.
- *Auditory Function*: No indications of hearing impairment were found during or after compression.
- *Visual Function*: Changes in visual acuity and accommodation were observed, but these were relatively small, transient, and functionally insignificant.
- *Speech Generation and Distortion*: Rapid compressions and acute exposures to 800, 1200, and 1600 fsw in He-O_2 did not interfere with neuromuscular or other functions in speech formulation or articulation.
- *Perceptual, Memory, Cognitive, and Performance Functions*: Susceptibility to compression and pressure effects varied widely in different subjects. During the initial compressions to 1200 fsw, mental slowness, delayed response and reaction times, increased errors, and occasional failures to follow test procedures were observed, usually in association with prominent discomfort in subjects. While remaining at stable pressure after the first day, subjects appeared close to full mental capacity, alertness, and manual dexterity in performing technical functions.
- *Sleep*: Neither sleep quality nor electroencephalographic activity during sleep was observably altered during saturation exposure at 1200 fsw.
- *Electroencephalographic Changes*: EEG changes, which were generally progressive with depth as pressure increased beyond 640-800 fsw, included disorganization of background activity and decreased frequency of background activity components, irregular low-frequency forms, and occasional paroxysmal lower-frequency activity. Most EEG changes did not correlate directly with symptoms or performance. The conduction latency of the secondary N2 component of the somatosensory-evoked cortical response was the only measured index of peripheral and central nerve conduction time that changed significantly. This change, which could have been a nonspecific effect, occurred only during the first few hours after initial compression to 1200 fsw. Visually evoked cortical

responses consistently had small amplitude decrements and latency increments as absolute pressure increased.

- *Tremor*: Integrated amplitudes of intentional and postural tremor doubled during rapid compression to 800 and 1200 fsw, reversing partially or completely within two to four hours at stable pressure. Despite early adaptation, tremor amplitudes again approximately doubled during 400-fsw excursions on exposure days two and three. However, the increased tremor amplitudes were nearly invisible and caused no detectable functional impairments.
- *Cardiac Electrical and Mechanical Function*: Cardiovascular functions did not appear to be affected by either compression or hydrostatic effects in combination with high helium pressures.
- *Pulmonary Mechanical Function*: Superimposed upon pulmonary function decrements caused by increased gas density alone, additional transient decrements in maximal ventilatory volumes and flow rates occurred during rapid compression to 1200 fsw. These changes, partially effort-dependent, were most evident when symptoms and other effects of compression and pressure were prominent. They also receded with time as symptoms diminished. Ventilatory responses were adequate to support a moderate level of exercise during and immediately after rapid compressions to simulated depths of 800, 1200, and 1600 fsw.
- *Breathholding Capacity*: Breathholding duration during stable exposure to a pressure equivalent to 1200 fsw was equal to that at one atmosphere.
- *Thermal Homeostasis*: As previously found (26), exposure to increased He-0_2 pressures was associated with an increase in comfort temperature and a narrowing of the comfort zone. Presence of a mild cardiovascular stimulus was reflected by measurable elevations in resting heart rate and cardiac output. Despite reasonable caloric intake and undetectable change in whole body oxygen uptake, body weight decreased slightly and progressively during exposure to high He-O_2 pressures.
- *Decompression from Excursion Exposures*: Using the results of previous U.S. Navy investigations of helium-oxygen, saturation-excursion diving (36) as a guide, excursion-decompression procedures were developed to allow decompression from a 1200 to 1600 fsw excursion in less than one tenth of the time required for decompression in a 400-foot excursion from sea level. Specifically, decompression to 1200 fsw after 55 minutes at 1600 fsw was accomplished in 90 minutes, as compared to the nearly 18-hour decompression usually employed after a 60-minute excursion to 400 fsw from the surface. An episode of vestibular symptoms occurred in one subject, with therapeutic resolution.
- *Underwater Work Performance*: The underwater work task consisted of a programmed sequence that involved the timed dismantling and reassembly of large valve flange and other oil wellhead components in the water-filled chamber compartment (Figure 6). Prior to the initial compression for Phase Two, training for the underwater work was performed at one atmosphere, both in dry conditions and under 10 to 12 feet of water. The average values of pulmonary ventilation and oxygen uptake for all four divers in air at 1.0 ATA were about 60 and 2.0 liters per minute, respectively. After establishing a range for the

four best time trials at 10 fsw, each diver performed the timed underwater work sequence at 1210 fsw during saturation exposure, at 1610 fsw on excursion, and at 1360 fsw during a stable phase of saturation-decompression. With the exception of one run by one diver at 1610 fsw, all of the time trials at simulated depths of 1210-1610 fsw were within or below the range for the four best trials at 10 fsw.

Fig. 6. Diver-subject performing underwater task sequence at 1610 fsw pressure equivalent, on excursion from 1200 fsw (32).

All of the time trials at extreme depths were performed after periods of adaptation, when effects of compression and pressure were minimal or absent, and diver-subjects demonstrated capabilities for practical underwater work at a simulated depth of 1600 fsw (32).

Hyperoxia Predictive Studies

Predictive Studies V, VI, and VII are referred to here collectively as the Hyperoxia Predictive Studies, extending from previous years of detailed study concerning the physiological effects of acute hyperoxia related to limits of closed-circuit oxygen diving (2, 5-7). The previous studies complemented earlier Navy-supported investigations by Behnke, et al (37, 38) at the Harvard School of Public Health. Those studies also accompanied extensive investigations of human oxygen tolerance by Donald (39) in the Royal Navy and Yarbrough, et al (40) in the U.S. Navy, which supported the initial use of closed-circuit oxygen diving for military covert operations during World War II (41, 42). Additional applications of hyperoxia in diving include its use in decompression (43) and in the therapy of decompression sickness (44, 45). Although Behnke and Shaw (44) proposed therapeutic administration of oxygen in decompression sickness in 1937, it was not until 1965 that oxygen treatment tables developed by Goodman and Workman (45) were formally accepted by the U.S. Navy. Concurrently, hyperbaric oxygenation was employed by Boerema (46) in surgical procedures and by Brummelkamp, et al (47) in the treatment of anaerobic infections. Subsequently, therapeutic applications of hyperbaric oxygenation were expanded to include several categories of ischemic wounds, compromised grafts and flaps, thermal burns, selected acute and chronic infections, and carbon monoxide poisoning (48, 49). Results of the Hyperoxia Predictive Studies have relevance to all of these applications.

Predictive Studies V

Predictive Studies V, performed from 1982 to 1987, involved continuous exposures to the different inspired-oxygen pressures of 3.0, 2.5, 2.0, and 1.5 ATA, to practical neurological and pulmonary limits of human oxygen tolerance (50). Early studies of pulmonary tolerance to continuous oxygen breathing at 2.0 ATA (51-53) provided a basis for later, more extensive studies of systemic oxygen poisoning with emphasis on visual and other neurological effects

(Figure 7). Concurrently, functional components of major organ systems were investigated (Table 2) in experiments designed to help define the consequences of exposures over a range of useful hyperoxic pressures (54, 55).

Fig.7. Measurement of retinal electrical activity (electroretinography) in response to a light flash while subject breathes oxygen at 3.0 ATA. Chamber lights are out for actual measurement.

The intended applications were related to manned undersea and aerospace activity, the expanding field of special forces self-contained diving operations, clinical hyperbaric oxygen therapy in general, and to the therapy of undersea and aerospace decompression accidents, specifically.

Table 2
HYPEROXIA PREDICTIVE STUDIES
Scope of Measurements

Electroencephalography	**Pulmonary Function**
Clinical interpretation	Flow-volume loops, spirometry
Response to phonics stimulation	Density dependence of flow
Visual Function	Pulmonary compliance
Peripheral visual fields	Airway resistance
Electroretinography	CO diffusing capacity
Visual evoked cortical response	Arterial Pco2, Po2, pH
Visual acuity	Closing volumes
Pupillary reaction	Ventilation uniformity
Accommodation	Peak respiratory pressures
Color vision	**Bronchoalveolar Lavage**
Auditory-Vestibular Function	Cellular composition
Audiometry (standard, high frequency)	Chemical composition
Brainstem auditory evoked response	**Respiration**
Caloric stimulation	Respiratory control
Eye tracking	Pulmonary gas exchange
Performance	**Muscle Power**
Perceptual, Cognitive, Psychomotor	Skeletal, respiratory
Cardiovascular Function	**Temperature**
Electrocardiography	**Hematologic Effects**
Cardiac output, rate, stroke volume	**Blood Chemistry**
Blood pressure, systemic vascular resistance	**Liver Blood Flow and Function**
Orthostatic reflex response	
Renal Function	

Predictive Studies VI

Predictive Studies VI, from 1988 to 1992, was designed to use the previous measurements of neurological and pulmonary responses to continuous oxygen exposure as baseline control data for the investigation of practical human oxygen tolerance extension by systematic alternation of hyperoxic and normoxic exposure periods. Extensive investigation in animals (56, 57) provided a basis for the selection of effective intermittent exposure patterns that could be evaluated in humans. Collaborating with those who had previously investigated human tolerance to continuous oxygen exposure at 2.0 ATA (51), Hendricks, et al (58), in an initial study, demonstrated that the progression of pulmonary oxygen poisoning at 2.0 ATA could be effectively delayed by alternating twenty-minute periods of oxygen breathing with five-minute periods of normoxia. Two additional patterns of intermittent

exposure at 2.0 ATA were evaluated as part of Predictive Studies VI, with comparable results (57).

Predictive Studies VII

Predictive Studies VII, performed from 1992 to 1997, complemented the baseline Predictive Studies V measurements by investigating conditions known to decrease human tolerance to the neurological effects of oxygen toxicity by causing them to occur more rapidly, or at lower oxygen pressures. These conditions include exercise during exposure to hyperoxia, underwater immersion, and accumulation of carbon dioxide from any of several possible sources. Occurring individually or in combination, at least some, if not all of these influences, exert their adverse effects on neurological oxygen tolerance by increasing brain blood flow and oxygen dose (57). Predictive Studies VII also demonstrated effective reduction of arterial PCO_2 and brain oxygen dose during hyperoxic exercise by voluntary hyperventilation (57).

Predictive Studies VIII

Predictive Studies VIII, in contrast to its hyperoxic predecessors, was designed to investigate the hypoxic end of the oxygen spectrum. The physiological effects of exposure to hypoxic, hypercarbic-inspired gas mixtures were studied with regards to NASA interests in the potential transient flooding of a spacecraft atmosphere with a hypoxic gas to suppress fire. Respiratory, cardiovascular and brain circulatory responses to hypoxia alone, and with concurrent hypercarbia, were studied at rest and during exercise. In this environmental extreme, the concurrent increments in brain blood flow and oxygenation associated with elevated partial pressures of carbon dioxide have a beneficial effect on human tolerance, rather than the adverse effects caused by the same physiological changes in a hyperoxic environment.

INSIGHTS FROM THE HYPEROXIA PREDICTIVE STUDIES

Major components of the results from the Hyperoxia Predictive Studies have been published in open literature (54, 55, 59-65). Other components, not yet published, are available in the Environmental Biomedical Stress Data Center at the University of Pennsylvania (57). Focussing on those that provide new information or insights that complement or extend earlier results, selected examples of specific observations from the Hyperoxia Predictive Studies are summarized in this presentation.

CNS Oxygen Poisoning.

Of 14 subjects who breathed oxygen at 3.0 ATA for up to 3.5 hours, one had a typical oxygen convulsion at 3.0 hours of exposure. As part of the emphasis on neurological effects of oxygen toxicity, brain electrical activity, ventilatory changes, and end tidal PCO_2 were monitored in each subject as potential manifestations of CNS oxygen poisoning.

In agreement with previous observations (66), there were no electroencephalographic changes prior to the actual seizure. However, there were previously unreported respiratory changes, characterized by prolonged expiration, decreased rate of breathing, decreased alveolar ventilation, and increased alveolar PCO_2 (50). These changes, which appeared to start about thirty minutes before the convulsion, produced a progressive PCO_2 elevation that peaked immediately before the time of seizure onset. It is likely that the associated increments in brain blood flow and oxygen dose accelerated the progression of CNS oxygen poisoning.

Visual Effects.

The most prominent visual effect was loss of peripheral vision, nearly complete in some subjects, as observed by Behnke, *et al* (38). Peripheral visual field changes in 14 subjects, who breathed oxygen at 3.0 ATA for up to 3.5 hours, are shown in Figure 8 (50). The visual field area was maintained in nearly all subjects for about two hours and then decreased rapidly.

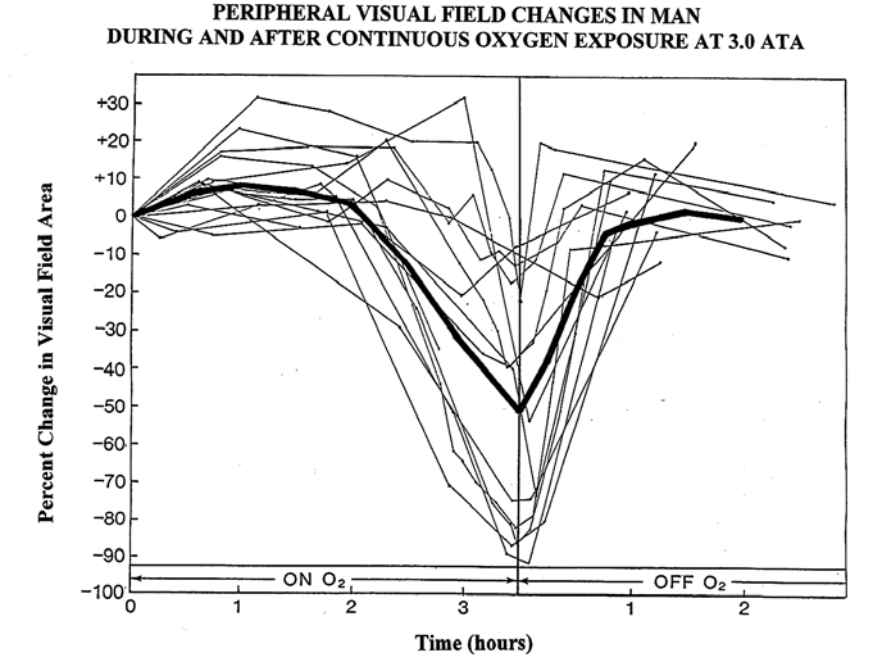

Fig. 8. Fine lines show changes in visual field area for individual subjects. Heavy line represents the average of 14 subjects (50).

About half of the subjects experienced nearly total loss of peripheral vision; the other half had less significant changes. In all subjects, essentially complete recovery occurred within about 45 minutes of air breathing. These measurements confirmed, and with the aid of better equipment, greatly extended the earlier observation of Behnke, et al in a single subject (38). Repeated measurements of visual field area in many additional subjects defined the rates of development and recovery, as well as the range of individual variability for this neurological manifestation of oxygen poisoning. Similar measurements of the decrease in visual field area at lower oxygen pressures revealed it to be of a progressively slower onset and smaller magnitude (57).

Syncope.

One of the subjects exposed to oxygen at 3.0 ATA had a transient syncopal episode at 2.5 hours (50, 67). Continuous recording of the electrocardiogram demonstrated a rapid onset of bradycardia, which culminated in a 13-second cardiac pause immediately before the loss of consciousness. The pause was ended by a sinus beat and gradual return to normal sinus rhythm. Consciousness was regained within one minute. In 1935, Behnke, et al reported the transient loss of consciousness associated with an absence of the radial pulse and fall in blood pressure (37). Similar episodes were later observed by Donald (39). Previous investigators have shown that the bradycardia that occurs during oxygen breathing, even at 1.0 ATA, is mediated by vagal action

on the heart (68). It is likely that the 13-second sinus pause in our subject represents an exaggerated example of vagal activity, which may be related to CNS oxygen toxicity.

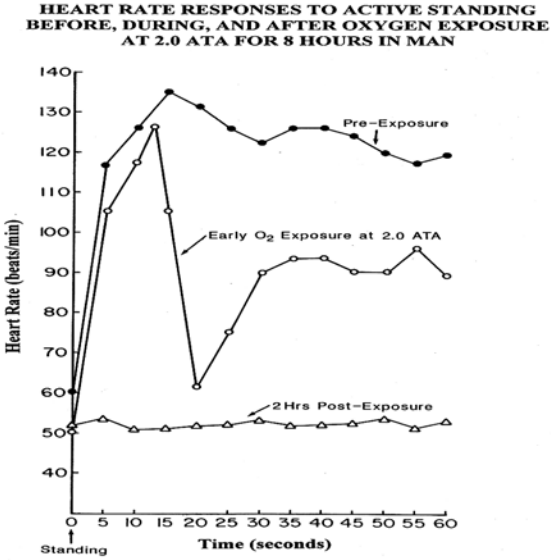

Fig. 9. Changes in heart rate during a 60 secon after standing upright from a resting, supine po

Another example of exaggerated vagal activity is illustrated in Figure 9 (67). One of the cardiovascular functions monitored at regular intervals during exposure to oxygen was the reflex response to an abrupt change in posture, from the supine position to the standing position. The data shown in Figure 9 were obtained in a subject who breathed oxygen at 2.0 ATA for 8.0 hours. Changes in heart rate during the first sixty seconds after abruptly standing upright were measured before exposure, during early exposure, and two hours after the exposure. The normal response to standing upright is rapid acceleration of heart rate, followed by stabilization at a higher level. During early exposure, this response was modified in that the initial acceleration was not maintained, and the heart rate stabilized at a level only slightly higher than the resting level. The most unusual response was recorded two hours after the end of the exposure. At that time, heart rate remained absolutely constant for an entire minute after the subject stood upright. Despite the absence of an increase in heart rate, however, blood pressure was maintained and the subject did not lose consciousness. This may reflect an increase in systemic vascular resistance to compensate for the sustained period of bradycardia. While one component of the reflex response to standing was suppressed, another remained fully active.

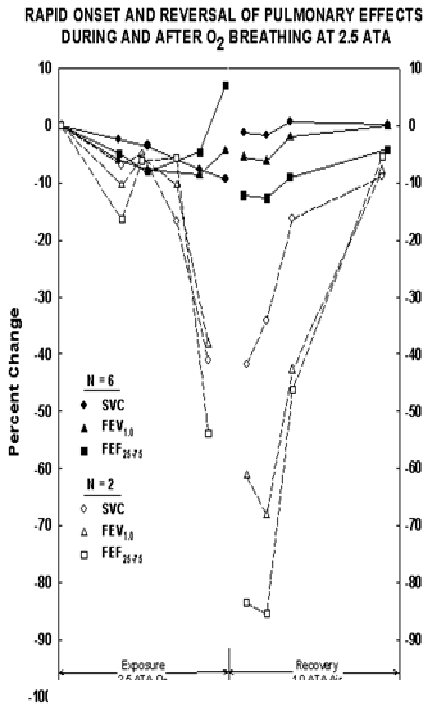

Fig. 10. Example of rapid onset and reversal of pulmonary effects during and after breathing xygen at 2.5 ATA for 5-6 hours (55). See text for discussion

Pulmonary Effects.

Figure 10 shows changes in pulmonary function measured during and after breathing oxygen for five to six hours at 2.5 ATA (55). The measurements included slow vital capacity (SVC), one second forced expired volume ($FEV_{1.0}$), and maximal mid-expiratory flow rate (FEF_{25-75}). Average values for six subjects are compared with those in two other subjects who had much larger pulmonary function decrements during and after the oxygen exposure.

Changes in the two subjects are characterized by an early onset during oxygen breathing, large magnitudes of effects, and rapid reversal upon the resumption of air breathing at 1.0 ATA. Subjectively, both subjects experienced a feeling of chest tightness and an inability to exhale rapidly despite exerting maximal effort. The rapid onset and reversal of these effects, as well as the large magnitudes, are all consistent with neurological interaction to magnify the direct pulmonary effects of

oxygen toxicity. Vagally-induced bronchoconstriction would provide a mechanism for such an interaction.

Exercise Effects.

As stated, a primary goal of Predictive Studies VII was the investigation of conditions known to decrease human tolerance to the neurological effects of oxygen toxicity. Early studies in both the U.S. Navy (40) and the British Royal Navy (39) showed that exercise during exposure to hyperoxia caused convulsions to occur more rapidly or at lower oxygen pressures than at rest. The data shown in Figure 11 are average arterial PCO_2 measurements in six men who performed incremental levels of bicycle ergometer exercise while breathing oxygen at 2.0 ATA (63). Prior to the start of exercise, arterial PCO_2 decreased from a normoxic value of 40.5 mm Hg to 34.3 mm Hg during oxygen breathing. This well-documented response to hyperoxia is caused by the modification of blood CO_2 transport with associated responses that include a PCO_2 elevation in central respiratory control centers, mild hyperventilation, and arterial hypocapnia (6). The related reduction in brain blood flow and oxygen dose (57) should have a protective influence. However, the ventilatory response to exercise during exposure to hyperoxia is such that the protective influence is removed by progressive elevation in arterial PCO_2. These responses provide a physiological basis for the adverse effects of exercise on CNS oxygen tolerance.

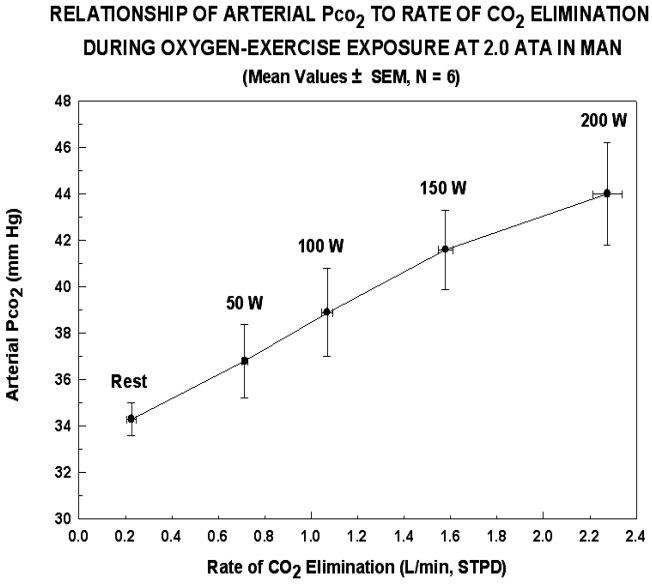

Fig. 11. Progressive rise in arterial PCO_2 during incremental exercise while breathing oxygen at 2.0 ATA. Rate of CO_2 elimination was measured as an index of work intensity (63).

CONTINUING RELEVANCE OF HYPEROXIA PREDICTIVE STUDIES

The results of the Hyperoxia Predictive Studies have relevance to diving and decompression, the therapy of decompression sickness, and the expanding applications of hyperbaric oxygen therapy. This relevance is likely to increase with improved understanding of current applications and the development of new uses. Although hyperoxia will always be toxic, its therapeutic properties can be exploited while remaining within the pressure-duration limitations imposed by concurrent toxicity. Effective extension of oxygen tolerance by systematically interrupted exposure or other methods will cause the limitations to be less restrictive. As basic mechanisms of oxygen toxicity are elucidated, it should be possible to ameliorate and/or further extend these constraints. Information and insights from the Hyperoxia Predictive Studies supplement the investigation of basic mechanisms by defining the functional deficits associated with early, reversible degrees of oxygen poisoning in specific organs and tissues. Further understanding of oxygen poisoning mechanisms requires identification of the many intermediate

actions and reactions that precede known functional derangements, as well as the reactive species and cellular responses that initiate them (62, 66).

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