日高圧医誌 Vol. 15 No. 1

An overview of hyperbaric oxygen in diving and clinical medicine

A. R. Behnke, Jr., M. D.

It is a privilege to return to Japan having attended the Fourth International Congress on Hyperbaric Medicine in Sapporo, September, 1969. This conference was unsurpassed in quality of papers presented and in the book compilation of Drs. Wada and Iwa—all in an atmosphere of spontaneous cordiality and unstinting hospitality.

During the past decade there have been two additional International Congresses, one in Vancouver (1973), the other in Aberdeen, Scotland (1977). In addition to the International Meetings, there is a comprehensive survey, Hyperbaric Oxygen Therapy (1977) edited by Drs. Jefferson Davis and Thomas Hunt under sponsorship of the Undersea Medical Society. Recently, another Undersea Medical Society publication has become available, 'Hyperbaric Oxygen Review' which will be published quarterly.

In view of the general availability of this information and the advances in the field of hyperbaric oxygen (HBO) by members of your Society, it is with bridled temerity that I present an overview of some secular developments in which my intimate knowledge is confined to diving operations and treatment of associated maladies. Nevertheless, I have had the privilege of association with investigators who are concerned with the larger spectrum of clinical HBO therapy. I shall present a syncopation of guidelines from my circumscribed experience and chiefly considered statements of colleagues derived from their investigative and clinical experience.

PRELIMINARY CONSIDERATIONS

During the past decade it has become apparent that HBO affects living systems in many ways and that no single mechanism or generalization can provide an explanation either of clinical benefits or adverse reactions. Currently, we are well into the stage of investigation of the multiplicity of factors involved, and their underlying mechanisms. Illustrative and exemplary are studies of wound healing by 1) Hunt, Niinikoski, Zederfeldt, and Silver, 2) by Hohn in elucidation of the role of oxygen in microbicidal action of leucocytes, and 3) by Mader and Brown in their model investigation of the beneficial effect of HBO on staphylococcal osteomyelitis.

The role of the liver, as a result of my association with Dr. Ralph Brauer in the Sixties, will be accorded evaluation both as a prime organ for HBO investigation and clinical application.

In therapy, the initial dramatic results of HBO in the treatment of gas gangrene by Boerema, Brummelkamp, and Meijne have been extended to include over 1200 cases. Notably, in the hyperbaric chambers of Brooks Air Force Base, the healing of chronic lesions refractory to other modalities of therapy, has been most encouraging.

Advances in basic investigation over the past

decade are twofold, 1) knowledge of the role of hypoxia as a deterrent to wound healing; the beneficial effects of graded tensions of oxygen both in stimulating growth of tissue elements and promoting bacteriocidal capability of leucocytes, and 2) the elucidation by Fridovich (also, Michelson, McCord, and Fridovich) of the hyperactive radical, superoxide, and of superoxide dismutase which dismutes this radical to less toxic form. Other natural defense mechanisms against HBO damage are antioxidants as reduced glutathione, alpha-tocopherol (vitamin E), and ascorbate (vitamin C). Clearly delineated is the resistance of aerobic organisms which contain abundant superoxide dismutase, against the superoxide radical, and the lethal susceptibility of anaerobic organisms which contain no superoxide dismutase.

The elastic tube manometer permeable to diffusion from tissue of oxygen and carbon dioxide, has advanced the essential measurement of wound gas tensions under experimental conditions. Inflammation and repair augment metabolic demands of tissue such that vital portions of the repair process take place by diffusion of oxygen in the severely hypoxic wound margins. Thus it appeared to investigators that within limits the rate of tissue repair might be proportional to arterial oxygen tension. Indeed, Hunt and Niinikoski in their soft tissue wound experiments found that healing rate was accelerated in 40% oxygen and retarded in animals maintained in an atmosphere of 10 to 15% oxygen.

With reference to bone healing, chondrogenesis rather then osteogenesis may supervene if insufficient oxygen is present. Shaw and Bassett in observations of explants of embryonic chick tibiae, showed that maximum osteogenesis took place when the oxygen concentration was 35 percent. On the other hand, both collagen fiber formation and osteogenesis were suppressed either by lowering the oxygen concentration to 5% or raising it to 95 percent.

Osteomyelitic bone in the rabbit model of Mader and Brown is characterized by decreased blood flow, pH, and markedly reduced partial pressures of oxygen (20.9 torr) compared to normal bone (44.7 torr). Phagocytic killing of *S. aureus* was markedly reduced under oxygen tensions found in osteomyelitic bone. Under the oxygen tensions found in osteolytic bone treated with HBO, phagocytic killing returns to normal when compared to the phagocytic killing found under oxygen tensions in normal bone.

Multifold Actions of Oxygen: In summation, oxygen tensions above normal inhibit growth or kill organisms through at least one mechanism, superoxide-H_2O_2 formation, and also in revivification of hypoxic leucocytes. Synthesis of hydroxyproline requires an adequate supply of oxygen. HBO promotes wound healing by stimulating growth of microvasculature, formation of fibroblast endoplasmic reticulum, and epithelialization of previously denuded areas.

The specific dosages of oxygen most favorable to each facet of tissue response impose the difficult problem of translating elevated pulmonary tensions of oxygen into the several gradations required in peripheral tissues. The tension of oxygen required to kill bacteria may inhibit collagen formation. Hence, our interest in parapulmonary (as well as pulmonary) direct application of regulated oxygen pressure to peripheral areas. Fortunately, the overall range of therapeutic effectiveness of inhaled oxygen is within boundaries of oxygen tolerance established initially by Navy diving operations.

Oxygen Tensions in Tissues via Pulmonary Inhalation: At 3 ATA, it has been affirmed repeatedly that oxygen in physical solution in circulating blood is adequate to meet tissue requirements without the need for hemoglobin. Mixed venous blood withdrawn via jugular cannula from the right ventricle may not be reduced at 3 ATA (O_2) but in individual organs, there is wide variation in arterial-venous O_2 differences. In heart muscle, for example, because of the high extraction rate of oxygen, it would require 3500 torr of arterial oxygen to supply heart muscle solely with oxygen in solution. It may well be that the high extraction rate of heart muscle for oxygen is a shield against oxygen toxicity. The cerebral cortex on the other hand, would require an arterial tension of 2000 torr (equivalent to a pulmonary O_2 tension of 3 ATA),

and resting muscle only 240 torr, if oxygen were supplied only in physical solution. These estimates are derived from data of Lambertsen.

Apart from metabolic demands of tissue, the vasoconstrictive effect of oxygen and the counteracting carbon dioxide vasodilatation serve to augment the variable extraction rate of oxygen in tissues despite a constant pressure of oxygen in the lungs.

A major consideration, therefore, is control and manipulation of elevated oxygen tensions above 0.2 ATA in order to produce the desired clinical effects. From experiments of Hunt and his co-workers, it is evident that many problem wounds can be cared for with oxygen at atmospheric pressure and even at a level of 40 % of one ATA.

Further, a paramount question is, should oxygen be inhaled solely by mask as routinely employed in multiplace chambers or in addition, should patients be enveloped in oxygen as in the monoplace chamber? Current practice is far too restricted with reference to the topical (body surface) administration of oxygen, and no experiments have been conducted to observe the effects of parenteral administration of oxygen, for example, in the effort to raise the O_2 tension in the portal vein. Attention will be directed in this paper to relevant considerations that stem from our earlier experiments dealing with percutaneous diffusion of nitrogen and helium.

Factors Influencing Tolerance to Hyperbaric Oxygen: The clincial application of HBO therapy cannot be separated from long-standing utilization of oxygen to expedite decompression of divers and to treat decompression sickness (DCS). If the following tabular death of visual cells in the rabbit and decline in the beta-wave of the electroretinogram, it is probable that the early signs of visual impairment found in man at 3 ATA (Behnke et al., 1935) would have terminated any further oxygen inhalation at this level.

Oxygen Pressure	*Time of Exposure*	*Visual Cell Death*
0.50 ATA	12 days	none
0.55 to 0.60 ATA	7 days	in 50% animals
1.0 ATA	40 hrs.	in 100% animals

Oxygen Pressure (ATA)	*Duration of Latent Period Prior to Beta-wave decline in ERG (min)*
3	100
4	80
5	60
7	20

Tabular data from Werner K. Noell

The only residual changes referable to vision following repetitive exposures have been an increase in myopia. Anderson and Farmer have reported 1.6 diopters of myopia in individuals exposed repeatedly to 2 ATA oxygen. Three months following the last exposure, the HBO-induced myopia had disappeared. Had there been any parallel between the adverse effects of free radicles of HBO and those of ionizing radiation, one would have anticipated cataract formation. Overall, the remarkable absence of pulmonary complications and of residual nervous system involvement in thousands of HBO exposures in healthy men, supports the following generalization: HBO is innocuous if air replaces oxygen, when symptoms of carinal irritation supervene at 2.5 ATA or less, or symptoms referable to the nervous system above 2.5 ATA.

Dr. James Clark has provided guidelines with reference to HBO-induced decrease in vital capacity in healthy men exposed to 1-3 ATA (Table 1).

At 3 ATA, visual and circulatory changes predominate. The end of the latent period of oxygen tolerance is indicated by a reversal of bradycardia, rise in systolic and diastolic blood pressure, as well as visual decrements (Table 2, Behnke et al., 1935).

Adrenergic Action of HBO: In our early HBO tests at 4 ATA, it was the usual experience that a switch from compressed air to pure oxygen induced a stimulating respone which we designated, 'adrenergic effect'. Empirically, the apprehensive individual is much more susceptible to the untoward effects of HBO than the phlegmatic person. Experimental evidence is convincing that HBO stimulates the sympathetic nervous system.

The confirmatory tests of Edström and Röckert are impressive. Rats exposed to O_2 (6 ATA) for eight weeks with exposure time so adjusted as to give a low incidence of convulsions, manifested,

1) no lung damage at autopsy, and 2) slight motor symptoms of a paralytic nature after two weeks exposure, which disappeared during the course of five additional weeks. Histologically, there was no evidence of degenerative changes in the nervous system. The observed changes in the stellate ganglion and the adrenal gland were characterisitc of a stress reaction.

Ganglionic blocking agents reduce both pulmonary damage and the incidence of seizures. The overall impression from these and collateral studies is that HBO has a profound effect on the sympathetic nervous system.

Role of Carbon Dioxide: Apart from the adrenergic stimulus, elevated CO_2 tensions appear to be the chief factor responsible for individual and intra-individual variability. Specifically, cerebral circulation is augmented. In experiments in which a Forbes window was inserted into the cranium of an anesthetized cat, the pial vessels dilated 33 % in response to inhalation of 2 % CO_2 in oxygen at 4 ATA.

In the basic study of Hempel et al., the oxidation of cerebral cytochrome aa_3 in the cortex of the anesthetized cat could be achieved only at 4 ATA with an inhalation mixture of 5 % CO_2-95 % O_2. Maximum oxidation was achieved only through the relaxation of oxygen-induced vasoconstriction of cerebral vessels. A large blood volume response accompanied the increase in inspired carbon dioxide. An important conclusion of this study is that the capacity of cerebral mitochondria for oxygen utilization extends beyond those tensions at which the brain normally functions. Although cerebral cytochrome aa_3 is almost 100 % oxidized in oxygenated suspensions *in vitro,* it is found to be highly reduced in the brain cortex *in vivo* during resting air-breathing conditions.

Hypercapnia markedly increases the susceptibility of animals to convulsive seizures. In part, this augmentation may be attributed to increased cerebral blood flow and greater pervasivenss of oxygen pressure. Hypercapnia also counteracts the buffering capability of the brain to handle ammonia. Evidence is indicative that ammonia may play a central role in HBO-induced seizures (Banister and Singh). Glutamic acid, the precursor of gamma amino butyric acid, detoxifies ammonia. It is replenished by amination of ketoglutamic acid via the citric acid cycle. Repletion is accomplished by CO_2 fixation, involving pyruvate, to form oxaloacetic acid, which enters the citric acid cycle and proceeds to form ketoglutarate. The reaction in the brain is analogous to that which occurs in the liver (Harper)*.

*Harper, H. A. *Review of Physiological Chemistry* 14th edition Los Altos, California. Lange Medical Publications, 1973, p. 314.

Influence of Hormones: J. Argyll Campbell reported a major finding that has a profound effect on all applications of HBO, namely, that pituitary and thyroid hormones as well as increased temperature and metabolism augment oxygen toxicity. Bean and his co-workers systematically extended Campbell's observations by their unequivocal experiments in effect, that adrenal, thyroid, and pituitary hormones not only amplify the neurotoxic effects of oxygen but pulmonary pathology as well. Our early characterization of oxygen as having a direct action on the lungs ignored the unquestionable role of hormones in the toxicologic process.

Histologically, a striking effect of HBO is depletion of lipid in the zona fasciculata of the rat's adrenal cortex. The small mammal with a higher metabolic rate per kg of tissue, may be more sensitive to HBO than man. Nevertheless, the experiments of Race et al., reported in the 1969 Sapporo Conference, are cause for concern. Following one hour exposure at 2 ATA (HBO), mitochondria in the zona fasciculata of the adrenal cortex were swollen and vesiculated; lipid was decreased and there was nuclear involvement. Repair of mitochondrial membranes occurred within a matter of one to two hours following removal of the rats from the HBO environment. In tabular form factors influencing oxygen toxicity are:

Augmentitive	*Restrictive*
Adrenocortical hormones	Gamma-amino butyric acid
ACTH	Adrenergic blocking drugs
Thyroid hormone	Ganglionic blocking agents

Catecholamines	alpha-tocopherol, succinate
Elevated temperature	Hypothermia
Increased metabolism	Fasting

The 'natural allies' which make for clinical effectiveness of HBO appear to be hypothermia and fasting.

EQUIPMENT AND PROCEDURES

One step down in the astronaut's moon landing was a great leap for mankind, and one step into a hyperbaric chamber may well herald a new era in clinical therapy—with the qualification that patients get into the chamber in time.

The attractive facilities for compressed air therapy in the previous century elicit admiration. Yet, as early as 1878, Paul Bert provided the perspective in regard to equipment, pertinent to current orientation. Thus from his Monograph (p. 464), "M. Foley does not hesitate to predict the brightest future for treatment by compressed air." "Make (he says) a sedan chair closing hermetically.....attach it to a safety valve, a blower, and a manometer: in a word arrange everything, so that in this little chamber the air pressure may reach 2.5 atmospheres, at the most. And certainly you will possess a piece of equipment which will allow you to relieve many asthmatic old men, to save many children attacked by croup, and also to cure many adults afflicted with congestional, toxicohemic diseases".

"Without discussing the value of these hopes (Bert continues) we must call attention of the "realizers", as M. Foley calls them, to the fact that the construction of the apparatus is certainly more complicated and more expensive than he seems to think".

The facilities constructed by Cunningham would be ideal for long term residence in controlled hyperbaric atmospheres with provision for ancillary care of such refractory conditions as chronic osteomyelitis and radionecrosis of tissue, as well as enhancement of the effects of ionizing radiation.

In my era of hyperbaric activity beginning nearly 50 years ago in the Harvard chamber and continuing at the Navy Experimental Diving Unit in Washington, D.C., the fabrication and operation of chambers was relatively inexpensive. The funds provided for tests were also minimal. Operative procedure was readily mastered, namely, "Turn valve on! or, Turn valve off!"

Predominantly in our favor in the treatment of decompression sickness (DCS) was the critical matter of immediate access to pressurization, and the fact that all personnel were habituated to a chamber environment—the diver's second home. Ancillary therapy, such as parenteral administration of fluid was not required. We relied on natural ingestion of fluids especially following therapy.

The collapsible rubber bag reported by Ajiki et al. at the 1969 Sapporo Conference is a major contribution where hyperbaric oxygen is the prime modality of therapy as in treatment of diving accidents, CO and other poisonings. In these cases, 'Small is not only beautiful', small is mandatory as emphasized in our (Behnke) discussion.

Today, the large multi-place and the practical monoplace chamber are expensive to install and operate. Such equipment in the usual hospital setting is a 'foreign body'. Trained personnel are required to monitor stringent safety regulations, and to utilize sophisticated procedures for patient care. In surveillance of injury to the central nervous system, the clinician utilizing a monoplace chamber may employ 1) an arterial line, 2) a central venous pressure line, and 3) measurement of continuous intracranial pressure, and 4) in specified instances computerized encephalography.

Adverse Criticism of Current Practice: Multiplace chambers may be limited in pressurization to 2 ATA, and to oxygen administration by masks which supply only 60 % effective oxygen. Such equipment is inadequate for many types of therapy such as treatment of gas gangrene (*C. perfringens*) where a pressure of 250 torr is required to stop bacterial alpha toxin production, and where more than 600 torr are required to kill the pathogen.

A singular routine omission in the multiplace chamber is lack of provision for topical (parapulmonary) administration of oxygen. In the monoplace chamber, the patient of course is enveloped in oxygen but both pressure level and duration

of exposure limit the range of topical oxygen administration. Combining an isobaric cabinet, or a cubicle capable of some pressurization within the multiplace chamber would remove strictures that now curtail the scope of HBO therapy.

HYPERBARIC OXYGEN IN THE TREATMENT OF DECOMPRESSION SICKNESS

The Problem: Repeatedly we have observed in rapidly decompressed animals accumulation of bubbles in the lesser circulation associated with pulmonary tamponade, central venous hypertension, to bring about circulatory stasis.

The prime objective in therapy is restoration of blood supply by immediate recompression. There is no therapeutic procedure more effective than recompression as applied to the asphyxiated, pulseless patient whose lesser circulation has been bubble-occluded.

Air recompression therapy, certainly if limited to relatively low pressures, is ineffective. Consider then, the role of oxygen.

Genesis of Oxygen Therapy: The early investigators (Bert 1878, Zuntz 1897, Heller, Mager, and von Schrotter) concluded largely on theoretical grounds that recompression combined with oxygen inhalation provided a rational and effective treatment for decompression sickness. From the paper of Behnke and Shaw (1937), "Oxygen inhalation, however, has been neglected probably for the following reasons; conclusive experimental evidence as to its value was lacking; man's tolerance for oxygen was not known; and facilities were not available for economic administration". As a result of their experiments, Behnke and Shaw stated that recompression could be simplified to two stages in which oxygen was utilized. "In the first stage, the patient breathing a 50 percent oxygen-nitrogen mixture is recompressed to 75 pounds pressure for a minimum period of 15 minutes. Symptomatic recovery and absorption of all or nearly all of the nitrogen bubbles are the objectives of this procedure. Treatment at a pressure of 75 pounds (51.3 m) can be prolonged for two hours, if necessary. In the second stage, after the pressure has been reduced to 30 pounds, pure oxygen is breathed for a period of one to two hours. Treatment is then completed by decompression in 30 minutes to atmospheric pressure. Unrelieved or partially relieved symptoms require treatment by prolonging the recompression at 30 pounds (patient breathing air). At the end of 24 hours oxygen is breathed for two hours. Toxic symptoms from oxygen should not occur (contraction of visual fields, rise in blood pressure and pulse rate) with 3 hours of oxygen breathing in any 24-hr period".

"Since 90 percent of the cases of compressed air illness are mild and exhibit symptoms designated as 'bends' (pain in the extremities), recompression to a pressure of 30 pounds with the inhalation of oxygen for 1 hour, followed by a 30-minute decompression, should be sufficient".

The low (30 psig) HBO therapy relieved acute asphyxia in dogs rapidly decompressed from high pressure, but not paralysis. "From these experiments, it can be concluded that whenever bubble evolution is massive (i. e., after a 10-second decompression from 65 pounds, 1.75 hrs exposure) application of pressure to 65 pounds is necessary to prevent or to arrest the progress of incipient paralysis".

Spinal Cord Injury Following Decompression: The etiology of diver's paralysis may be embolic and/or the result of venous stasis in the azygos venous plexus secondary to elevation of central venous blood pressure. My experience based on post decompression observations of animals, is that there is progressive engorgement of the lesser circulation with nascent bubbles which bring about an eventual cessation of circulation. A hypothesis is that distension of veins stimulates peri-vascular sensory nerves in peripheral areas, which elicits pain. Engorgement of central veins results in pulmonary hypertension and tamponade. These events bring about asphyxia and contribute to paralysis of spinal cord origin.

A method of monitoring the degree of pulmonary vascular blockage is suggested by the result of clinical breath-by-breath infra-red analysis of carbon dioxide. When venous embolism supervenes during the course of anesthesia, there is an abrupt decline of exhaled carbon dioxide (Brechner and Bethune).

The experimental lesions observed in the spinal cord of decompressed goats, consist of infarction of white matter, peri-vascular edema and hemorrhage in gray matter (Palmer et al.).

Prolonged recompression of divers brings about recovery in paraplegic cases involving the lower extremities, if treated early, and even after a delay in some cases as long as 60 hours from onset of paralysis.

Current Therapy of Spinal Cord Injury Following Delayed Treatment: Many hours may elapse prior to recompression of injured divers. During this critical period, there is an exponential decline in the patient's condition, and ancillary therapy is paramount. In contrast to experimental diving with a chamber at hand and where recompression alone suffices for therapy, the rescue of a sport diver, by contrast, may entail many hours of delay. Dr. Xavier Fructus has outlined life-conserving measures employed in France during the transport of the CNS (Type II) injured diver.

Initially, the interim treatment comprised, 1) inhalation of oxygen, 2) one liter of fruit juice by mouth over a period of one hour, and 3) one gram of aspirin by mouth. Subsequently, in addition to oxygen, large doses of corticosteroids, aspirin (one gm, i.v.!) and 500 ml of dextran-40 were administered. "This therapeutic protocol has proved to be so effective that a potential danger may arise. The results obtained may be transient, and may then be followed by a serious recurrence of DCS if recompression is not carried out".

In this seemingly drastic type of pre-recompression therapy, consideration was accorded to a patient's possible idiosyncrasy to aspirin. However, involving all patients is aspirin-induced exacerbation of hemorrhage into tissue, so evident in histologic examination of the spinal cord of the goat following decompression injury. Likewise, Ringer's lactate solution or similar ionically-balanced preparations may be preferable to dextran. Experimentally, it has been shown that after a single dose of aspirin (975 mg) bleeding time is prolonged for as much as 5 days.

Iatrogenic Problems: In rapidly decompressed animals, fluid administration has been

*Results of Combined Transport and Recompression Treatment**

	Complete Relief (A)	*Minor Sequelae (B)*	*A + B*	*Major Sequelae*
Cerebral cases	11	4	15	1 (fatality)
Spinal cases	13	14	27	6
Mixed cases	0	6	6	0
Total: 55 cases %	44	44	88	12

* Delay in recompression therapy was 3 to 24 hrs (avg. 10 hrs.)

*Effective Table for Recompression of CNS Injury**

Meters	*Feet*	*Stay (min)*	*% Oxygen*
30	98	30	40
24	79	30	60
21	69	30	60
18	59	30	60
15	49	30	60
12	39	30	100
9	30	30	100
6	20	30	100
3	10	30	100
3-0	10-0	6	100

* French Navy (GERS, 1968) RC Treatment Table B.

life conserving in the absence of recompression. With recompression facilities available, it is the author's experience that it suffices to give fluids orally. When the lesser circulation becomes engorged with bubbles in association with pulmonary hypertension and a potential cor pulmonale, it is mandatory not to overload the right ventricle by administration of fluid intravenously.

Removal of frothy blood (pneum-exeresis) from the right ventricle via jugular cannulation, and concomitant fluid replacement remains to be implemented.

Minimal Level for HBO Inhalation and the Matter of 'Air Breaks': There is no need 'to lose the value of pressure' by HBO therapy at stages below 10.3 m (15 psig). In the San Francisco Bay Area (BART) Project, oxygen therapy was simplified by maintaining essentially two pressure levels, one at 25 to 27 psig (17.1-18.5 m) and the other at 15 psig (10.3 m) during the entire course of treatment. Since patients, particularly caisson workers 'who had made the rounds', were extremely fatigued (alcohol+serotonin effects?), they were

in the treatment of such conditions as acute coronary thrombosis, lessening pain and limiting cardiac damage" (Behnke, 1940).

Twenty nine years later I was talking to one of our medical personnel on the BART tunnel project when he experienced an acute heart attack (later confirmed as coronary occlusion). We were within 3 meters of a recompression chamber and except for the administration of oxygen by mask and of demerol, we did not utilize the HBO facility. The reasons: the patient had not been in a recompression chamber, he was apprehensive, and there were no in-chamber supporting services except hyperbaric oxygen. As a result the patient, after the injection of demerol and continued administration of oxygen, was transported to a hospital emergency treatment room. The problem we faced, despite immediate availability of HBO, was lack of in-chamber facilities for handling a cardiac patient.

With reference to treatment of near-drowning, HBO is prime therapy but again where are the facilities not only for administration of HBO but for immediate care of patients who require more than O_2 therapy.

HBO in Radiation Therapy: The experimental basis for the two to three-fold increase in effectiveness of ionizing radiation in a high tension oxygen milieu was systematically developed before introduction into tumor therapy. Now after a decade, the following considered evaluation, "While some studies, especially head and neck tumors are impressive, it has not been demonstrated unequivocably that radiation under hyperbaric conditions is superior to well fractionated, well conceived, conventional radiotherapy. Any resulting gain in survival from addition of hyperbaric oxygen will be limited, especially with more advanced stages of the disease. Well controlled studies, especially with earlier stage disease, are still necessary" (Glassburn, Brady and Plenk). This last statement is the usual conservative refrain. The problem is the difficulty of achieving a controlled *clinical* study where the primary modality, radiation, does not cure cancer but is mainly palliative.

Carbon Monoxide Poisoning-Necessity to Protect the Heart: An unchallenged application of HBO is relief of hypoxia specifically in treatment of CO poisoning. Carbon monoxide combines not only with hemoglobin but with cytochrome oxidase a_3 as well. Hence, there is failure both in oxygen delivery/to and utilization by neural and cardiac tissue.

The frequency of nervous and mental sequelae of CO poisoning are grave, but have been reported as relatively infrequent. Out of 21,143 cases of CO poisoning in New York City, only 43 patients had after-effects, and of these, only 9 had chronic signs and symptoms referable to the nervous system (Shillito, Drinker, & Shaughnessy). In CO poisoning it is the heart that is vulnerable in all patients, and every effort must be made to conserve function of heart muscle. Following a hospital fire, limited to combustion of x-ray film but involving inhalation of CO and other gases by doctors and associate personnel, individuals who remained absolutely quiescent, survived. Those who engaged in physical exertion died. A mandatory measure therefore, in first aid treatment of carbon monoxide gassed patients, is their handling as stretcher cases.

Is Carbon Dioxide Required in HBO Therapy of CO poisoning?: Apart from manner of application and dosage of oxygen, is the question of ancillary modalities. Carbon dioxide markedly augments cerebral blood flow and as a consequence, brain volume which could contribute to vasogenic edema (Peirce and Jacobson). In the investigation of Forbes, Cobb, and Fremont-Smith (1924), cerebral edema and headaches were recognized as sequelae of carbon monoxide asphyxia. Yet Drinker and Shaughnessy (1929) reported, "No experimental or clinical evidence has been uncovered to demonstrate any damage from 7 percent carbon dioxide, and 300 cases of carbon monoxide poisoning treated with a mixture of 7 percent carbon dioxide and 93 percent oxygen for the first 5 to 20 minutes, completing the treatment with the usual 5 percent carbon dioxide - 95 percent oxygen, have shown good results. It is stated that breathing is more active and consciousness returns more quickly".

There is conflict then between employment of

allowed to sleep through 'air intervals'. Further, it is probable that resaturation with nitrogen is appreciable during the 'air breaks' based on studies of Dr. J. D. Adams, Brooks Air Force Base, who has quantified at one ATA (O_2) nitrogen uptake during air intervals and the compensatory oxygen make-up time required (Table 3).

Air Intervals During the Course of Prolonged HBO Therapy: In treatment of patients with Type II injury, specifically involving the spinal cord, 'air breaks' are requisite. With a 20-min(O_2)—5 min (air) schedule, about 5 hours of net oxygen inhalation time is available over a period of 12 hours. A patient that I treated for spinal cord injury (following inadequate initial therapy) developed carinal irritation during the course of prolonged HBO recompression therapy. Nevertheless, he was able to benefit from 7.5 hrs of net oxygen inhalation (2.82 ATA) during the course of 13 hours. It is recalled that at this HBO level, light exercise (ergometer cycling) is not tolerated by healthy subjects for more than 18 min, and they are prone to develop convulsive seizures.

Experimental Spinal Cord Injury with Clinical Application: In the experiments of Kelly et al., the spinal cord of laminectomized dogs was traumatized and examination was made of tissue Po_2 during the course of different inhalation mixtures. The tissue Po_2 in the intact spinal cord of dogs can be increased by ventilating the animals with 100% oxygen or carbogen (95% O_2-5% CO_2). The tissue Po_2 of the traumatized spinal cord, however, responded only to hyperbaric oxygenation (2 ATA). "The results of treatment of experimental paraplegia with hyperbaric oxygen are equal to those of local hypothermia in this experimental model". A conservative statement, surely, comparing 'two allies', namely HBO and hypothermia.

In a review by Yeo, Stabback, and McKenzie, and of their own experiments with sheep, it was concluded that ischemia plays a major role in the pathogenesis of post traumatic spinal cord necrosis, and results in the associated loss of motor function below the level of the lesion. "In support of this theory are reports that HBO improves motor recovery in paraplegic animals". It was concluded that HBO appears to be a form of treatment for trial in paraplegic patients. As a follow-up, HBO therapy administered to three paraplegic patients produced promising results. The recommendation was made that HBO be given for treatment of post traumatic ischemic cord lesions, *provided that patients are admitted within 12 hrs of the injury.*

The Logistic Problem: In the treatment of the paralyzed diver, it is feasible to administer HBO and to keep him in compressed air for prolonged periods of time. With reference to the surgical intervention required to take care of a traumatized spinal cord, one would need a pressurized operating room and an adjunct holding facility for nursing care.

COMMENTS ON CLINICAL ENTITIES AMENABLE TO HBO

The Committee on Hyperbaric Oxygenation of the Undersea Medical Society has provided a categorical classification of various clinical conditions in regard to degree of benefit from employment of oxygen at increased pressures. This type of analysis provides guidelines for those concerned with cost impact and cost reimbursement. It is however premature and artificial to categorize various ailments until procedures for application of HBO have attained maturity and until we have exploited all of the multiple facets of the HBO modality. Consider for example, Category III, "Disorders for which no HBO animal studies or preliminary clinical trials have shown promise or for which there is a good theoretical indication, are included in this section. However, definitive evidence that HBO is as effective as or superior to other forms of therapy is inadequate for these conditions, either because the data are conflicting or insufficient." In this category are near-drowning, hepatic necrosis, and myocardial infarction.

With reference to myocardial infarction, no firmer theoretical basis exists for HBO therapy of this malady. I admit to some bias since in 1940, I pointed to myocardial infarction as a prime entity for HBO treatment. "The diffusion of oxygen into tissues emphasizes its specific value

HBO+CO_2 and HBO alone. The addition of CO_2 to HBO greatly increases the oxidation of cytochrome aa_3 (Hempel et al.), and presumably would render HBO more effective in displacement of CO from the respiratory enzyme. This dilemma in choosing measures which render HBO more effective but have potential undesirable side effects is the immediate problem for clinical solution and not the overall matter of controlled clinical trial.

HBO in Burn Therapy: The problem of controlling infection on the burned skin surface is formidable. If the burned skin areas are enveloped in oxygen in a cubicle within a multiplace chamber, HBO therapy is feasible with the patient breathing air, nitrox mixture (O_2, 0.5 ATA), or heliox mixture, at pressures not mandated by current pulmonary inhalation of oxygen.

If the burned surface could be cooled, and the core of the body kept warm, it may well be possible to maintain the patient in a satisfactory condition during the critical 48 hours following burn injury. These potential applications have been evident to a number of investigators from the time of J. B. Haldane who introduced the 'oxygen bath' (1 ATA) for treatment of skin ulcers 60 years ago.

Despite the limitation of manipulative control of surface oxygen tension, the experience of Ikeda et al. in the clinic of Wada and Iwa, has been confirmed repeatedly, namely that in the HBO atmosphere surface wounds are dry, show less infection, and exhibit a tendency toward more rapid healing. Notably, fluid loss from the burned surface is decreased. Although the oxygen tensions lethal for bacteria might well impair regeneration of tissue, there can be rigid control (yet to be achieved) of the tension of oxygen in contact with damaged tissue.

Percutaneous Diffusion of Gases: Cutaneous respiration experiments in man (Shaw, Messer, Weiss, 1929) revealed that when the carbon dioxide tension of the air is higher than that of the blood, carbon dioxide is absorbed; likewise, when oxygen tension is lower than that of the blood, oxygen is excreted. Intact skin is a slightly permeable barrier to gas exchange. If, in the anesthetized cat, skin is removed and muscle exposed, the rate of carbon dioxide excretion from exposed muscle tissue is about 14 times greater than from skin. Likewise, nitrogen diffuses through intact skin in measurable amounts but if the skin is incised, nitrogen loss from the body via pulmonary transport is greatly augmented. The significance of these experiments is not only the effectiveness of topical oxygen in diffusion into the open wound, but the loss of carbon dioxide, presumably in elevating the pH of wound tissue. It would appear necessary with respect to wound healing to create a controlled, closed gaseous envelope over the wound.

Hepatic Necrosis: Category III (from HBO Committee Guidelines): "Hepatic necrosis is a catch-all term which probably describes underlying conditions. As it is impossible to ascribe causative effects here, the use of hyperbaric oxygen could be capricious. Until it is further defined, and a theoretical mechanism can be described for hyperbaric oxygen, it would have to remain a research area".

In their 1967 review, Behnke and Saltzman devote a paragraph to carbon tetrachloride and chloroform poisoning. "Chloroform administered to dogs is less toxic if oxygen instead of air is used to vaporize the anesthetic. There is some degree of improvement in oxygen saturation of blood in the portal vein. The significance of this finding is that the primary manifestation of some poisonings, notably the chlorinated hydrocarbons, is acute hepatic insufficiency". Brauer has analyzed the many derangements associated with hypoxic conditions of the liver. After the primary insult to liver cells by a toxic agent, it is possible to modify the course of injury by administration of HBO to counteract among other effects, impairment of capillary blood distribution. Any procedure such as administration of HBO that will improve oxygen saturation of blood in the portal vein and hepatic artery, will serve to interrupt a 'vicious cycle of liver disease' in which without oxygen, the effect of the initial injury is compounded. Thus, exposure of the rat to oxygen (3.5 ATA) during the first three hours after CCl_4 administration markedly reduces the tissue damage

produced.

The Liver As a Target Orgen In HBO Investigation: During a period of 8 years, I had the opportunity to observe the usefulness of the isolated perfused rat liver in many studies of liver function conducted by Brauer, Leong, and Holloway. The rat liver for many hours replicates *in vitro,* various functions *in vivo.* Histologically, electron microscopic preparations of liver tissue can be analyzed in relation to functional decrements produced by various agents and procedures.

In the skilled hands of Brauer and his colleagues, the following parameters have been examined with the isolated rat liver preparation perfused with blood, plasma, albumin, and Locke's solution, 1) perfusate flow, 2) chromic phosphate extraction, 3) bromsulphalein (BSP) extraction efficiency and concentration in bile, 4) bile flow rate, 5) cholate concentation in bile, 6) perfusion pressure at standard flow rate, 7) and function at 37 and at 28°C to illustrate the protective effect of hypothermia when circulation is impaired.

An example of the value of the isolated rat liver which elucidates the need of blood cells in perfusate rather than plasma alone at 3 ATA (O_2), is the following: "One might be led to infer that under these conditions (3 ATA, O_2) the oxygen physically dissolved is adequate to supply requirements of tissues or even small mammals... Yet in some tissues at least (liver and lung) the situation may not be so simple. If the erythrocytes in perfusate of the isolated perfused rat liver were functioning merely as a reservoir of oxygen, then hepatic O_2 consumption should be independent of the hematocrit. On the contrary, hepatic O_2 uptake varies nearly linearly with the hematocrit. One may wish to consider whether in the HBO-oxygenated subject, the erythrocytes are really inert, or whether tissue oxygenation may not involve a portion of oxygen passing from plasma to the erythrocytes, rather than diffusing directly from plasma to tissues....This question could well have an important bearing upon the physiologic status of patients or animals rendered anemic for one reason or another during hyperbaric oxygenation, and it may also lead one to inquire about a more active role of erythrocytes in connection with development of oxygen toxicity". (Brauer, unpublished analysis)

In vivo, following partial excision, the rat liver regenerates, such that organ weight attains the pre-excision value. There is no better preparation, largely neglected, for metabolic and morphologic studies of HBO relative to pressure level in relation to duration of exposure, than rat liver, *in vivo* and *in vitro.*

Cyanide Poisoning: The antagonism of two toxic substances, oxygen at high pressure and cyanide, is a phenomenon of special note. Bean and Bohr found that oxygen (3 to 6 ATA) sharply decreased the tonus of the isolated pyloric sphincter muscle of rabbits. Investigators who inhaled oxygen at 3 and 4 ATA were aware of 'periodic waves of nausea' as an early and recurrent symptom of idiosyncrasy to oxygen. Cyanide applied to the isolated sphincter muscle counteracts this specific effect of oxygen.

High pressure oxygen on the other hand, protects against cyanide poisoning with subsequent thiosulphate detoxification. Whether thiosulphate treatment is essential following cyanide poisoning remains to be determined. I have witnessed experiments (exposure of the cat) in which HBO (3 ATA, 0.5 hrs) alone restored an animal injected with an otherwise lethal dose of cyanide to apparent normality. The case cited by Dr. William Trapp is an example of recovery in man following massive cyanide poisoning and treatment with HBO (3 ATA) and thiosulphate as well.

The mode of action of cyanide is known in broad outline and merits further investigation as exemplified by experiments of Takano, Miyazaki, and Nashimoto. The combination of the cyanide ion with an atom of oxygen gives a metal-cyanide complex; this combination inhibits cytochrome oxidase in the terminal segment of the electron transfer chain to bring about a generalized inhibition of cellular respiration:

Cytochrome oxidase + CN $\rightleftarrows$
Cytochrome oxidase cyanide

Barcroft showed that cyanide is detoxified within the organism by conversion to a non-toxic thiocyanate,

Thiosulphate + CN → sulphite + thiocyanate
Hyperbaric oxygen does not affect this reaction.

Skene, Norman, and Smith state, "If oxygen at increased tension has no effect on the rate of detoxification, it is possible that it exerts its effect by disturbing the equilibrium between cytochrome oxidase + CN, and cytochrome oxidase cyanide driving the reaction to the left and freeing increased amounts of cytochrome oxidase for continuance of cellular respiration".

Pertinent is the finding, previously mentioned, of Hempel et al., that the capacity of cerebral mitochondria for oxygen utilization extends beyond those tensions at which the brain normally operates. "A highly reduced cytochrome aa_3 in normoxia could possibly explain the initiation of synthesis or increase in activity of this enzyme with increases in the oxygen needs of the organ or tissue involved". However, pure oxygen even at 4 ATA could not be used to obtain maximum oxidation of cytochrom aa_3 because of the vasoconstrictor effect on the cerebral vessels of the cat. *The fully oxidized state is achieved only with addition of 5% CO_2 to 95% O_2 at 4 ATA.*

In cyanide poisoning, CO_2 should render the beneficial action of HBO more effective - this remains to be demonstrated experimentally.

A CATEGORY IV SPECULATION

(Disorders....for which no theoretical basis for treatment exists)

The distinguished British investigator of the early Thirties of this Century, J. Argyll Campbell, exposed mice in an atmosphere of 0.24 % carbon monoxide for 225 days. He found that in addition to hypertrophy of the heart, *that the development of neoplastic conditions in mice was retarded!* I am not aware of any follow-up of Campbell's investigation but the above finding suggests a study of gaseous substances which may inhibit tumor growth.

The various avenues of possible applications of HBO, and of HBO and ancillary substances should not be circumscribed at this time by delimiting categorization. Consider then, that cyanide a potent lethal agent, is nevertheless, unlike carbon monoxide, restricted to injury emanating from histotoxic anoxia. It is not a cumulative poison and in non-fatal cases recovery is generally complete. Rarely are neuro-psychiatric sequelae observed as in carbon monoxide poisoning. Certainly, basic chemical information is required to elucidate the specific mechanism of HBO-CN antithesis, and to resolve current cumbersome ancillary therapy.

Chemotherapy in the treatment of various types of malignancy is fraught with abject debilitation. Ionizing radiation, although dosage may be reduced in oxygenated tissue, is relatively uncontrolled, and destructive to body economy as well. It is a carcinogenetic agent !

It is warranted then, to examine the potential of an agent applied locally (and possibly systemically) with circumscribed and clearly defined asphyxial action, against which hyperbaric oxygen is an effective antidote.

In the United States, four noted cancer centers will attempt to evaluate the controversial but widely employed lay substance, 'Laetrile' (amygdalin) as having any merit in treatment of cancer. Amygdalin is a glucoside which is split by an enzyme into benzaldehyde, glucose, and a minute amount of hydrocyanic acid. Fatal cyanide poisoning has been reported from accidental ingestion of Laetrile.

As in the evaluation of HBO as a useful adjunct in radiation therapy, the attempt will be made to conduct 'strictly controlled' clinical trials of the combined 'shot-gun' elements that make up Laetrile. Since more than a decade has elapsed without a definitive answer as to the value of HBO in radiation therapy (currently without categorization), we may well have the same indeterminate results in the effort to approach the mirage of the so-called controlled clinal trial series.

However, the evaluation of amygdalin may be focussed initially on a single objective. It is conceivable that the only active element in Laetrile, namely a tiny amount of cyanide, may exert an inhibitory action on the growth of cancerous tissue. The specific objective would be to evaluate the localized action of cyanide on tumor tissue with HBO available to counteract

systemic toxicity.

CONCLUDING NOTE - AN OXYGEN MOSAIC IN SUPPORT OF CELLULAR METABOLISM

The regulation of tissue oxygen tensions most favorable to the diversified role that oxygen plays in the healing process, can be achieved at this time. The administration with oxygen of nutrient substances as glucose and amino acids which can diffuse into cells, and of osmolar solutions, is routine.

Procedures which are favorable to the action of hyperbaric oxygenation as fasting and hypothermia can be employed discriminately. The new era which may be imminent is to supply with oxygen those intracellular substances which support the 'respiratory chain' in mitochondria. From lipid dispersed in aqueous solution, one can form vesicles which already have shown capability of transfer of substances through cellular membranes. It may well be that adenosine triphosphate (ATP), the source of energy for organ metabolism can be transfered into cells, to supply what cells really need. The last figure, visionary to be sure, suggests that where hyperbaric oxygen alone has failed, together with an exogenous supply of ATP, the aging process may be inhibited, if not in some degree reversed.

REFERENCES

1) Ajiki, H., J. Wada, K. Ikeda, S. Sugii, K. Karino, and T. Iwa: Our Collapsible Rubber Bag. In: Proceedings of the Fourth International Congress on Hyperbaric Medicine. Eds. J. Wada and T. Iwa. Tokyo: Igaku Shoin, 1970 pp. 501-504.

2) Anderson, B., and J. C. Farmer: Hyperoxic myopia. Trans. Amer. Opthal. Soc. 76: 116-124, 1978.

3) Banister, E. W., and A. K. Singh: The central role of ammonia in OHP induced convulsions. 7th Symposium on Underwater Physiology, Undersea Medical Society, July 5-10, 1980 (From Programs, Abstracts, and Mini-papers), pp. 24-25.

4) Bean, J. W.: Hormonal aspects of oxygen toxicity. In: Underwater Physiology Symposium, Ed. L. Goff. Washington, D. C. Nat. Acad. Sci- Nat. Res. Council, Publ. 377, 1955, pp. 13-19.

5) Behnke, A. R., H. S. Forbes, and E. P. Motley: Circulatory and visual effects of oxygen at 3 atmospheres pressure. Amer. J. Physiol. 114: 436-442, 1935.

6) Behnke, A. R. and L. A. Shaw: The use of oxygen in the treatment of compressed-air illness. Nav. med. Bull., Washington, 35: 61-73, 1937.

7) Behnke, A. R.: High atmospheric pressures; physiological effects of increased and decreased pressure; application of these findings to clinical medicine. Ann. Int. Med. 13: 2217-2228, 1940.

8) Behnke, A. R., and H. Saltzman: Hyperbaric Oxygenation (Medical Progress) New England J. Med. 276: 1423-29, 1478-84, 1967.

9) Bert. P.: *Barometric Pressure* trans. M. A. and F. A. Hitchcock. Bethesda, Md. republished Undersea Medical Society, p. 464.

10) Brauer, R. W., G. F. Leong, and R. J. Holloway: Liver injury in the isolated perfused rat liver preparation exposed to chloroform. Amer. J. Physiol. 200: 548-550, 1961.

11) Brauer, R. W.: Liver circulation and function. Physiol. Rev. 43: 115-213, 1963.

12) Brechner, V. L., and R. W. M.: Bethune. Recent advances in monitoring pulmonary air embolism. Anes. & Analg. 50: 255-261, 1971.

13) Campbell, J. A.: Hypertrophy of the heart in acclimatization to carbon monoxide poisoning. J. Physiol. 68: 81-96, 1929-30.

14) Campbell, J. A.: Effects of oxygen pressure as influenced by external temperature, hormones, and drugs. J. Physiol. 92: 29-31, 1938.

15) Clark, J. M.: Table of Constant Degrees of Pulmonary Oxygen Poisoning at Different Inspired Oxygen Pressures, Institue for Environmental Medicine, Univ. Pennsylvania (personal communication).

16) Drinker, C. K. and T. J. Shaughnessy.: The use of 7 percent carbon dioxide and 93 percent oxygen in the treatment of carbon

monoxide poisoning. J. Ind. Hyg. 11: 301-314, 1929.

17) Deneke, S. M. and B. L. Fanburg: Normobaric oxygen toxicity of the lung. N. E. J. Med. (Medical Progress). 303: (2)76-84, 1980.

18) Edström, J. E., and H. Röckert: The effect of oxygen at high pressures on the histology of the central nervous system and sympathetic and endocrine cells. Acta Physiol. Scand. 55: 255-263, 1962.

19) Forbes, H. S., S. Cobb, and F. Fremont-Smith: Cerebral edema and headache following carbon monoxide asphyxia. Arch. Neurol. Psychiat., Chicago. 11: 264-281, 1924.

20) Fridovich, I.: Superoxide radical and superoxide dismutase. Accounts of Chem. Res. 5: 321, 1972. (Also, Michelson, A. M., J. M. McCord, and I. Fridovich. *Superoxide and Superoxide Dismutases.* London. Academic Press, 1977).

21) Fructus, X.: Treatment of serious decompression sickness. In: The Twentieth Undersea Medical Society Workshop on Treatment of Serious Decompression Sickness and Arterial Gas Embolism. 11-14 Jan. 1979, Undersea Medical Society, pp. 37-49.

22) Glassburn, J. R., Brady, L. W., and H. L. Plenk: Hyperbaric oxygen in radiation therapy. Cancer 39: 751-765, 1977.

23) Heller, R., W. Mager, and H. von Schrötter: *Luftdruck-Erkrankungem.* Vols. 1 and 2. Vienna. A. Holder, 1900.

24) Hemple, F. G., F. F. Jöbsis, J. L. La Manna, M. R. Rosenthal, and H. A. Saltzman: Oxidation of cytochrome aa_3 by oxygen plus carbon dioxide at hyperbaric pressures. J. Appl. Physiol. 43 (5): 873-879, 1977.

25) Hohn, D.C.: Oxygen and Leucocyte Microbial Killing, In: *Hyperbaric Oxygen Therapy.* Eds. J. C. Davis and T. K. Hunt. Bethesda, Md. Undersea Med. Society, 1977. pp. 101-110.

26) Hunt, T. K., J. Niinikoski, B. H. Zederfeldt, and I. A. Silver: Oxygen in Wound Healing Enhancement. ibid. pp. 111-140.

27) Ikeda, K., H. Ajiki, H. Nagao, K. Karino, S. Sugii, T. Iwa, and J. Wada: Experimental and Clinical Use of Hyperbaric Oxygen in Burns. In: Fourth Int. Cong. Hyperbaric Medicine, Eds. J. Wada and T. Iwa. Tokyo. Igaku Shoin, 1970. pp. 377-80.

28) Kelly, D. L., Jr., K. R. L. Lassiter, A. Vongsvivut, and J. M. Smith: Effects of hyperbaric oxygenation and tissue oxygen studies in experimental paraplegia. J. Neurosurgery, 36 (4) 425-429, 1972.

29) Ketchum, S. A. lll, A. N. Thomas, A. D. Hall: Angiographic studies of the effect of hyperbaric oxygen on burn wound revascularization. In: Proceedings Fourth International Congress on Hyperbaric Medicine. Eds. J. Wada and T. Iwa Tokyo, Igaku Shoin, Ltd. 1970. pp. 387-399.

30) Lambertsen, C. J.: Effects of oxygen at high partial pressue. In: *Respiration,* Vol. II, Handbock of Physiology, Eds. W. Fenn and H. Rahn. Washington, D. C. Amer. Physiol. Soc., 1965, pp 1034-1055.

31) Mader, J. T., and Brown, G. L.: A mechanism for the beneficial effect of hyperbaric oxygen on staphylococcal osteomyelitis. 7th Symposium Underwater Physiology, Undersea Medical Society, (Program, Abstracts, and Mini-papers) July 1980, pp 40-41.

32) Mosso, A.: La mort apparente du coeur et les secours dans l'empoisonnement par l'oxyde de carbone. Arch. ital. Biol. 35: 75-89, 1922.

33) Noell, W.K.: Effects of high and low oxygen tensions on the visual system. In: *Environmental Effects on Consciousness.* Ed. K. E. Schaefer, New York. The Macmillan Co. 1962. pp. 3-18.

34) Niinikoski, J.: *Oxygen and Trauma.* Final Technical Report, Europaen Research Office, United States Army, ISBN 951-99011-6-6, 1972.

35) Niinikoski, J., and T. K. Hunt: Oxygen tensions in healing bone. Surg. Gynec. & Obst. 134: 746-750, 1972.

36) Niinikoski, J., T. K. Hunt, and J. E. Dunphy: Oxygen supply in healing tissue. Amer. J. Surgery, 123: 247-252, 1972.

37) Palmer, A. C., W. F. Blakemore, and A. G. Greenwood: Neuropathology of experimental

decompression sickness (Dysbarism) in the goat. Neuropath. & Appl. Neurobiol. 2: 145-156, 1976.

38) Peirce, E. C., II, and J. H. Jacobson, II.: Cerebral edema. In: *Hyperbaric Oxygen Therapy.* Eds. J. C. Davis and T. K. Hunt. Bethesda, Mad. Undersea Med. Coc. 1977, pp. 287-301.

39) Richardson, H. F., B. C. Coles, and G. E. Hall: Experimental gas embolism. Canadian Med. Assn. J. 36: 584, 1937.

40) Race, G. J., J. L. Mathews, J. W. Finney, and J. H. Martin: Ultrastructural changes in rat adrenal cortex following hyperbaric oxygen (OHP). In: Proceedings Fourth International Congress on Hyperbaric Medicine. Eds. J. Wada and T. Iwa. Tokyo. Igaku Shoin Ltd. 1970. pp. 170-178.

41) Shaw, L. A., A. C. Messer, and S. Weiss: Cutaneous respiration in man. Amer. J. Physiol. 90: 107-117, 1929.

42) Shaw, J. L., and C. A. L. Bassett: The effect of varying oxygen concentrations on osteogenesis and embryonic cartilage *in vitro.* J. Bone & Joint Surg. 49: 73-80 (Jan) 1967.

43) Shillito, F. H., C. K. Drinker, and T. J. Shaughnessey: The problem of nervous and mental sequelae in carbon monoxide poisoning. J. Amer. Med. Assn. 106: 669-674, 1936.

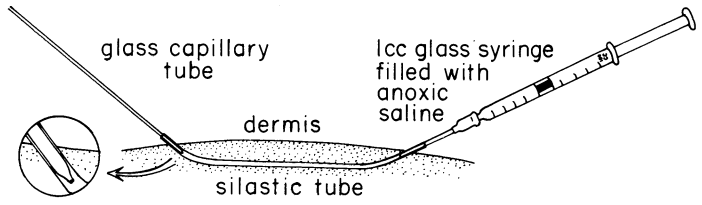
44) Skene, W. G., J. N. Norman, and G. Smith: Effect of hyperbaric oxygen on cyanide poisoning. In: Proceedings Third International Congress on Hyperbaric Medicine. Eds. I. W. Brown, Jr., & B. G. Cox. Washington, D. C. Nat. Acad. Sci. & Nat. Res. Council. 1966. pp. 705-710.

45) Takano, T., Y. Miyazaki, I. Nashimoto, and K. Kobayashi: Effect of normobaric and hyperbaric oxygen on cyanide intoxication. 7th Symposium on Underwater Physiology, Undersea Medical Society (Program, Abstracts and Mini-papers) July, 1980, p. 20.

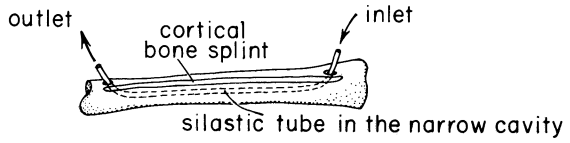
46) Trapp, W. G.: Massive cyanide poisoning with recovery: A Boxing-day story. Canad. med. J. 102: 517, 1970.

47) Yeo, J. D., S. Stabback, and B. McKenzie: A study of the effects of hyperbaric oxygen on experimental spinal cord injury. Med. J. Aust. 2: 145-147, 1977.

48) Zuntz, N.: Zur Pathogenese und therapie der durch raschi Luftdrunkänderungen erzeugten Krankheiten. Fortschr. Med. 15: 632-639, 1897.



A. Soft tissue (Niinikoski, 1972)



B. Bone (Niinikoski and Hunt, 1972)

Fig.1 Measurement of tissue gas tensions using an implanted silastic tube and capillary sampling technique. Equilibration of tissue gases takes place through the wall of the silastic tubing (Niinikoski, and Niinikoski and Hunt, 1972).

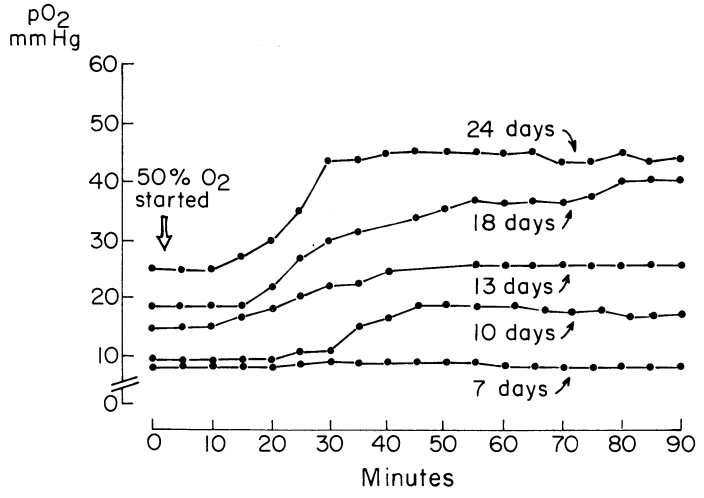


Fig.2 Response of wound po_2 to breathing 50% oxygen (rabbit ear) After Niinikoski, Hunt, Dunphy, Am. J. Surg. 1972.

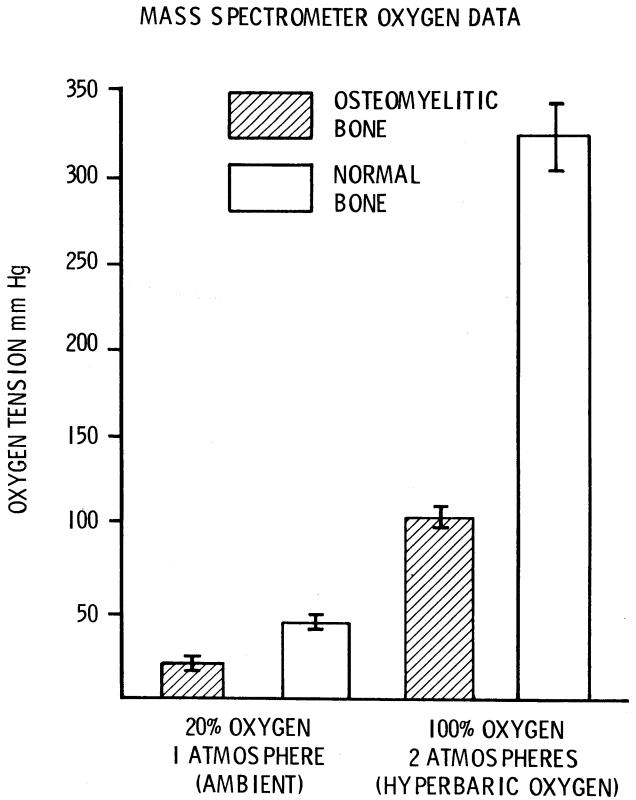


Fig.3 Mass spectrometer oxygen data. Oxygen tension is lower in osteomyelitic rabbit bone than in normal bone (Mader and Brown, 1980).

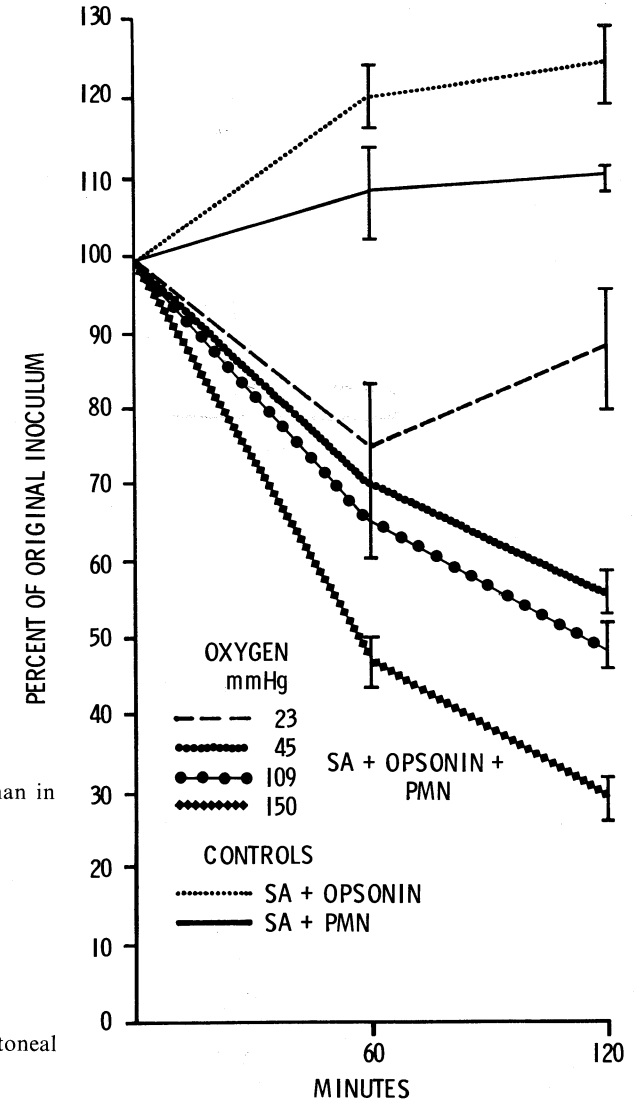


Fig.4 Phagocytic killing of S. Aureus (SA) with opsonin (10% human serum) by rabbit peritoneal leucocytes PMN, under oxygen tensions from 23 to 150 torr. (Mader and Brown, 1980).

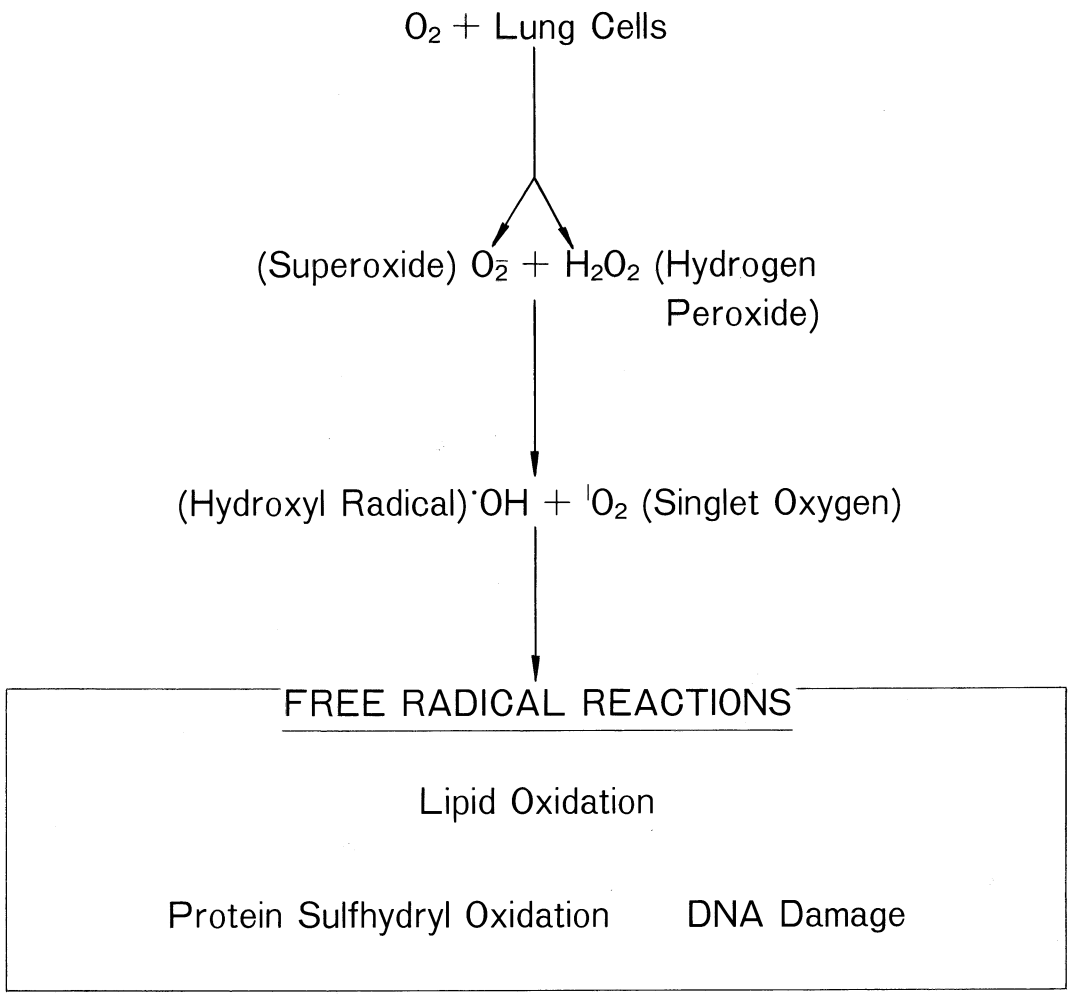


Fig.5 Chemical mechanisms of oxygen toxicity - one schema from a biochemical wilderness (Deneke and Fanburg).

HYPEROXIC (H-O)
+ 0.2 to 1 ATA

HYPERBARIC (HBO)
+ 1 ATA

Mode of Application ?

Fig.6 Again and again a recurring problem. How much oxygen ?

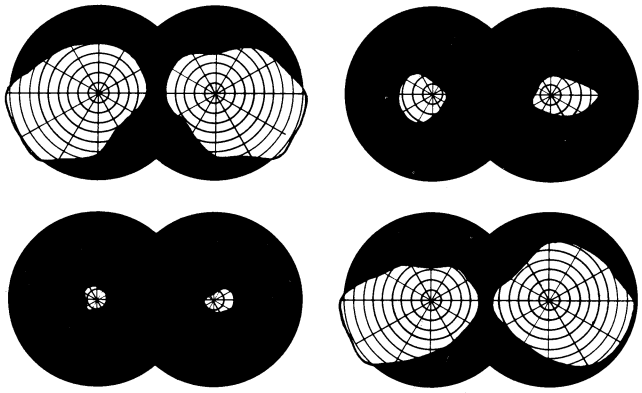


Fig.7 Obliteration of the visual fields during the course of oxygen inhalation (3 ATA). Duration 3.5 hours and recovery in an air atmosphere (Behnke, Forbes, and Motley, 1935).

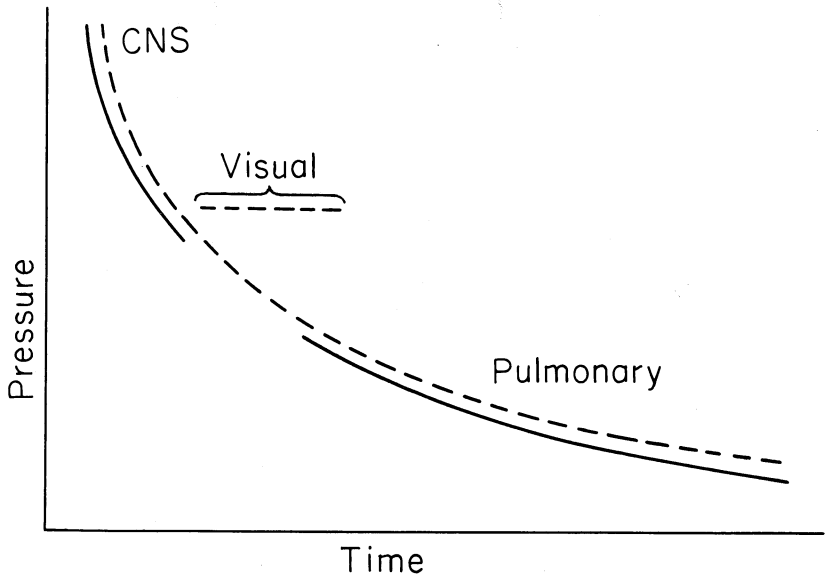


Fig.8 Dichotomy between pulmonary and nervous system effects of HBO. The visual system of rabbits is adversely affected from one to six ATA (based on data from Noell, 1962).

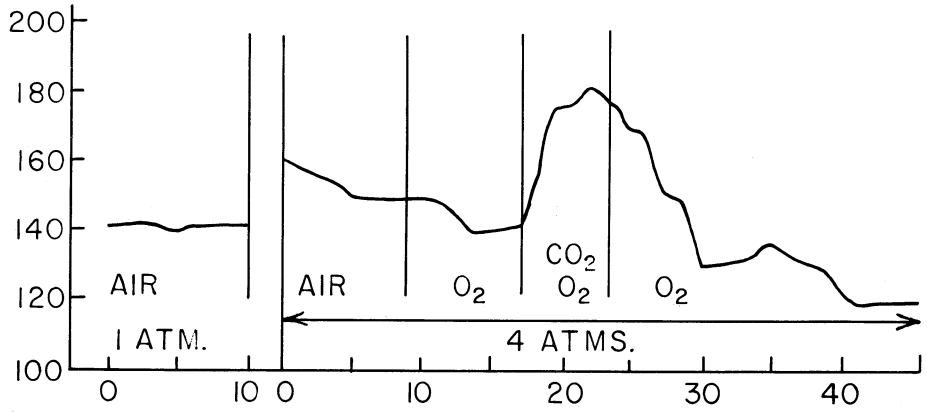


Fig.9 Dilatation of the pial arterioles of the cat by inhaled CO_2 at 4 ATA. Note the minor effect of HBO (Behnke, Forbes, Motley, 1935).

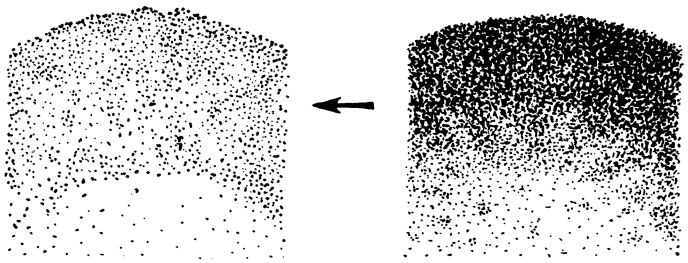


Fig.10 HBO lipid depletion from the cortex of the adrenal gland (J. W. Bean, 1955).

One Step Down in the Astronaut's Moon Landing—
A Great Leap for Mankind!

One Step Up into a Hyperbaric Chamber
Heralds a New Era?

Renaissance of an Old Modality in Clinical Therapy

Fig.11

Fig.12 The Cunningham Sanatorium and Pressure Chambers, Cleveland, Ohio, 1928. The sphere to the right of the cylindrical chamber, is six stories in height and contains 72 rooms and all amenities for long term residence.

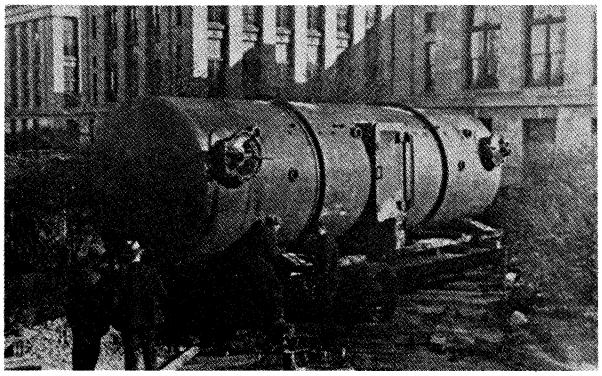
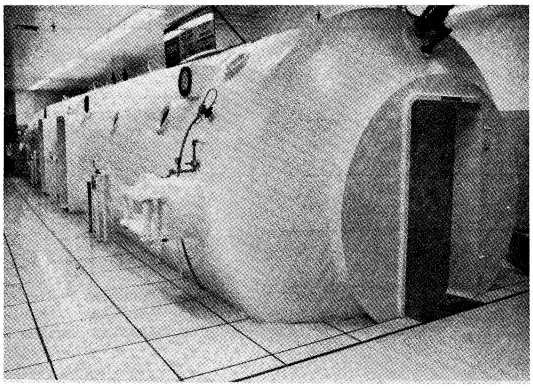
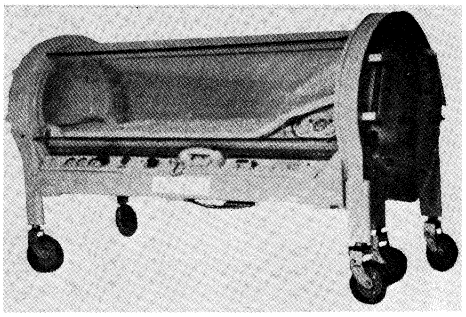


Fig. 13 Installation of the hyper-hypobaric chamber at the Harvard School of Public Health, 1928.



MULTIPLACE CHAMBER —
Inhalation of oxygen by face mask,
head tent, or endotracheal tube.



MONOPLACE CHAMBER —
Patient enveloped in oxygen.

Fig. 14 Current examples of multiplace and monoplace chambers.

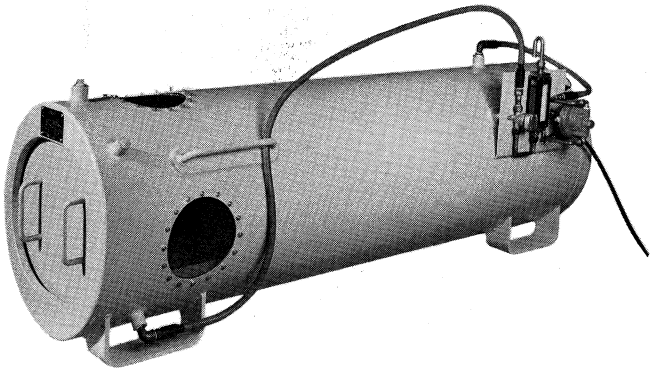


Fig. 15 A portable chamber. Conspicuous by absence is the pressurized rubber bag of Ajiki et al. 1970.

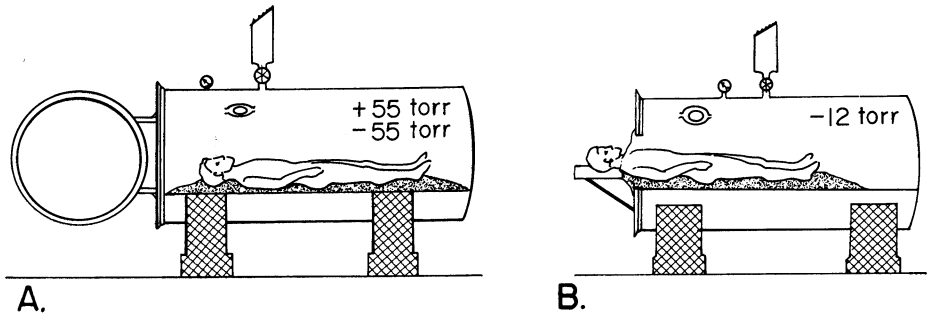


Fig.16 Chambers to sustain respiration. **A.** The barospirator of Professor Thunberg. **B.** Diagram to illustrate principle of the Drinker respirator, circa 1928.

BASIC THEME - TOPICAL APPLICATION OF OXYGEN

ANALOGY TO PERCUTANEOUS DIFFUSION OF INERT GAS

Fig.17

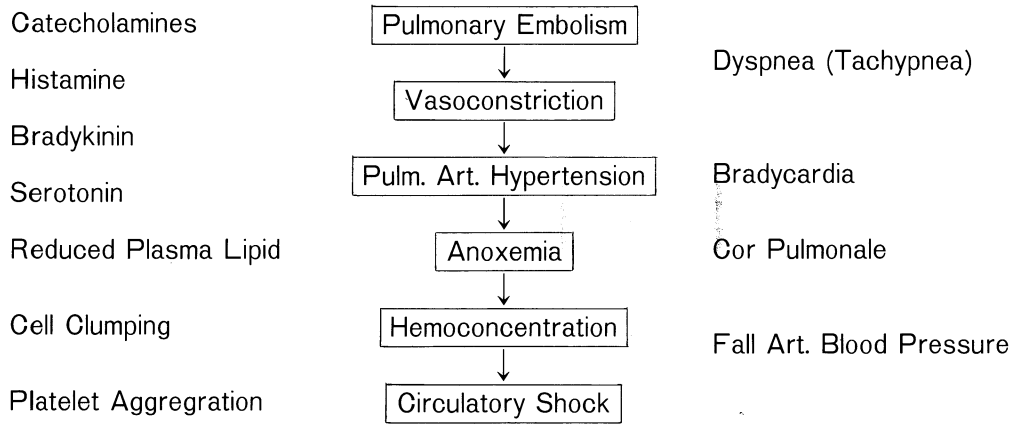
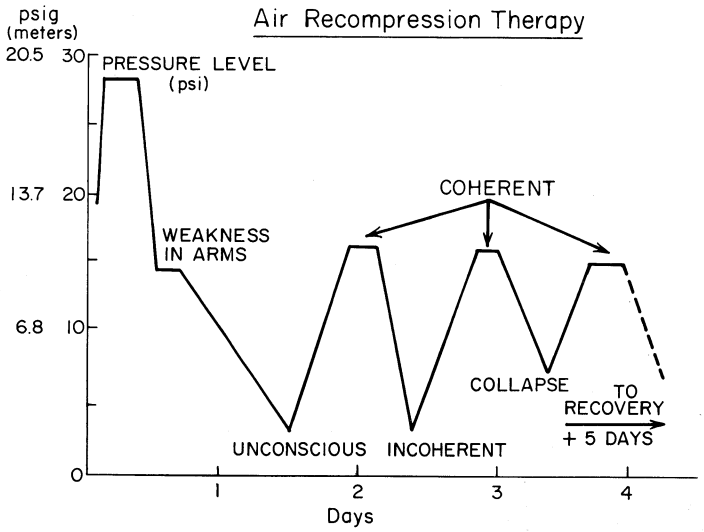


Fig.18 Diagram showing sequence of events which accompany multiple embolization of the lesser circulation resulting in pulmonary tamponade and hypertension.



Clinical response in relation to pressure level (above atmospheric) in a Type II (serious) case of decompression sickness.

Fig.19 Ineffectiveness of Air Recompression Therapy (adapted from Golding et al. Brit. J. Med. 17: 167, 1960).

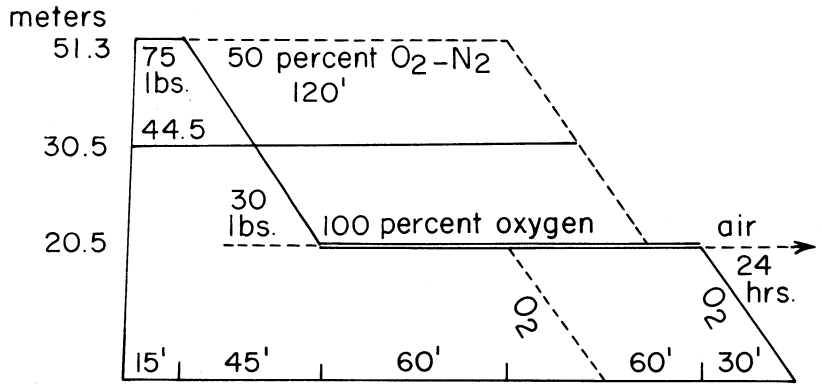


Fig.20 Diagram showing the prototype oxygen treatment table of Behnke and Shaw, 1937. Current therapy (HBO) of Type II DCS revolves around an upper level of 30.5 m (44.5 psig) with varying oxygen-nitrogen mixtures.

Fig.22 Infra-red monitoring of respiratory CO_2 during the course of clinical air embolization (Brechner and Bethune). This technique awaits application in diagnosis of degree of pulmonary tamponade following too rapid decompression.

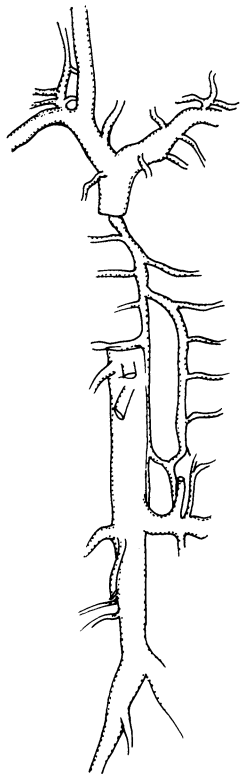


Fig.21 Bubble-induced stasis of blood in the vena cava and azygos veins aggravates decompression injury of the spinal cord.

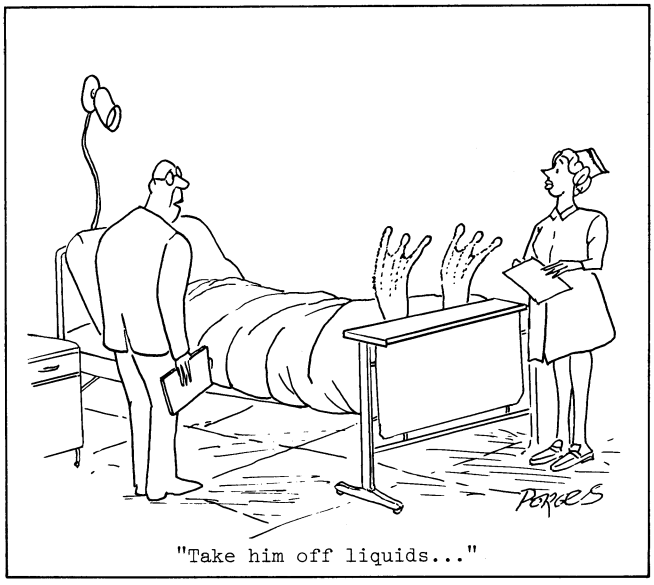


Fig.23 Cartoon to emphasize an iatrogenic problem, namely abuse of intravenous administration of fluids. The patient (Type I, DCS) received 5 1/2 liters of fluid over a period of 16 hours. (adapted from a sketch by the Cartoonist Porges).

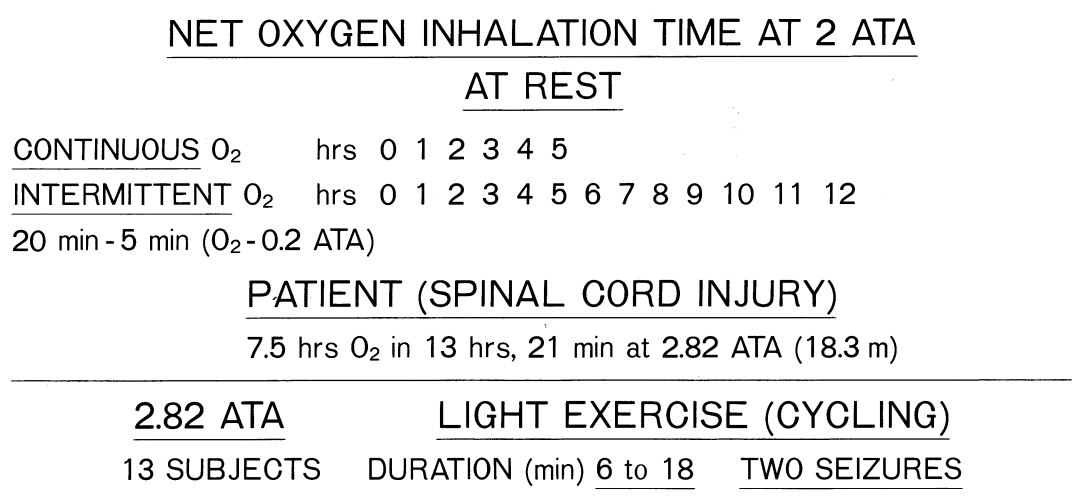


Fig.24 Net oxygen inhalation is prolonged by air 'breaks' (The question of continuous vs intermittent oxygen) A patient (spinal cord injury) breathed oxygen at 2.82 ATA for 7.5 hrs during the course of +13 hrs of pressurized therapy.
Bottom: Light exercise, by contrast, at 2.82 ATA is not tolerated for more than 18 min by healthy subjects who are prone to have convulsive seizures (data of Behnke and White, 1946).

CATEGORIES OF CLINICAL ENTITIES AMENABLE TO HBO THERAPY

(Undersea Medical Society Recommendations)

I. ASSURED, II. LESS ASSURANCE,
III. DOUBTFUL, IV. ANECDOTAL

Fig.25

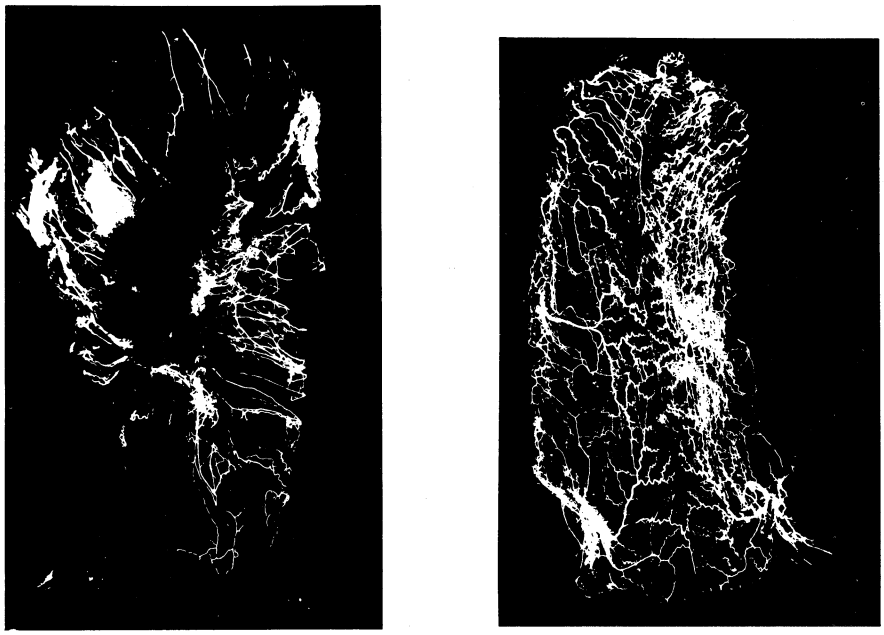


Fig.26 One aspect of HBO-induced benefit in burn therapy, namely, proliferation of vasculature (rat) at 22 days of therapy, six 1-hr exposures daily at 3 ATA. (from Ketchum, Thomas, and Hall, 1970.)

NEW DIRECTIONS

HBO IN POISONINGS WHICH DAMAGE THE LIVER.
AN APPLICATION OF HBO AND CYANIDE ANTAGONISM.

Fig.27

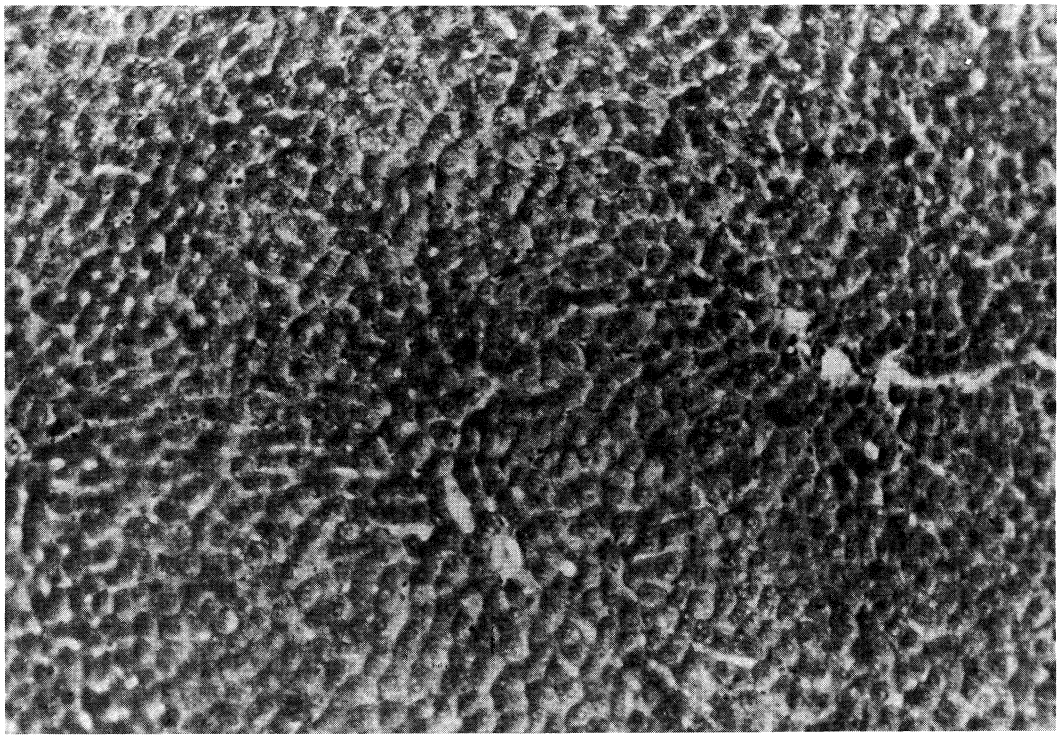


Fig.28a Protection of the liver against tetra chloride poisoning by HBO.

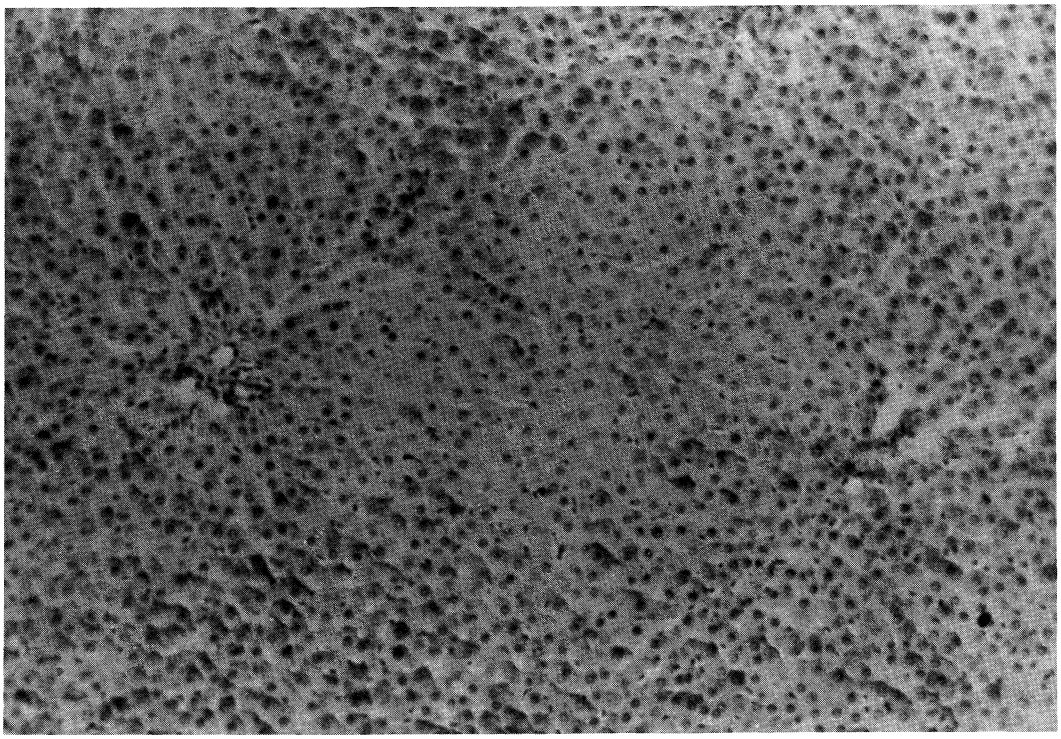


Fig.28b Control. Histopathology of liver as a result of CCl_4 poisoning. (Photos, courte syot Dr. Ralph Brauer)

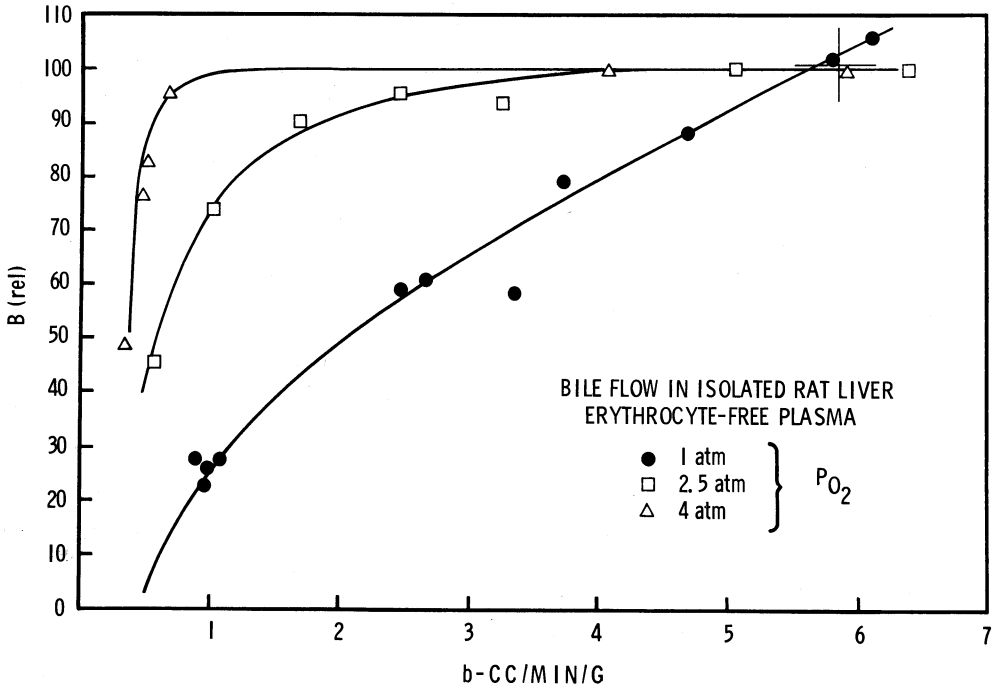
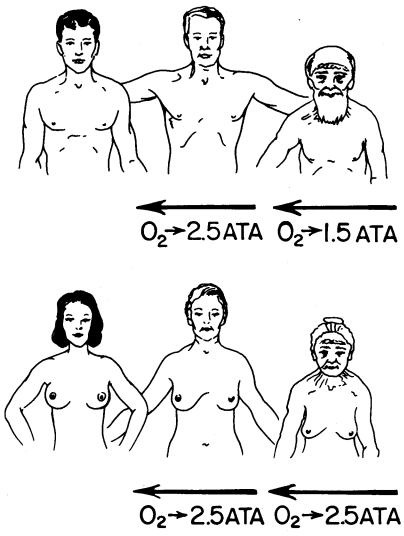


Fig.29 Liver as a target organ for HBO investigation. Bile flow in the isolated rat liver at 1, 2.5, and 4 ATA (Courtesy of Dr. Ralph Brauer).



Projected HBO reversal of morphologic aging

UM5 Category IV

Fig.30 Visionary diagram - Reversal of the aging process with Hyperbaric Oxygen + Intracellular Nutrients (Sketches adapted from lecture material of Dr. Edith Boyd.).

（本稿は，昭和55年10月 9 日開催の第15回日本高気圧環境医学会総会における講演を基に寄稿されたものである。）