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THE TWENTY-FIRST UNDERSEA MEDICAL SOCIETY WORKSHOP

INTERACTION OF DRUGS IN THE HYPERBARIC ENVIRONMENT

Bethesda, Maryland

13-14 September 1979

Chairman and Editor:

J. MICHAEL WALSH

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INTERACTION OF DRUGS IN THE HYPERBARIC ENVIRONMENT

BETHESDA, MARYLAND

13-14 September 1979

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CHAIRMAN AND EDITOR:

10 J. Michael Walsh

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UNDERSEA MEDICAL SOCIETY, INC.
9650 Rockville Pike
Bethesda, Maryland 20014

1980

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FOREWORD

This volume represents the proceedings of the 21st workshop conducted by the Undersea Medical Society. This workshop series, sponsored largely by the United States Navy, seeks to provide the latest information on a wide variety of subjects related to diving medicine by bringing together experts in the field.

This workshop, "Interaction of Drugs with the Hyperbaric Environment," was held on 13-14 September, 1979, at the Undersea Medical Society Administrative Office and brought together individuals representing various aspects of the drug-pressure problem. The information presented in these proceedings represents a current, up-to-date statement of the knowledge of how drugs work in the hyperbaric environment.

Notwithstanding the evidence available in this workshop, it is important to recognize the experimental nature of the topic addressed herein and neither the U.S. Navy, the Undersea Medical Society nor the participants can be responsible for any actions based on the information contained in these proceedings.

C. W. Shilling

INTRODUCTION

The impetus for this workshop grew out of a survey conducted by the Workshop Committee of the Undersea Medical Society. Through this survey the UMS membership expressed a strong need for more information about the use of drugs in the hyperbaric environment.

The investigation of drugs in the hyperbaric environment has become a multi-faceted area of research. Within the context of hyperbaric medicine, drugs are used by basic researchers in many different ways: a) as tools to examine physiological processes; b) as keys to unlock the mysteries of anesthesia, and c) as variables to manipulate in an attempt to understand hyperbaric phenomena (e.g. nitrogen narcosis, HPNS, decompression sickness, etc.). Clinical researchers are evaluating drugs to determine their safety and efficacy in the hyperbaric environment to provide medical treatment and prevention of illness or injury to diving personnel.

In spite of the many uses of drugs in the hyperbaric environment, literature about the actions and effects of drugs is scarce. The workshop planners speculated that more was known than the literature reflects, but that the grand scope of the area, the diverse backgrounds of the investigators working in the area, and a lack of communication have contributed to this general lack of knowledge about drugs in the high pressure environment.

The purpose of this workshop was to bring together experts in the research, clinical, and operational aspects of diving and to provide a forum for communication and exchange of information on "hyperbaric pharmacology."

The goals of this workshop were threefold:

1) To summarize current knowledge on the effects of drugs in the hyperbaric environment, including basic and applied research, and clinical application.

2) To provide clinicians with the best information available concerning use of drugs by and for diving personnel.

3) To recommend new directions for research to resolve major problem areas.

PREFACE

The organization of the workshop was designed to provide maximum opportunity for discussion, and formal presentations were therefore limited. This programming resulted in a voluminous transcript in addition to the formal statements submitted by the contributors. The formal papers represent the most current information available on the subject of drugs in the hyperbaric environment. These papers encompass a variety of disciplines and provide a broad background concerning the current "state of the art." The transcript of the panel discussions has required extensive editing to separate fact from sea stories, however, it is in these discussion sections where much important practical information may be found.

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CHAPTER 1

DRUG - PRESSURE INTERACTIONS

INTERACTIONS BETWEEN HYPERBARIC PRESSURE AND DRUGS ON EXCITABLE CELLS (NERVE AND MUSCLE)

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For the past several years, our laboratory has been concerned with the interaction between hyperbaric pressure and several types of drugs. These have been primarily anesthetic drugs and, to a lesser extent, muscle relaxants. Our aim has been to decipher the basis for the high pressure nervous syndrome (HPNS) and for pressure reversal of anesthesia. With respect to the goal of this workshop, we have described a number of ways in which hyperbaric pressure alters the properties of excitable cells. Our findings include several specific interactions of drugs with pressures encountered in moderately deep to very deep dives (500 feet and deeper). We believe that the evidence is sufficient to show that responses to certain types of drugs will be significantly modified at hyperbaric pressures, and that their use in clinical situations will be risky until they are evaluated specifically for use at hyperbaric pressure.

Using isolated systems to investigate anesthetic-pressure interactions, we have found the following:

1. Hyperbaric pressure to 200 atmospheres has little effect on the action potential in peripheral nerves, except to slow conduction velocity. There is a limited pressure antagonism to conduction block by some drugs, including general anesthetic agents and some local anesthetics (Fig. 1).

2. At least in some nerves, repetitive action potential generation is induced at high pressure, i.e., pressure has an excitatory effect. Anesthetics inhibit this phenomenon.

As a result of both (1) and (2), there are likely to be complex alterations in the impulse pattern of many nerves in the central nervous system. There is little information as yet on their nature or on possible drug interactions.

3. Hyperbaric pressures above 20 atmospheres depress excitatory synaptic transmission. First described at a cholinergic synapse, this effect of pressure has been observed at every excitatory synapse examined to date. There is every reason to expect that it occurs in human divers at these pressures. It may be the result of a decrease in the amount of transmitter released from the presynaptic nerve terminal, but this is not yet firmly established. General anesthetic agents not

only do not relieve pressure-induced block of synaptic transmission, they add to it. This pressure-induced block of synaptic transmission is probably the clearest instance of a direct effect of pressure that almost certainly will significantly modify the actions of many types of pharmacologic agents (Fig. 1).

4. Neuromuscular block. Hyperbaric pressure depresses transmission at the neuromuscular junction, as it does at other types of synapses. Although *in vitro* studies suggest that the blocks will be subthreshold at pressures encountered by human divers, this is true only in the normal neuromuscular junction. Where junctional transmission has already been depressed by drugs, disease, or abnormal metabolic state, pressure may tip the balance toward transmission failure (Fig. 2). Any drug which has effects on the neuromuscular junction therefore has the potential for an interaction with hyperbaric pressure.

5. Muscle contractility. There is an enhancement of muscle contractile force at pressures above 30 atmospheres. The mechanism for this is not known, but there is some evidence for a direct effect of pressure on the contractile apparatus. This effect of pressure will clinically override the pressure-induced subthreshold neuromuscular blocks, but again only when the neuromuscular junction is otherwise intact. In the presence of a neuromuscular blocking agent, pressure-induced enhancement of contractile tension will mask a partial block up to the point where transmission fails at a large number of units, because tension will be enhanced in the remaining units (Fig. 2). The underlying block therefore will be deeper than is clinically apparent. Rapidity of onset and recovery from block will also be modified by these opposite effects of hyperbaric pressure.

6. Cardiac effects. Other laboratories have described two effects of hyperbaric pressure on isolated cardiac tissues: bradycardia and a decrease in conduction velocity. These pressure effects also have an obvious potential for interacting with a wide variety of pharmacologic agents.

The implications of these findings for considering drugs in the hyperbaric environment may be summarized as follows:

There are certain drugs known to interact with pressure in intact animals. They will certainly behave the same way as in man. These are primarily the anesthetics involved in pressure reversal of anesthesia and in drug-induced amelioration of HPNS. They include the general anesthetics (and narcotic inert gases); the barbiturates, both as sedatives/hypnotics and as anticonvulsants; and our favorite anesthetic, alcohol.

There are certain drugs known to interact with pressure in isolated preparations. They will probably exert similar effects in animals and man. However, because of the complexity of the intact organism versus the isolated preparation, the extent of their modification in the hyperbaric environment cannot be predicted. These include

all cholinergic blocking agents, both nicotinic and muscarinic; blocks by these agents are strongly enhanced by pressure. It is probable that this effect is clinically important. They also include local anesthetics, whose conduction block is slightly relieved by pressure. It is not probable that the latter is of clinical significance.

Finally, there are drugs which have not been tested at hyperbaric pressures but which are suspect because of the above findings. These include, but are not limited to, the following categories:

Any drug active at nerve synapses. It is highly likely that pressure, which depresses synaptic transmission, will modify the response to those drugs which act at synapses. Pressure may thus enhance responses to adrenergic blocking agents. Pressure may also enhance the paralytic side effects of agents which interfere with neuromuscular transmission, such as certain antibiotics. On the other hand, pressure may diminish the response to agents which improve synaptic transmission, such as certain antidepressants and anticholinesterases.

The effects of pressure on cardiac function, namely bradycardia and slowed conduction, make any cardioeffective pharmacologic agents suspect. These include any drug with arrhythmic side effects, any drug associated with bradycardia, and antiarrhythmic agents.

The drugs of abuse are strong candidates for interesting potential interactions with the hyperbaric environment. Alcohol and the barbiturates have been mentioned already. It is probable that not only the state of intoxication but also the state of withdrawal may be modified by pressure. Hydrocarbon solvents or similar contaminants in the atmosphere may conceivably exacerbate these problems, although this is an area in which comparatively little research has been done as yet.

Finally, there are those drugs with an anesthetic-like component, which may certainly be expected to interact with compressed-air mixtures and possibly with hyperbaric pressure as well: certain of the sedative/tranquilizer families, and the antihistamines and related anti-motion sickness agents. It is probable that a good deal of data is already available on these widely prescribed agents; it should be systematically collected and analyzed.

The findings outlined above make it clear that there are many classes of drugs whose desired therapeutic or undesired side effects may be modified at hyperbaric pressures. Few have been tested in human divers for interaction with hyperbaric pressures. Considering the cost of such testing, and the relative infrequency with which some may be used in the hyperbaric environment, human testing on a large scale should probably not be done. However, there are two types of pharmacologic agents which should be brought at least to the level of animal testing at hyperbaric pressure. These are first, those likely to be used in an emergency situation at pressure and which are known or strongly suspected of an interaction: anesthetics, cholinergic blocking agents, sympathomimetics, antiarrhythmic agents. Second, those for which the suspicion of a marked alteration at pressure is less, but which are widely prescribed and/or taken by divers: antibiotics, antihistamines, drugs of abuse and psychoactive agents such as antidepressants.

FIGURE LEGEND

Fig. 1

Effects of pressure and anesthetics on conduction and synaptic transmission. In the rat superior cervical sympathetic ganglion and its attached preganglionic nerve trunk, pressure exerts different effects on conduction and on synaptic transmission. Top row, preganglionic nerve trunk: pressure alone has little effect on the action potential, but restores the original amplitude following partial conduction block. Bottom row, pressure alone depresses ganglionic transmission and adds to drug-induced synaptic blockade.

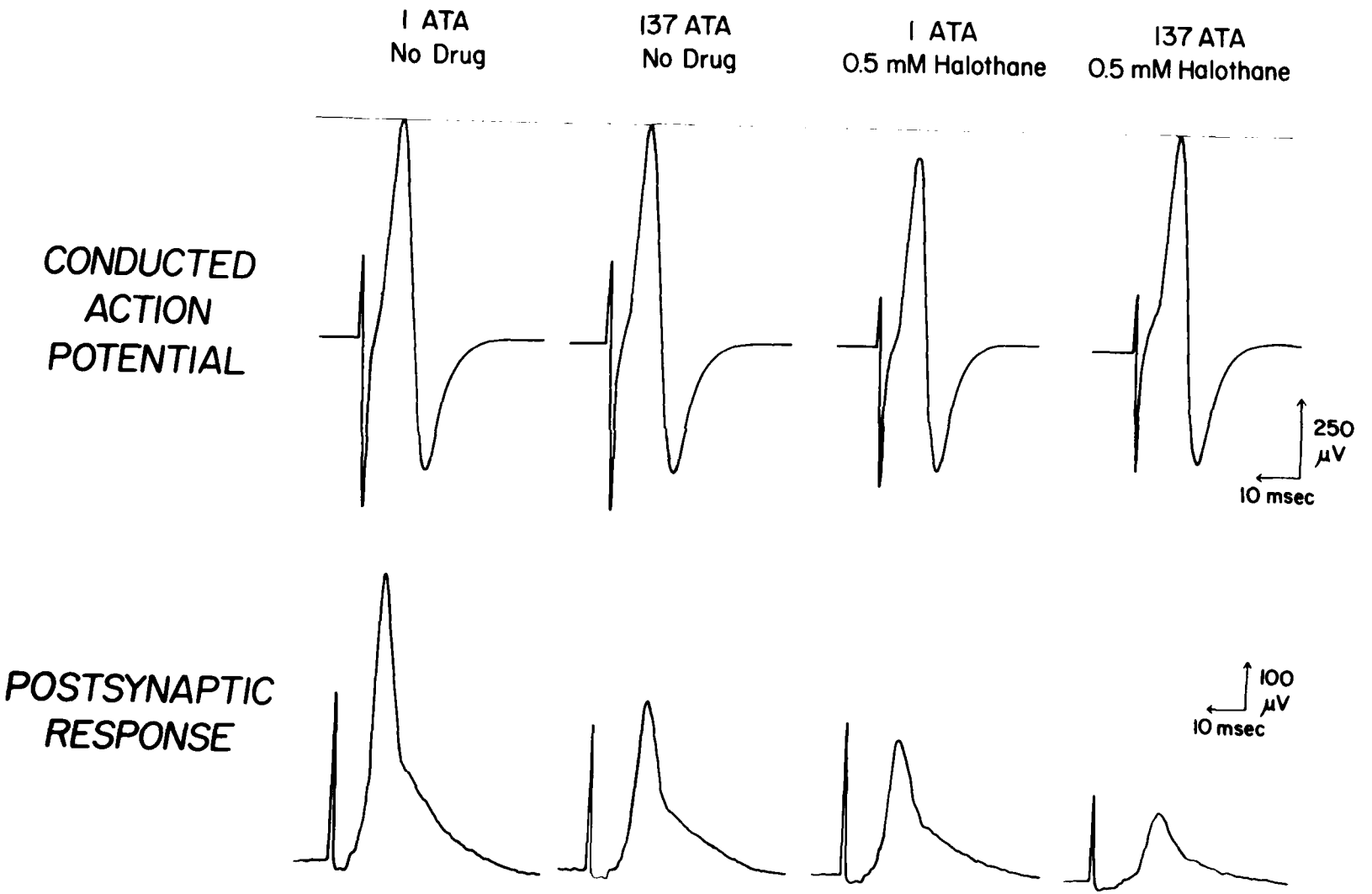
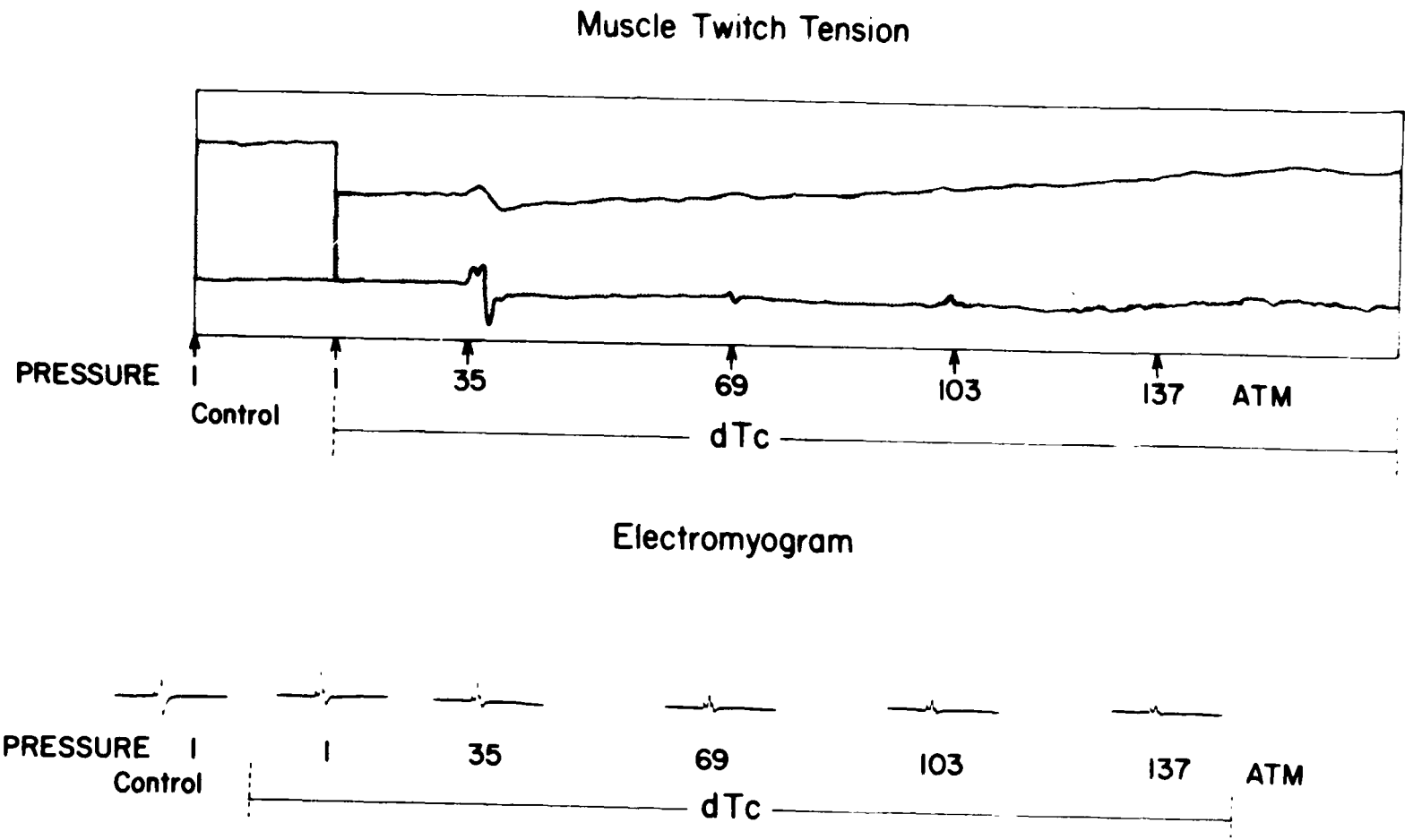

1 ATA
No Drug
137 ATA
No Drug
1 ATA
0.5 mM Halothane
137 ATA
0.5 mM Halothane
CONDUCTED
ACTION
POTENTIAL
250
μV
10 msec
POSTSYNAPTIC
RESPONSE
100
μV
10 msec

FIGURE LEGEND

Fig. 2

Interaction between hyperbaric pressure and neuromuscular blocking agents. In the rat phrenic nerve-diaphragm preparation, hyperbaric pressure enhances twitch tension and thus appears to antagonize blocking curare (dTc). When the indirectly evoked electromyogram is monitored, however, it is seen that dTc block at the neuromuscular junction is enhanced by pressure.


Muscle Twitch Tension
PRESSURE
1
Control
1
35
69
103
137
ATM
dTc
Electromyogram
PRESSURE
1
Control
1
35
69
103
137
ATM
dTc

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DRUGS AND DIVING

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Introduction

Drug interactions with the hyperbaric milieu is a largely under-investigated problem but it is possible to identify a number of areas and questions which are deserving of closer scrutiny and which require answers in order to improve the safety and efficiency of sports, commercial and military diving.

Conditions under which drugs may be used in conjunction with diving:

1. Over-the-counter drugs (OTCs) such as antihistamines, nasal decongestants, anti-motion sickness agents, mild sedatives, etc., are used not infrequently by sports and commercial divers for self-medication of upper respiratory problems (sinusitis, colds, allergic rhinitis) or mild anxiety, in order to avoid aborting a planned dive. Many of these agents have significant CNS-depressant properties which could impair judgement, especially if mild inert gas narcosis, or inexperience, are contributing factors. We do not know under what conditions of diving it is safe to use these agents.

2. The frequency of individuals taking long-term medication for the treatment of a chronic disease has increased dramatically in recent years. Such individuals are generally screened out of military or commercial diving populations, but a middle-aged sports diver, recently prescribed antihypertensive mediation, may wish to know what limitations this places on his diving activity. At the moment we would be hard-pressed to provide a definitive answer.

3. The use of "social" drugs such as alcohol or cannabis in conjunction with diving is well-recognized as a potential hazard and is discouraged by all reputable diver-training agencies. The precise nature of the interactions of such agents with air at pressure requires elucidation.

4. Drugs may be used as adjuncts to recompression therapy in the treatment of aeroembolism and decompression sickness. While the use of some agents such as plasma expanders and corticosteroids may be well-founded in medical practice, the use of others, such as platelet-inhibiting agents, rests largely on theory and requires clinical confirmation.

5. On theoretical grounds, it may be possible to use drugs to counteract inert gas narcosis and HPNS.

6. The development of saturation diving techniques makes it possible to administer medication while at pressure. Little is known about modification of drug effects under these conditions.

A. Platelet-Inhibiting Drugs

It is now well-established that a decompression dive is followed frequently by a reduction in circulating platelet count, progressing for 24-48 hr post-dive and gradually recovering thereafter. Reductions of 15-50% have been reported (1,2). A shortening of platelet survival has also been reported in some human and animal experiments, and the detection of platelet aggregates and thrombi in the long bones of divers who died of decompression sickness has led Japanese workers to hypothesize that such thrombi play a role in the pathogenesis of dysbaric osteonecrosis and possibly of decompression sickness (3). Drugs which are capable of inhibiting platelet adhesion/aggregation reactions have been shown to reduce morbidity and mortality from decompression sickness in animal experiments (4) and we have shown in several studies that certain experimental platelet-inhibiting drugs partially or completely block the post-dive thrombocytopenia (5-7).

Recently (2) we obtained suggestive but inconclusive evidence that aspirin prevents post-decompression thrombocytopenia and may even influence bends incidence. Herewith is a brief report of a further study on the effects of aspirin on diving-induced blood cellular and chemical changes.

Methods: Sixteen young male divers (students in the Seneca College Underwater Skills Program) undertook a simulated dive (compressed air) to an equivalent depth of 30 M with bottom time of 60 min. Decompression was continuous and was regulated by the DCIEM electronic analogue decompression meter. Divers dived in groups of four and were randomly assigned within each dive group to placebo [2] or treatment [2] with ASA, 330 mg three times daily, on a double-blind basis. Treatment commenced 24 hr before the dive and continued for 72 hr after surfacing. Blood samples were collected daily 48 and 24 hr predive, immediately pre- and post-dive and for three days thereafter. A variety of parameters were studied as previously described (2,7).

Results: 1. Platelets. On a day-to-day basis, no significant post-dive loss of circulating platelets occurred in either group. When the lowest post-dive platelet count was selected out, there was a 22% reduction in count in both groups ($\pm$ 5.82 and 4.59 SEMs). Partial confirmation of compliance was obtained from platelet aggregation studies which showed, in the ASA group, inhibition of ADP induced second phase aggregation and significant reductions (approximately 75%) in collagen-induced aggregation after treatment was begun. These changes were not observed in the placebo group.

2. A modest (3.4% $\pm$ 1.34 SEM) but statistically significent ($P < 0.05$) reduction in packed-cell volume was observed in the ASA

group 24 hr post-dive. This was not seen in the treatment group. Hemoglobin concentration was also depressed slightly (1%) in the ASA group at 24 hr post-dive but the difference was not statistically significant.

3. No noteworthy changes were observed in white cell counts, plasma cholesterol, CPK or GOT levels. In the placebo group there was a trend toward significant increases ($P < 0.1$) in GPT (30%) and isocitrate dehydrogenase (ICD) (80-190%) 48 hr post-dive. The latter enzyme is specific for liver damage. The ASA group showed similar elevations in ICD but not GPT.

4. One subject in the ASA group required treatment for decompression sickness (shoulder pain). This subject had experienced a fairly severe ankle sprain three days before the dive.

This study unfortunately sheds little light on the effects of ASA in diving. The modest changes in cellular and biochemical parameters are indicative of a low level of decompression stress which tended to minimize differences between groups. Nevertheless there was no evidence that ASA moderated even the slight changes which were observed.

B. CNS Drugs and Animal Experiments

There is mounting evidence that the hyperbaric environment, even as it is encountered by the sports diver, may alter the response of the individual to centrally-acting drugs. Frenquel has been shown to reduce the decrement in performance of divers at 11 ATA air (8), alcohol is synergistic with air at pressure (standing steadiness test) (9) and even apparently innocuous drugs ASA, acetaminophen, caffeine, diphenhydramine, dimenhydrinate, may cause significant decrements in performance at 3-7 ATA (10). Numerous animal experiments have also demonstrated drug-pressure interactions. Herewith are some results of recent experiments in our laboratory.

1. Barbiturate Sleeping time, Pressure and Cold: Mice were anesthetized with sodium pentobarbital (35 or 45 mg/kg i.p.) and maintained at 1, 4 or 7 ATA air at 20°C until awakening was detected by the righting reflex. Both cold and pressure prolonged sleeping time significantly and 35 mg/kg at 20°C produced sleeping times roughly equivalent to 45 mg/kg at 25°C, at all pressures.

Table I

Breathing Mixture	Pressure	Sleeping Time (min) SEM t = 20°C	t = 25°C
1. Nembutal 45 mg/kg	1	41.20 ± 6.90 (5)	36.78 ± 2.62 (9)
Air	4		48.22 ± 4.59[a] (9)
	7	71.40 ± 15.40 (5)	54.62 ± 5.44[b] (8)
$He-O_2$ (80/20)	7		40.71 ± 6.52 (7)
2. Nembutal 35 mg/kg	1	32.85 ± 6.18 (7)	16.57 ± 1.67 (7)
	4	42.50 ± 3.52 (6)	26.25 ± 6.05 (7)
	7	[c]56.14 ± 5.33 (7)	16.87 ± 1.39 (8)

[a], $p < 0.05$ [b], $p < 0.005$ [c], $p < 0.02$

2. Amphetamine and Pressure:

a. Convulsions: A convulsant LD_{50} for mice was established at 30 mg/kg d-amphetamine i.p. at 22°C. This dose caused 100% convulsions.

Exposure to pressure markedly reduced lethality and the effect was not entirely related to N_2 narcosis since substitution of He/O_2 (80/20) resulted in some convulsions and one death - convulsions were completely abolished at 7 ATA air (Table II).

Table II

Pressure	# mice	Dead 24 hr after injection	% Lethality
1 ata air	10	5	50
4 ata air	4	0	0
7 ata air	8	0	0
7 ata $He-O_2$	6	1	16.7

b. Stereotyped behavior: d-amphetamine at 10 mg/kg i.p. causes stereotyped sniffing and gnawing in mice.

In order to determine if there was any significant effect of exposure to 7 ata air on steotyped gnawing, the distribution of stereotypy scores among 8 mice over a 2 hr period at 1 ata air, was compared with similarly treated mice at 7 ata air using X_2 analysis.

After 110 mins at 7 ata air, all of the mice exhibited stereotypy scores of two or less, whereas those at 1 ata exhibited a score of four or more (Table III). Lower stereotypy scores can be correlated with lower doses of amphetamine, and this would indicate that the amphetamine may be metabolized faster at 7 ata than 1 ata, since the effect disappears more quickly at 7 ata or simply that the depressant activity of pressure becomes dominant as blood levels of amphetamine fall below some critical level.

Table III

Time after injection (mins)	10 - 100	110	120
Significance	NS	$p < 0.02$	NS

3. Analgesic Effect of Pressure: The injection of phenylquinone, 5% in aqueous alcohol (0.1 ml/10 gm) i.p., causes pain-induced writhing in mice which can be blocked by narcotic and non-narcotic analgesics. Air at pressure has analgesic properties which correlate both with PN_2 and with total pressure (Table IV). The injection of naloxone (15 mg/kg s.c.) did not antagonize this analgesic activity, suggesting that the mechanism does not involve the participation of endorphins.

Table IV

Pressure (ata)	#Writhes ± SEM in 10-20 min period post injection		% Analgesia
1	23.2 ± 3.3	(12)	-
5	15.2 ± 3.3	(12)	35
7 (saline)	10.89± 4.3[a]	(9)	53
7 (naloxone)	10.11± 3.2[b]	(9)	56

[a] $p < 0.05$ [b] $p < 0.01$, numbers in ( ) indicate number of animals

In conclusion, there is ample experimental evidence that drug effects are modified at pressure. Much basic work is required to elucidate the mechanisms of these interactions which, if successfully identified, will shed light not only on the safety of drug usage at pressure but also on the basic pharmacological properties of pressure itself.

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BEHAVIORAL EFFECTS OF DRUGS IN THE HYPERBARIC ENVIRONMENT

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Of utmost concern in evaluating scientific research is the reliability and generality of the data. The behavioral analysis of drug effects fulfills these requirements and has contributed to the understanding of hyperbaric phenomena and the way the effects of drugs change in the underwater environment. Because behavior is the end-point or output of the functional integrity of the central nervous system, these data provide unique information about a diver's sensory, motor, and cognitive functioning. Behavioral evaluations provide the best answers thus far to the clinical questions of whether a drug will impair a diver's physical or mental capabilities to an extent that will be injurious or detrimental.

In general, the behavioral studies, evaluating human as well as animal subjects, have shown that the nature of the behavioral action of a drug in diving conditions is not always predictable from its behavioral action under normobaric conditions. In addition, the drug-induced changes that have been observed are not always in accord with what would be expected by our current understanding of hyperbaric phenomena (Walsh, 1976; Thomas and Walsh, 1978; Walsh, 1979).

Animal Evaluations

The basic experimental paradigm used in our laboratory at the Naval Medical Research Institute, Bethesda, Md., calls for the establishment of various patterns of behavioral baselines in a large number of animals. Initially, these animals are repeatedly exposed to pressure to a point of adaptation where behavior under pressure is equivalent to surface behavior. At this stage the drug variable is imposed and multiple determinations are made both on the surface and under pressure, at different depths, and across a broad dose range. This experimental design results in dose-response relationships being determined not only for a variety of depths but also for a variety of gas mixtures, at each dose level, and at each depth (level of pressure).

The results of these studies indicate that the behavioral effects of drugs do change under pressure at depths as shallow as 50 ft. (Walsh, 1974). The effects of certain classes of drugs are potentiated, some are antagonized, and yet others yield entirely different effects than those observed under normal atmospheric conditions. It is difficult to make specific statements about general classes of drugs without

going into detailed evaluation of each drug at each dose level and at each pressure investigated. Suffice it to say that in most of the drugs evaluated (i.e., amphetamines, barbiturates, autonomic blocking agents, major and minor tranquilizers, mono-amine-oxidase-inhibitors, antihistamines, analgesics, alcohol, etc.), we have consistently observed modulation of the dose-response curves when the behavior was recorded under pressure (Thomas, 1973; Walsh, 1974; Walsh and Burch, 1977; Thomas and Walsh, 1978). Depending on the drug, the dose-response curve may be displaced quantitatively in either direction. That is, for one compound the behavioral effect of a 1-mg dose at depth may be equivalent (quantitatively) to a 10-mg dose at surface, yet another drug may yield the opposite effect: a 1-mg dose at depth might be equal to a 0.1-mg dose under normal surface conditions.

The most persistent finding throughout these research efforts is that the behavioral effects of a drug under pressure are not predictable from the drug's surface characteristics--a point clearly illustrated by our psychopharmacological evaluations of the amphetamines. D-amphetamine sulfate and methamphetamine sulfate were evaluated as potential prophylactic agents against the behavioral deficits associated with nitrogen narcosis, since neurophysiological evidence indicated that nitrogen narcosis resulted from a generalized depression of central nervous system (CNS) activity. It was hypothesized that the introduction of a powerful CNS stimulant might antagonize some of the performance decrements. When the amphetamines were evaluated under the conditions of increased pressure, an increase rather than a decrease in behavioral dysfunction was observed. In fact, pressure interacted synergistically with the amphetamines to produce behavioral disruptions not evident with either drug or pressure alone. In terms of diver safety, this evidence suggests that a diver taking amphetamine could have serious behavioral problems at shallow depths even when taking a dose that produces very little effect on the surface (Thomas, 1973; Walsh, 1974; Thomas, 1976).

The studies discussed above have dealt with pressures in the 2-10 ATA range with all of the drugs evaluated in subjects breathing compressed air. Additional evaluations have been conducted at approximately 20 ATA (650 ft.) using a helium-oxygen mixture. Changes in the dose-response curves were observed for amphetamine, chlordiazepoxide, and chloropromazine, but they were of a lesser magnitude than those observed with the same doses at relatively lower pressures (8.5 ATA [250 ft.]) while animal subjects were breathing air (Thomas and Walsh, 1978).

Although most evaluations have yielded significant drug pressure interactions, a few have indicated no changes in the hyperbaric environment. Animal evaluations of caffeine, theophylline, dimenhydrinate, and a thiazide diuretic have shown these compounds to be behaviorally inert at very high doses under increased pressures of air and helium-oxygen. Pseudoephedrine (a decongestant) and diphenhydramine (an antihistamine) were evaluated in hyperbaric air up to 7 ATA (200 ft.) without behavioral effect at the recommended dosage. At high dose levels (5 to 10 times normal) performance decrements were readily apparent and these changes were accentuated by 3-, 5-, and 7-ATA

pressure levels (Walsh and Burch, 1977). The analgesic effects of morphine-sulfate were evaluated at 1.0 and 7.0 ATA with animals breathing a helium-oxygen mix (PO_2 maintained at 0.2 ATA). Results indicated that increased pressure did not alter the analgesic effect of this drug (Curley, Walsh, and Burch, 1980).

Animal assessment of hyperbaric drug effects has provided significant insights into the problems and mechanisms of hyperbaric pharmacology. However, extrapolations from animals to humans are difficult and often criticized. It is only when the evaluations have been completed using human subjects can one be relatively safe in making therapeutic recommendations.

Human Evaluations

Drug evaluations using human subjects in the hyperbaric environment are extremely limited. It is generally acknowledged that divers routinely use a variety of drugs (e.g., decongestants, antihistamines) and there is anectdotal information available concerning the use of drugs in emergency recompression chamber therapy. However, due to the lack of experimental evidence, there is a significant gap in our knowledge concerning the safety and efficacy of drugs in humans under hyperbaric conditions.

In our laboratory, human evaluations have focused on the behavioral effects of several doses of five commonly used preparations: Aspirin; acetaminophen (Tylenol); caffeine; diphenhydramine (Benadryl); and dimenhydrinate (Dramamine). These drugs were evaluated in U.S. Navy divers breathing compressed air in a dry hyperbaric chamber and while immersed in a wet-tank at pressures of 1.0, 2.8, 4.6, and 6.5 ATA. The subjects were trained on a repeatable learning task, consisting of a 10-step sequence of discriminations, for which different but equivalent forms were easily generated. The task was comprised of two components: Learning and Performance. In the Performance component the discrimination task remained the same from session to session, which provided a measure of the subject's ability to perform a "well learned" assignment. In the Learning component the subjects were required to learn in a trial-and-error manner new discrimination sequences each session, which provided an index of cognitive functioning.

In the pressure evaluations all drugs yielded decrements in the Learning portion of the assessment; the decrements were manifested by increases in error rate and a 20-50% increase in time to complete the task. Highest error rates (three times base-line) were observed with the antihistamine diphenhydramine (Benadryl); the effects of caffeine and dimenhydrinate (Dramamine) were dependent on individual susceptibility, and the analgesics produced minimal learning deficits. Behavior on the Performance component was essentially unchanged across all drug conditions. Immersion in water and breathing from a scuba rig did not appear to increase the drug/pressure interaction. Although the time to complete the tasks were considerably longer in the water, the magnitude of the changes observed in the drug condition were equivalent to those

recorded in the dry chamber. Using this technique, we have detected subtle deficits in cognitive functioning in all drugs evaluated under pressure; however, at the typically prescribed doses, no debilitating behavioral or physiological changes were observed, nor did there appear to be any changes in predisposition to decompression sickness.

Conclusions

The safe and effective use of drugs in divers requires the knowledge of the behavioral as well as pharmacological effects. Thusfar we have only begun to investigate the effects of drugs underwater, and efforts must continue in order to determine whether hyperbaric drug interactions produce changes in cognitive processes, attitude, judgment, and neuromuscular coordination, which could seriously impair a diver's ability to function safely. Future research in this area should use animal models for extensive screening, but final evaluations must eventually be carried out with human subjects whenever possible.

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DRUG/PRESSURE INTERACTION

DISCUSSION

The principal outcome of this section was the acknowledgment that there is a significant lack of information concerning basic mechanisms of drug action in the hyperbaric environment. As Dr. Philp noted, if you consider the gas and pressure variables as drugs and then add some medication, you are dealing with a very complex multiple drug situation. Therefore there are a number of variables that must be controlled in an experimental situation, and the investigator must broaden his thinking to look for unpredictable effects.

Some discussion evolved concerning the best representative systems upon which drug research should be focused. Dr. Bove commented: "Should we think about several representative organs or tissues upon which to study the effects of these drugs in hyperbaric environments? The central nervous system tissue is one but I wonder whether that is a representative tissue for the whole body. Should we be dividing interest in several areas to obtain an overview of things? I could see changes in behavior being a problem in diving, but it would be worse for a diver to have a significantly reduced exercise capacity which was not detected at rest. You could put this diver in the water on a certain drug and when he was stressed physically, he would fail."

Dr. Walsh replied: "I am hoping we can generate interest on the research end of this field and try to get some money flowing into this because I think this area is still wide open. I think we barely scratched the surface. Dr. Philp is one of the few people around who is looking at the basic effects of drugs. A couple of years ago there was money to do this kind of work and everybody was concentrating their efforts in the 600 to 1,000 ft. range on mixed gases and the fact of the matter is that 98% of the diving that is done is in the 150 ft. range or less. Dr. Nicodemus is looking at some drugs in the 165 ft. air and 60 ft. O_2 recompression environment which is also very important. But again I think we are just getting started." The panel agreed that a multidisciplinary approach to this broad area is warranted and should be encouraged.

Dr. Bove noted that hyperbaric oxygen (HBO) inhibits the toxic effects of lidocaine and questioned whether HBO would also inhibit the therapeutic effects of lidocaine on arrhythmias (for example). Dr. Nicodemus replied: "At the depths where I use lidocaine (60' O_2) I don't think there is a pressure effect. I don't see any action on the membrane, and since lidocaine acts on the membrane I don't see any antagonism or synergism at this pressure other than the stimulating effects of oxygen itself." Dr. Kendig noted that the group at Buffalo (Ornhagen, Perry et al.) have been looking at cardiac function under pressure and have described a very extensive bradycardia or slowing which looks very similar to the slowing of conduction velocity which she sees in the isolated peripheral nerve. The Buffalo group has also described some kinds of arrhythmia that are related to slowed conduction

and these have a very obvious potential for interacting with many of the drugs that are used in medical emergencies. The drugs the Buffalo group places under the highest suspicion for producing an unexpected response in the hyperbaric environment are those which are concerned with either blocking or enhancing synaptic transmission, and if you look over the armament of drugs, a very large number of drugs typically used in an emergency case requiring anesthesia are going to fall into this category.

Dr. Kendig remarked that she had strong feelings against using human subjects for drug research, especially where a class of drugs is suspected to produce an unexpected response. For much of the needed information, one should carry out preliminary studies on animals. Dr. Bennett argued that we need to look at the human response, that we cannot extrapolate from rat to man. Dr. Philp commented: "This is a discussion which takes place every time you have basic scientists and clinicians together: the question of extrapolation of data from animals to humans. My feeling is that animal data are very useful for establishing the basic mechanisms, but not much use in predicting dosages and pharmacokinetic effects. I would like to point out, to anyone who is looking at animal data, particularly for use in working in a clinical setting, the fact that the dosages are very often totally unrealistic in the human context. Most small animals metabolize drugs very differently than does man. They tend to metabolize more quickly and frequently by different pathways. Aspirin is a typical example. We were criticized recently for using what appeared to be high levels of aspirin in some thrombosis experiments in rats. We actually did some pharmacokinetic work and the fact of the matter is that in the rat, 100 mg per kg intravenously produces a 1 minute blood level of 22 mg per decaliter which is a therapeutic range that you aim for when treating rheumatoid arthritis. The half-life of aspirin in the blood was 30 minutes. In man it is more like 6 to 10 hours. So when you are working with pressure you must be aware of the fact that in small animals the drug effect can disappear very rapidly.

CHAPTER II

PRACTICAL CLINICAL ASPECTS OF DRUG TREATMENT

DISCUSSION OF CASE HISTORIES INVOLVING PROBLEMS WITH DRUG REACTIONS IN DIVERS OR IN HYPERBARIC THERAPY

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It has been this Centre's policy to avoid use of drugs in diving wherever possible. This approach to the use of drugs under pressure is summarized in the following, written one year ago for the medical protocol of a saturation dive and reflects the suspicious caution shown.

"There is always reluctance to administer any drug other than in an emergency. However, working efficiency and safety do demand that divers get some sleep in noisy surroundings and bad weather, and they are subject to the usual medical complaints of upper respiratory tract infections, and sore throats. Thus, with reservations, certain items are locked in. Hypnotics are definitely best avoided and small doses of Diazepam (Valium) assist sleep. It is recommended that no therapy should be taken apart from nasal or ear drops in the 18-hour period before a dive. Drugs have variable and unpredictable effects under pressure and may not be rapidly excreted leading to cumulative effects. Antihistamines or "common cold" remedies can effect working efficiency. Antibiotics also behave differently and should be avoided unless really indicated."

An attempt has been made to obtain documentary evidence of drugs used in divers here since 1968. This is inevitably incomplete and concerns the more significant diving related problems. Advice given by radio/telephone authorizing medication in non-urgent cases is now recorded here, but previously would have been in the dive log to which we do not now have access. The Norwegian Government, in its "Act relating to worker protection and working environment" can command such information from the companies, down even to minor first aid treatments given.

In June, 1979, following the invitation to this Workshop, I asked a colleague, Dr. Jim Douglas, (now at Fort William), who was on a three-month attachment to this Centre, to examine the records of cases of decompression sickness and to collect as much information as possible about drugs used. The time this takes, and the deficiencies of past records were readily apparent. He selected the group who had sustained primarily spinal decompression sickness (although some had additional cochleo-vestibular involvement) and for whom there were adequate records and clinical details. For 29 divers involved in 31 incidents, he only found evidence of adjuvant therapy as follows:

Macrodex infusion: 9 cases
Steroid medication: 7 cases
Heparin: 3 cases

As the standard teaching, particularly in the event of delay, is recompression with intravenous therapy and steroids, these were surprising results. Therefore, the whole "bends incident file" which includes any case treated, managed from here or examined afterwards for assessment, was worked through and 163 cases were studied. Review of these records reveals few recorded problems of drug reaction. Discussion with one's colleagues here and elsewhere suggests there is very little available information at all; yet it is known that considerable quantities of medication are prescribed largely by medics offshore, to divers in saturation. If medication causes a problem, it is anticipated but by no means certain, that the medic would seek shore-based advice. It may be that subtle changes go undetected and unreported. Examination of North Sea commercial fatalities (46 to date) shows only four unexplained deaths and one attributed to unsuspected pre-existing medical conditions. If one is looking for the possible influence of drugs of medication or abuse, no assessment of "near miss" situation has been made. Childs (Aberdeen) in his analysis of 114 cases of loss of consciousness, did not find evidence of drug involvement.

One large company lists the following groups of drugs used in saturation diving in the last year.

1. Decongestants
2. Analgesics
3. Sedatives
4. Anti-colic (G.I. sedative)
5. Antibiotics
6. Topical ear preparations
7. Topical skin preparations

Another large company reveals that on three diving spreads in the 1978 diving season, the total number of medical consultations of saturation divers with the medic was 196. A breakdown from one barge reveals that 103 were actually in saturation, but for the remaining 93, no differentiation is made between a diver being treated at the surface or under pressure, in the medical return. Most, if not all, of these consultations were conducted by the Medic without reference to a doctor. A large number of these consultations appear to take place for a variety of minor conditions and presumably a variety of drugs were given.

The Analysis of 163 Divers Referred to the NSMC Over the Last Ten Years Is As Follows:

Pain only	C.N.S. Type II (including embolism)	Cochleo-vestibular	Other significant diving-related medical problems	Medical problem (not diving-related)
35	54	20	46	8

The drugs used in the management of these divers fall into the following groups:

	Depth used
Analgesics	
Aspirin (Acetyl salicylic acid)	1,000 ft.
Panadol (Paracetamol)	60 and 1,000 ft.
Fortral (Pentazocine)	450 ft.
Distalgesic (Dextropoxyphene)	450 and 1,000 ft.
DF 118 (Dihydrocodeine)	520 ft.
Fortagesic (Pentazocine - Paracetamol)	1,000 ft.
Antacids	
Mist Mag. Trisil	200 ft.
Asilone (Dimethicone - Alum. hydrox. - Sorbitol)	
Antibiotics	
Deteclo (Triple tetracycline)	30 ft.
Septrin (Trimethoprim - Sulphamethoxazole)	450 and 1,000 ft.
Lincocin (Lincomycin)	114 ft.
Ceporex (Cephalosporin)	400 ft.
Penbritin (Ampicillin)	520 and 1,000 ft.
Anticoagulants	
Heparin S.C.	60 and 165 ft. (3 cases)
Antisludging	
Dextran 40	Mainly around 60 ft or shallower — 7 cases
Dextran 70	13 cases
Antifungal	
Fulcin Forte (Griseofulvin)	250 ft.
Anti-inflammatory	
Brufen (Ibuprofen)	520 ft.
Antihistamines	
Piriton (Chlorpheniramine)	450 ft.
Actifed (Triprolidine, pseudoephedrine)	1,000 ft.
Antipyretics	
Aspirin	2 cases
Antispasmodics	
Pro-Banthine (Propantheline)	30 ft.
Largactil (Chlorpromazine)	132 ft.
Cardiac Drugs	
Adrenaline injection 1/10,000	One unsuccesful resuscitation attempt 1,000 ft.

Cough medicines	Depth used
Orthoxical linctus (Codeine and phos. - methoxyphenamine)	132 ft.
Benylin expectorant (Diphenhydramine)	1,000 ft.
Decongestant preparations	
Ephedrine nasal drops	
Otrivine nasal drops	
Sinex	
Eskornade (Isopropamide - Pnenylpropanolamine - Diphenylpyraline)	1,000 ft.
Triominic (Phenylpropanolamine - Mepyramine - Pheniramine)	1,000 ft.
Dermatological preparations	
Nupercainal, Lignocaine	
Bayolin (Heparinoid glycol salicylate)	
Synalar, Ultradil, Bentovate	
Flamazine (Silver sulphadiazine)	
Genticin (Gentamicin)	
Acriflex	1,000 ft.
Soframycin (Framycetin - gramicidin)	1,000 ft.
Tineafax (Zinc undecenoate)	1,000 ft.
Savlon (Chlorhexidine - cetrimide)	
Gastrointestinal	
Codeine phosphate	520 ft.
Mist. Kaolin	1,000 ft.
Hypnotics - Non-barbiturate	
Valium 5 mg and 10 mg	
Mogadon (Nitrazepam)	
Welldorm (Chloral)	
Steroids	
Prednisone	
Dexamethasone (9 cases) Tabs. and injection	
Hydrocortisone inj.	
Prednisolone tabs.	
Tranquilizers	
Valium 5 mg	30 ft. and 1,000 ft.
Topical ear preparations	
Dome-boro (Aluminium acetate in acetic acid)	
Otosporin	
Gentisone - HC	
Vasodilator	
Opilon 40 mg (Thymoxamine) (at the surface)	
Amyl nitrate (at the surface)	

Miscellaneous

Fluid and salt replacement therapy - 1 case
Stellate ganglion block - 2 cases in hospital
Bicarbonate infusion - 50 ml of 50 milliequivalents 8.4% solution.

None of these drugs has been used frequently. It is disappointing that little appears conclusive. The hypnotics, tranquilizers and sedatives appear effective at varying depth, and do not have recorded after-effect. Analgesics also appear effective.

Specific drugs used for decompression illnesses have never been tested in controlled circumstances, but with any delay or with serious residual signs or symptoms, one tends to use Dextran 70 in normal saline in not more than one litre per 24 hours, and possibly steroids for a maximum of three days. There is good evidence for using Heparin, but it is not widely used at present in the U.K. It may be of use in a serious spinal problem.

One does not expect so much of topical preparations, such as those used in the treatment of bacterial or fungal skin infections. These conditions need a reduced humidity to resolve and decompression is often necessary.

Anecdotally there was a case where in a deep saturation the next crew to go on a bell run was unable to sleep because of stiffness from over exertion on an earlier run. After four hours a request for sleeping tablets came up topside and was answered in the form of a placebo (one Paracetamol each) which was effective. Six hours later the bell run started with both divers appearing alert and cheerful, but one hour further on it had been aborted because of a series of unbelievable errors and misjudgements, fortunately without major consequence. It was not thought that the Paracetamol at 32 atmospheres could have been responsible. The rule - "no diving for 18-24 hours after any sedative" should be enforced both in air and saturation diving.

In an earlier case the diver took two aspirin and Ephedrine nasal spray before diving to 110 ft. on air for 60 minutes, employing surface decompression with oxygen. The dive was hard, as he was breaking concrete. Towards the end he "felt narked" and was uncoordinated on the ascent and aggressive once in the chamber. After a series of skirmishes he was left to sleep it off, having been sedated with an antihistamine. At the time hypoglycaemia was diagnosed, and he was not recompressed again. He had not eaten for a considerable period of time.

A deep bounce diver suffered the consequences of travelling between centres whilst on therapy, taking oral steroids and aspirin. He developed an acute gastric erosion and possible septicaemia before he could be tailed off his steroids.

An air diver in Nigeria was treated rather belatedly for a spinal bend and flew home 17 days later, having completed daily oxygen therapeutic tables for three days, with apparent relief. He complained on reaching the U.K. of weakness of the left quadriceps, loss of light

touch and pinprick sensation of the left leg and difficulty walking. He was assessed and given a trial of Dexamethasone (12 mg i/m stat. and 4 mg 8 hourly for 3 days). Subjectively his walking improved dramatically and he complained of relapse immediately upon ceasing this therapy. It was not restarted on advice from elsewhere.

A saturation diver complained of intermittent difficulty breathing in a welding habitat whilst buffing (and no welding) and later in the water and finally at rest in his bunk. He was seen for assessment and apart from smoking 20 cigarettes per day (when not diving) nothing relevant was revealed. General physical examination was normal as was pulmonary function testing, measuring lung volumes, mechanics and diffusion capabilities. However, on exercise testing he reached 180 watts and then just 200 watts with encouragement and was completely exhausted. He was found to have loss of ventilatory control at high work loads and to be less physically fit than expected for an athlete. It was subsequently suggested that there were factors unrelated to diving which were considered causative.

A diver jumped from 4 ft. into water 10 ft. deep and went down approximately 4 ft., coming up to vent off his dry suit. He then went down to swim under a supply vessel in the dark to his work site at an SBM in 10 ft. of water. He noticed within less than one minute that he had total loss of vision in one eye. After a 24-hour delay contact was established and on the advice of a consultant eye specialist at that locality (who had diagnosed a visible retinal arterial thrombus) the diver was refused recompression. Instead he was treated with amyl nitrate and has made a full recovery.

A saturation diver at 520 ft. developed diarrhoea early in the dive. He subsequently developed acute arthritis and effusions of the left knee and ankle. He than became pyrexial. Brufen (Ibuprofen) was selected for its apparent low gastric irritant capability because of intractable pain not relieved by paracetamol or dihydrocodeine. This was effective. After seven days, immediately upon withdrawing the Ibuprofen, the pain in the resolving effusion recurred and therapy had to be restarted. The final diagnosis was Reiter's Syndrome, (secondary to Salmonella enteritides).

It is now apparent that our own approach to drug therapy has changed little since the EUBS Workshop in 1976. If the types of diving problems and the medical problems occurring under pressure here over the last ten years are examined, relatively few are given any form of drug therapy, and most appear to get better. Where there is a medic or doctor, there is a considerably greater demand for medications of all kinds. At present a cautious approach is maintained towards use of drugs under pressure, and the conclusions of this Workshop are awaited with considerable interest.

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APPENDIX

OFFSHORE DIVING FATALITIES IN NORTH EUROPEAN AREA
1971 - 1978

This information is only a presentation of numbers and is not a statistical analysis. We only wish to stress the tendency that, despite more and deeper diving, the number of accidents had declined. This probably means there is also a definite decrease in accident rate. Another favourable aspect of this information is that the diving also has changed from predominantly air to more mixed gas diving, and from bounce towards saturation.

	1971	1972	1973	1974	1975	1976	1977	1978 5 month
British Sector	1	1	2	5	6	9	3	(1)
Norw. Sector	2			4	2			(1)
Irish Sector				1				
Dutch Sector					1		2	
Total 41	3	1	2	10	9	9	5	(2)

These accidents are sorted below according to type, depth, cause and other factors. These breakdowns are based, in some cases, on limited information.

Mode of Diving

Air diving		12)	Air 20
Air depth but unspecified		8)	
Dive mode not known		1)	
Diving 165 ft. - no bell		2)	4
Bell diving unspecified		1)	
Gas - unspecified	6)		
Gas - with bell	6)	12)	Gas 17
Saturation		5)	

There have since been 5 more deaths:

2 - Bell loss - 1 drowned; 1 DCS and hypothermia
2 - Bell loss - Both hypothermic
1 - Drowned - surface air

Depth of Incident (FSW)

Unknown	2
At surface	4
0 - 20	4
20 - 30	6
30 - 50	8
50 - 60	3
60 - 90	6
90 - 120	3
120 - 150	4
150 - 300	0
300 -	1

Cause of Death as Specified by the Pathologist

Injury	6
Drowning	13
Gas supply: Asphyxia - cut umbilical	4
Asphyxia unspecified	1
Wrong gas	1
Anoxia	1
Embolism/barotruma	6
Hyperthermia	2
Preexisting medical condition	1
Pneumothorax	1
Decompression sickness	1
Unexplained death	4

Possible Factors Cited as Cause of Death

Decompression sickness	1
Hypothermia	2
Inadequate equipment	3
Equipment malfunction	7
Bad weather	4
Inadequate training	2
Overwork	1
Diver error	7
Operator error	13
Fatigue	2
Panic/stress reaction	2
Medical unfitness	2
Medical condition or injury	7
Poor communication	3

THE USE OF DRUGS UNDER PRESSURE

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There is a lack of published information on the use of drugs under pressure and yet there is an increasing requirement for such data and, at the same time, much individual experience disseminated among a relatively small but geographically scattered number of clinical observers. The purpose of this paper is to bring together those scattered experiences in the hope that, collectively, they will provide an assessment of a wide pharmacopeia of drugs which can be used safely under pressure and have been demonstrated to be effective and without significant side effects in the hyperbaric environment.

The project was undertaken at the instigation of the Diving Medical Advisory Committee of the UK and the information was compiled from questionnaires which were sent to selected diving physicians, known to the author to have had experience in this field. Twenty-five physicians were approached and 15 responded with information

The narrative which follows is a summary of the data received, arranged according to therapeutic groups of drugs, specific drugs and a summary table. Further data, information and experiences will be welcomed by the author so that the account can be up-dated.

1. Sedatives

Valium (Diazepam) has been a traditional drug in the treatment of decompression sickness for many years and a wealth of experience has accumulated in its use. It seems to be equally effective under pressure to 1000 ft. at which depth it has been administered on 20 to 30 occasions. One observer commented that he felt its effect may not be quite so sustained under pressure and slightly larger doses may be required. It has been used parenterally to depths of 50 metres with no untoward side effects.

Phenobarbitone is effective in controlling convulsions under pressure and, as hypnotics, both Welldorm (Dichloralphenazone) and Mogadon (Nitrazepam) have been used and found to be quite effective in oxy-helium down to 1000 ft.

2. Steroids

Methylprednisolone has been used to a depth of 60 ft. in a dose of 1 to 2 g. without unexpected side effects and Dexamethazone has been frequently used on many occasions to 165 ft. It appears to have been extremely effective and does not lower the patient's tolerance to oxygen.

Hydrocortisone was effectively used on one occasion by intravenous administration.

3. Gastrointestinal Drugs

Agarol has been used for constipation in a dose of 20 to 40 ml. in both air and heliox, apparently with good effect. Mist. Kaolin and Morph has been used for diarrhoea to depths of 60 ft. and it has also been used in Trimix. Lomotil has also been used effectively for the control of diarrhoea. For indigestion, gastritis and oesophagitis, Mist. Mag. Trisili, Asilone, Gelusil and Gastrocote have all been used.

4. Analgesics

Perhaps the most commonly used analgesic has been Aspirin which is effective at least down to 1000 ft. and also in a 100% oxygen environment. It seems to have no unexpected side effects, but it can be a potential gastric irritant and cause acute gastric erosion, especially when used with steroids. The author feels that the practice of using steroids and Aspirin together is a dangerous one and should be discontinued.

Other analgesics which have been used include Pethidine to a depth of 60 ft., though only in relatively small doses of 25 to 50 mg.

Fortral, Fortagesic, Distalgesic, DF118, Paracetamol and Codis have all been used but I personally witnessed hallucinations in a diver given Distalgesic at about 100 ft. on air. Perhaps one

should express a little caution in the use of this drug under pressure.

5. Skin Preparations

Numerous skin preparations have been used under pressure and there does not appear to have been any problem with any of them. They all seem to have been equally effective as on the surface, but a word of warning should be expressed about the increased absorption of these substances in the hot, humid atmosphere of decompression chambers.

One observer noted that he thought antifungal preparations used in hyperbaric conditions were less efficient than on the surface but this is almost certainly due to the humid conditions in which they are used which favour the organisms, and not a direct effect of the hyperbaric environment on the drug.

6. Cough Medicines

Cough medicines are frequently required under pressure to relieve a dry, irritating cough which arises in mild oxygen toxicity. Linctus Codeine, Benylin and Orthoxicol have all been used for this purpose, Benylin down to 1000 ft. and Orthoxicol down to 165 ft. without unexpected effects.

Triominic and Actifed Compound Linctus have been used for the relief of the symptoms of upper respiratory tract infections. Triominic in particular has a sedative effect and divers should not enter the water for 18 hours after taking it.

7. Ear Drops

Antibiotic Ear Drops with and without steroids have been used without untoward effects under pressure. However, there is a grave danger of producing resistant organisms in pressure chambers and antibiotics should only be used in response to specific tests of sensitivity.

8. Antibiotics

Pencillin, Ampicillin, Deteclo, Septrin, Lincocin, Ceporex and Tetracycline have all been used effectively under pressure at various depths. Whenever possible the most specific antibiotic should be used in the circumstances to prevent the emergence of resistant organisms in the chambers.

9. Ear, Nose and Throat Preparations

Ephedrine nose drops are very effective when used under pressure and also Fenox and Sudafed. Eskornade, when used to relieve upper respiratory tract congestion, tends to be very sedative and divers who have taken it should not enter the water for 18 hours.

One observer reported severe vertigo and unconsciousness in a diver who had over-administered to himself a Nezeril spray before the dive.

10. Anti-spasmodics

The only anti-spasmodic which has been used significantly is Probanthine and it has had a good clinical effect without unexpected side effects. Buscopan was used inadvertently on one occasion by a diver who died. He was taking it for unknown reasons and developed dizziness and vomiting.

11. Diuretics

The only diuretic that was used is Frusemide in a dose of 20 mg. i.v. at 165 ft. and it seems to be effective and without any side effect.

12. Vasodilators

Opilon has been used as a vasodilator on two occasions to a depth of 150 ft. without any untoward side effects.

13. Anti-coagulants

Heparin is the only anti-coagulant which has been used significantly and it seems to work effectively in a dose of 2000 to 4000 units 6 hourly, but the evidence that it makes any significant contribution to the treatment of decompression sickness is not convincing and it should certainly never be used if there is any possibility of a vestibular bend.

14. Antihistamines

The only single antihistamine which has been significantly used is Chlorpheniramine maleate (Piriton) and this seems to have been just as effective as when used in normobaric circumstances and in the same dosage.

15. Anti-convulsants

Both Heminevrin given as intravenous infusion at 60 drops per minute for 5 minutes and Phenobarbitone with or without Flurazepam has been used successfully in the treatment of convulsions occurring with cerebral gas embolism. There were no reports of anti-convulsants being used to treat oxygen convulsions but Valium has sometimes been used with effect as a prophylactic.

16. Anti-inflammatory drugs

Butazolidin has been used by two observers on about six occasions and every time the treatment has had to be abandoned because of side effects. On one occasion the patient developed purple scintillae in his peripheral visual fields and on other

occasions the patients developed gastritis, sometimes with vomiting, and from the observations recorded on these occasions, it would seem that the drug was less efficient than when used on the surface.

On the other hand, Ibuprofen (Brufen) on the single occasion that it was used, proved to be extremely effective and without side effects in treating a case of Reiter's Syndrome.

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Name of Drug	No.of Times Used	Dose	Max. Depth (feet)	O_2HE	Comments
Alginic acid, aluminum hydroxide, magnesium trisil., soda. bic. (Gastrocote)	1	2 tab. p.c.	450	Yes	Effective in controlling symptoms of dyspepsia.
Ampicillin (Penbritin)	60+	250 mg/ 500 mg q.i.d.	1100	Yes	Normal therapeutic efficacy. One case of sensitivity reported.
Aspirin	148+	600 mg q.i.d.	1100	Yes	An effective analgesic in a dose of 600 mg q.i.d. but a real risk of acute gastric erosion especially when administered with steroids. One reported case in this series.
Cephalosporin (Ceporex)	2	250 mg q.i.d.	400	No	Normal therapeutic efficacy.
Chlormethiazol-edisylate. Inf. (Heminevrin)	2	60 drops/ min.	150	No	Given as an i.v. infusion at 60/drops/min for 5 min. Successful in controlling convulsions from cerebral arterial gas embolism.
Chlorpheniramine maleate (Piriton)	12	4 mg t.d.s.	1000	Yes	Appeared to be just as effective as on the surface.
Chlortetracycine, tetracycline, demeclocycline (Deteclo)	2	1 b.d.	30	No	Normal therapeutic efficacy.
Codeine phosphate methoxyphenamine, sod. citrate (Orthoxical)	1	10 ml q.i.d.	60	No	Used to suppress cough of O_2 toxicity.
Codeine phosphate syrup	2	5-10 ml q.i.d.	60	No	Normal therapeutic efficacy, especially for dry cough in hyperbaric O_2.

Name of Drug	No. of Times Used	Dose	Max. Depth (feet)	O_2HE	Comments
Dexamathasone (Decadron)	55	12-16 mg b.d.	165	Yes	Used in cases of decompression sickness with good effect, but may cause acute gastric erosion, especially when used with aspirin. It should be used shortly and sharply.
Dextropopoxyphene with paracetamol (Distalgesic)	23	2 t.d.s.	1000	Yes	One case of hallucinations when given at 100 feet on air.
Diazepam (Valium)	70+	5-10 mg 6 hourly 25 mg i.v.	1000	Yes	Traditional drug in some standard schemes for treatment of decompression sickness. Some evidence that slightly higher and more frequent doses may be needed under pressure than on the surface.
Dichloral phenazone (Welldorm)	5	650-1300 mg	1000	Yes	Normal therapeutic efficacy.
Dihydrocodeine tartrate (DF118)	3	60 mg t.d.s.	500	Yes	Normal therapeutic efficacy.
Dimethicone, aluminum hydroxide, magnesium oxide suspension (Asilone)	3	10 ml q.i.d.	260	Yes	Normal therapeutic efficacy.
Diphenhydramine, ammonium chloride, sodium citrate, menthol linctus (Benylin)	13	10 ml q.i.d.	1000	Yes	Normal therapeutic efficacy.
Diphenoxylate hydrochloride (Lomotil)	3	1-2 q.i.d.	250	Yes	Normal therapeutic efficacy.
Dopamine hydrochloride (Intropin)	3	4-8 mg/kg	66	No	Used in hyperbaric O_2.

Name of Drug	No. of Times Used	Dose	Max. Depth (feet)	O_2HE	Comments
Ephedrine nose drops	165	2 drops prn	1000	Yes	Effective in relieving nasal and sinus congestion.
Erythromycin	1	250 mg q.i.d.	30	No	Normal therapeutic efficacy.
Frusemide (Lasix)	45	20 mg i.v.	165	No	20 mg i.v. appeared equally effective to administration in normobaric conditions.
Flurazepam 30 mg with phenobarbitone 100 mg	5		660	Yes	
Griseofulvin (Fulcin)	1	500 mg daily	300	Yes	Appeared to be as effective as when given in normobaric conditions.
Gentamycin ear drops (Genticin)	5	2 drops t.d.s.	750	Yes	Very effective in infections with Pseudomonas.
Heparin	10	2000-4000 units 6 hourly	165	No	It is questionable whether this drug is really effective in the treatment of DCS and it is definitely contraindicated where there may be vestibular involvement.
Hydrocortizone	4	100 mg i.v.	150	No	Normal therapeutic efficacy.
Hyoscine butvl-bromide (Buscopan)	1	2 q.i.d.	?	?	One diver dived while taking this drug and developed dizziness and vomiting.
Ibuprofen (Brufen)	1	400 mg t.i.d.	520	Yes	Was very effective in controlling pain from effusion of knee in Reiter's syndrome.
Isopropamide phenylpropanolamine diphenylpyraline (Eskornade)	1	1 b.d.	?	?	Normal therapeutic efficacy, but not to enter water for 18 hours.

Name of Drug	No. of Times Used	Dose	Max. Depth (feet)	O_2HE	Comments
Lincomycin (Lincocin)	2	500 mg q.i.d.	114	No	Normal therapeutic efficacy.
Liquid paraffin, phenolphthalein (Agarol)	3	20-40 ml	900	Yes	Normal therapeutic efficacy.
Magnesium trisilicate	28	5-30 ml q.i.d.	260	Yes	Normal therapeutic efficacy.
Magnesium trisilicate, aluminum hydroxide tablets (Gelusil)	2	1-2 q.i.d.	1260	Yes	Effective in controlling symptoms of dyspepsia.
Mannitol	1	100 mg in 500 ml glucose saline	150	No	Effective in reducing cerebral oedema.
Methyl prednisolone	3	1-2 g	60	No	Has been used effectively with hyperbaric O_2.
Mist. kaolin et morph	2	5-10 ml q.i.d.	60	No	Normal therapeutic efficacy in hyperbaric O_2.
Nitrazepam (Mogadon)	7	5-10 mg	1000	Yes	Normal therapeutic efficacy.
Oxymetazocine hydrochloride	1	by nasal spray	136	No	Vertigo and unconsciousness after excessive use before a dive.
Paracetamol (Panadol)	60	2 tabs. 4 hourly	120	No	Normal therapeutic efficacy.
Penicillin	30	250 mg q.i.d.	500	Yes	Normal therapeutic efficacy.
Pentazocine with paracetamol (Fortagesic)	2	2 t.d.s.	1000	Yes	Normal therapeutic efficacy.
Pentazocine (Fortral)	6	25-50 mg t.d.s.	450	Yes	Normal therapeutic efficacy.
Pethidine	10	25-50 mg	60	No	Normal therapeutic efficacy in hyperbaric O_2.

Name of Drug	No. of Times Used	Dose	Max. Depth (feet)	O_2HE	Comments
Phenobarbitone	2	300 mg i.m.	150	No	Effective in controlling convulsions in cerebral gas embolism.
Phenylbutazone (Butazolidin)	6	100 mg t.i.d.	50	No	Patient developed purple scintillae in peripheral visual field. Increased tendency to gastritis. Treatment stopped in all cases because of side effects.
Phenylephrine, chlorbutol nose drops (Fenox)	10	5 drops in each nostril before each change of pressure	120	No	Normal therapeutic/prophylactic efficacy.
Phenylpropanolamine, mepyramine, pheniramine syrup (Triominic)	3	10 ml 4 hourly	300	Yes	Effective in controlling symptoms of minor upper respiratory tract infections but barred from entering water for 18 hours.
Polymixin, neomycin, hydrocortisone ear drops (Otosporin)	10	2 drops q.i.d.	750	Yes	Effective in appropriately sensitive infections.
Propantheline (Probanthine)	1	15 mg t.d.s.	150	No	Normal therapeutic efficacy.
Pseudoephedrine hydrochloride tabs. (Sudafed)	3	60 mg t.d.s.	450	Yes	Normal therapeutic/prophylactic efficacy.
Sodium fusidate (Fucidin)	1	500 mg t.d.s.	30	No	Normal therapeutic efficacy.
Sodium nitroprusside	3	2-10 mg/kg	66	No	Used in a dose of 2-10 mg/kg.
Soframycin and dexamethasone ear drops (Sofradex)	10	2 drops q.i.d.	750	Yes	Effective in appropriately sensitive infections.

Name of Drug	No. of Times Used	Dose	Max. Depth (feet)	O_2HE	Comments
Soluble aspirin and codeine (Codis)	60	2 four hourly	120	No	Normal therapeutic efficacy.
Tetracycline	30	250 mg q.i.d.	500	No	Normal therapeutic efficacy.
Thymoxamine hydrochloride (Opilon)	2	40 mg q.i.d.	150	No	Used in treatment of vestibular decompression sickness with oxygen from 60 feet.
Trimethoprim, sulphamethoxazole (Septrin)	37	2 tabs. b.d.	1000	Yes	Normal therapeutic efficacy. Used prophylactically in catheterized patients.
Triprolidine, pseudoephedrine, codeine linctus (Actifed)	2	10 ml 4 hourly	600	Yes	Effective in controlling productive cough.

DISCUSSION

Dr. Linaweaver related that his experience with recent sport diving accidents in Southern California, Hawaii, and the Carribean indicates that the majority of cases (approximately 70%) are severe massive life-threatening intensive care cases. This is contrary to the U.S. Navy experience where 98% of decompression sickness is pain only (Type I). A similar situation exists in the commercial operations. Because the rig-medics/corpsmen are doing an excellent job of monitoring DCS and do recompression treatment without a medical officer, the diving medical officer sees only the severe life-threatening cases. Therefore we need direction concerning drug effects on routine clinical procedures (e.g. to correct acid-base balance, steroids, etc.).

In light of the fact that many of these sport accidents involve middle age divers, the question was raised about anti-hypertension medications. Dr. Bove replied that a large number of hypertension drugs create a problem with exercise. These drugs block the sympathetic system, causing patients to have a low tolerance to exercise; they are likely to suffer syncope and severe dyspnea with low levels of exercise. Dr. Bove's approach for the sport diver is that anything beyond one thiazide diuretic/day is a contraindication to diving. Anything stronger results in a blocked response to exercise and the individual could physically fail if placed in a high stress situation.

What should the approach be for diabetics who wish to dive? Dr. Bove replied: "My approach is that a diabetic on insulin should not dive. Some sports diving organizations are beginning to say 'don't listen to your doctor, go ahead and dive anyway.' I explain to these individuals that sport diving is a recreation, and when the risk in your recreational sport includes death then that is not the right sport to engage in. There are a lot of things a diabetic can do, including running marathons, but I recommend that they stay out of diving if they are on insulin and that includes most juvenile diabetics. There are very few juvenile diabetics that are diet controlled or pill controlled." Dr. Linaweaver added: "I think that most physicians far underestimate the physical activity of diving. If you look at the O_2 consumption studies on swimming, they will astound you as to the level of work involved in just simply propelling oneself through the water. There is also a metabolic requirement for heat production and if you are wearing a nice quarter inch wet suit, you have a compliance problem in increasing the work of breathing to stretch the nice tight fitting wet suit. I think that many physicians tell their patients that they can go ahead and dive safely with these conditions without realizing how much work is required.

It was noted that many patients desiring to dive are on chronic antibiotic therapy for one condition or another and the question was raised whether antibiotics should contraindicate diving. The panel agreed that as long as the condition for which the drug is required

has no consequence for sport diving, the antibiotic is unlikely to cause interaction at these shallow depths.

It was acknowledged that most physicians lack a basic understanding of the physiology of diving and even those who do seem to forget that it is a very strenuous activity. After considerable discussion over regulations, regulating agencies, malpractice suits, and the infringement on physician/patient rights, the panel generally agreed that the development of regulations was not a viable approach. The recommended solution is to educate physicians to understand the physiology and medicine of diving so that decisions about drugs, etc., can be made intelligently.

Dr. Kendig asked about the thermal aspects of sport diving in relation to drug interaction, especially for those drugs which affect temperature regulation. The panel agreed that thermal protection was an important consideration for certain classes of drugs (e.g. phenothiazine-type) where disruption of thermal-regulating capacity is a known side effect.

In speaking about medications that should limit or bar a diver from diving the question arose whether the physician should be concerned about the medication or the condition for which the drug is being prescribed. The panel agreed that both the drug and the disease were important factors. The categorization of some drugs will indicate a significant underlying disease process and that is important. However, there are some drugs which would be bad to have on board while diving, regardless of the disease process.

Dr. McIver provided the following listing that he and his colleagues at the North Sea Medical Center recognized as problem drugs for long-term use by divers:

Antacids
GI-sedatives
Anti-spasmotics
Anti-ulcer
Anti-angina
Anti-dysrhythmics
Anti-hypertensives
Anti-migraine
Anti-coagulants
Analgesics
Hypnotics
Sedatives
Tranquilizers
Anti-depressants
Anti-emetics
Anti-convulsants
CNS stimulants
Muscle relaxants
Neuromuscular agents
Hormone replacement
Anti-amoebics
Anti-fungals
Anti-tuberculous
Sulphonamides
Iron preparations
Broncho relaxants
Cough suppressants
Mydiatrics
Cycloplegics

Dr. Bove commented that the OSHA standards for commercial divers specifically rule out coronary heart disease, cardiomyopathy, cancer of any kind that is active (unless removed or arrested for 5 years or longer), seizure disorders, chronic anemia, sickle cell disease, chronic pulmonary disease and insulin dependent diabetics.

What about chronic prophylactic-type drugs like antabuse or INH? The panel agreed that the CNS side effects of these compounds have the potential to produce catastrophic reactions in the water. Specifically if INH is required to treat TB infection, the underlying condition should preclude diving. If INH is being given prophylactically it may be prudent to take the diver off medication while diving. Antabuse, because of its side effects, is a drug which should not be available in a commercial diving system when the diver is in the water.

The UMS receives more inquiries concerning the effects of oral contraceptives while diving, than any other subject. There is no data in the literature on the effects of oral contraceptives in the hyperbaric environment. Because of the thrombogenic side effects of these drugs, some have suggested that they would increase susceptibility to DCS. Dr. Bove hypothesized that oral contraceptives were not likely to predispose a woman to decompression sickness but they might make her more prone to have a more serious case once the process began. Dr. Linaweaver commented that the Air Force fliqht nurse training data indicate that women are more susceptible to DCS than men. The Navy representatives indicated concern in training female Navy divers, who are exposed to deeper (285-300 fsw) depths and more decompression diving than sport divers. The panel agreed that the determination of the effects of oral contraceptives in the hyperbaric environment was a prime area for research.

In summary, the panel unanimously recommended that due to the fact that the safety of most drugs in the hyperbaric environment has not been proven, physicians should consult the PDR (or similar reference) to refamiliarize themselves with the actions/side effects/and adverse reactions of a compound before prescribing to a patient who is a diver. In addition, at times absorption problems occur in the hyperbaric environment and these should also be considered when selecting drugs.

CHAPTER III

HYPERBARIC ANESTHESIA

ANESTHESIA AT HIGH PRESSURES

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In the UMS National Plan for the Safety and Health of Divers in their Quest for Subsea Energy (Part II Use of Drugs and Other Medical Treatment Under Hyperbaric Conditions by Richter et al., 1976) it was stated that although many animal studies infer that hyperbaric exposure reverses anesthesia, in present clinical practice, at relatively low pressures, general anesthesia by gaseous anesthetics has rarely been attempted. Instead reliance has been placed on intravenous or local techniques. For example, in "The Ordeal of Donald Boone," Carter and Goldsmith (1970) vividly describe the surgery on an eviscerated diver at 190 fsw using local anesthesia, a narcotic and an antihistamine.

Intravenous Anesthetics

In 1975 an editorial in the British Medical Journal maintained that there had been so few surgical emergencies under high pressure that there is hardly any experience to draw upon and commented "Pressures may be as high as 20 atm when conventional anesthesia is unpredictable. Under these conditions most surgeons would prefer to rely on local anesthetics with heavy doses of morphine as necessary." This led Lloyd (1976) to reply in argument that this ignores the dangers of vomiting and respiratory depression produced by morphine and suggested instead that although ketamine is unsatisfactory in adults at even normal pressure due to its hallucinogenic effects it may be combined with diazepan.

Ketamine induces a form of anesthesia termed 'dissociative anesthesia' with total absence of pain but with an increased activity of the brain leading in patients to vivid dream activity and unpleasant hallucinations during recovery. Other side effects include increased activity of the sympathetic nervous system producing tachycardia and hypertension. Diazepam either given concomittantly or prior to the ketamine has been found to control these side effects and permit effective anesthesia (Burnap, 1974; Gran, 1979). Presently Gran at Duke Medical Center is studying the combined effects of diazepam and ketamine as an anesthetic at raised pressures in rats. They are preferably given simultaneously by drip so as to overcome the ketamine induced increase of arterial and intracranial pressures (Burnap, 1974). Previously McCracken, Tobey, Bailey and McElroy (1974) studied ketamine sleep responses in guinea pigs at pressures of 20-30 ata helium-oxygen and compared the results with earlier studies with thiopental (Tobey,

McCracken, Small and Homer, 1978). They studied loss of righting reflex and duration of sleep and noted that ketamine's action was indeed antagonized by pressure but to less of an extent than thiopental. For ketamine it was considered highly unlikely that more than 1.3 to 2.3 times the surface dose would be required at 20-30 ata for the same anesthetic effect in contrast to 3 to 5 times the surface dose for thiopental.

More recently Halsey, Wardley-Smith and Green (1978) investigated pressure reversal of anesthesia achieved by continuous infusion of different types of intravenous anesthetics given to rats including ketamine, thiopentone, propanidid, and methohexitone at pressures in some cases up to 100 atmospheres. The overall degree of pressure reversal was found to be greatest for methohexitone and least for ketamine and showed that the drugs have a wide spread in their pressure reversal characteristics.

Althesin - a steroid anesthetic exhibited a plateau effect at pressures greater than 50 atm whereas thiopentone pressure reversal continued to increase non-linearly. Interestingly in a preliminary screening of 21 potentially suitable drugs in tadpoles for prevention of the High Pressure Nervous Syndrome, Halsey and Wardley-Smith (1975) showed that this new steroid anesthetic Althesin -- a mixture of alphaxalone and alphadolone acetate gave a dramatic degree of pressure protection. Later studies by Bailey, Green, Halsey and Wardley-Smith (1977) in rats showed that the apparent potency of Althesin was reduced by 43% at 68 ata helium and that sub-anesthetic doses of Althesin protected against the coarse tremors and the onset of HPNS convulsions.

Although Elliott and Hanson (1976) maintain that Althesin alone does not provide sufficient anesthesia, Lloyd (1976) believes that a combination of Althesin or propanidid with neuroleptanalgesia may be satisfactory.

Neuromuscular Relaxants

There is remarkably little data on the action of neuromuscular relaxants at increased pressures. According to Severinghaus (1966) "all the usual relaxants have been used with hyperbaric oxygen therapy and appear to function normally." It should be noted, however, that when paralyzing doses of relaxants are used, the motor signs of an oxygen convulsion will be masked and the EEG should therefore be monitored under these conditions.

Gountis-Bonikos, Kendig and Cohen (1977) notably have studied the interactions between high pressures of up to 137 atmospheres oxygen-helium and d-tubocurarine or succinylcholine on the indirectly stimulated rat phrenic nerve -- diaphragm preparation. They found that the raised pressures tended to enhance muscular blockade by d-tubocurarine more than by succinocholine as indicated by electromyographic suppression but tended to antagonize the succinocholine effect on twitch tension more than d-tubocurarine. This is in agreement with previous reports concerning the High Pressure Nervous Syndrome that high pressures increase muscular twitch tension but decrease excitatory synapses. These somewhat

different effects coupled with the need for confirmation in whole animals and man led the authors to advise caution in the use of neuromuscular blocking agents at pressure until further research has been performed.

Gaseous Anesthetics

The gaseous anesthetics have been left to the final stages of this brief paper to emphasize the greater desirability of using intravenous methods. Nevertheless gaseous anesthetics, particularly nitrous oxide and especially halothane have been used notably in connection with hyperbaric oxygen therapy.

One of the earliest suggested uses of pressure was by Faulconer, Pender and Bickford (1949) to permit the use of nitrous oxide alone as a surgical anesthetic. This occurred at a P_{N2O} of about 800 mmHg. The use of such a gaseous anesthetic is, however, obscured by two problems. One is due to the high lipid solubility and uptake by the tissues which markedly increases the risk of decompression sickness during decompression. Further massive elimination of nitrous oxide during the decompression may give rise to a "diffusion hypoxia."

Nevertheless Winter, Hornbein, Smith, Sullivan and Smith (1972) determined the anesthetic potency (MAC) and cardiorespiratory effects of nitrous oxide under hyperbaric conditions in nine normal volunteers anesthetized with 1.55 atm N_2O and 0.32 atm O_2. In 8 of the 9 subjects MAC was 1.05 ± 0.07 atm which agrees well with Faulconer et al. (1949).

Cardiovascular and metabolic changes suggested that N_2O is a sympathetic stimulant. At 1.55 atm sweating, dilated and divergent pupils, increased muscle tone and occasional movements were noted. On lowering the pressure to 1.1 atm the subjects showed loss of sweating, decreased muscle tone and decreased pupil size. Blood glucose, catecholamines, corticosteroids and white blood cells were increased above awake levels at both pressures.

However, halothane remains the gas most used clinically during documented cases of surgery with gaseous anesthesia under hyperbaric conditions (Jacobson et al., 1962; McDowall, 1964; Smith, 1965). This is due also to the requirements for anesthesia mostly being under hyperbaric oxygen conditions and the increased risk of explosion or fire which calls for a non-explosive and non-flammable anesthetic at atmospheric pressure such as halothane. But manufacturers' tests show that halothane can be ignited at 4 atm in the presence of diathermy although at pressures less than 4 atm it is safe when vaporized in 100% oxygen rather than oxygen and nitrous oxide as the latter will widen the flammability range of halothane. Halothane is also chosen because of its reduction of the cerebral blood flow through the cerebral cortex which seems not to be compounded by the hyperbaric oxygen.

A few further factors are of importance in regard to gaseous anesthesia with, for example, halothane. First, since the partial pressure exerted by a liquid is unaffected by the total pressure above the liquid most anesthetic vaporizers function is unaltered at pressure.

Thus the partial pressure of halothane will not change under pressure but the number of molecules of the gas will increase in proportion to the atmospheric pressure (e.g. halothane will vaporize from a copper kettle at 243 mmHg at 20°C irrespective of the total pressure with a concentration of 32 vols/% at 1 atm abs and 10.7 vols/% at 3 ata. Either way 32 volumes of oxygen are required to produce an anesthetic concentration with a partial pressure of 7.6 mmHg equal to 1% at 1 ata.

Secondly, attention must be given to the endotracheal cuff to ensure that the increased pressure has not deflated it and on decompression that the cuff is allowed to relieve any overpressure. Flow meters need to be carefully calibrated and specific attention paid to monitoring, especially the EEG and EKG if the anesthesia is for hyperbaric oxygen purposes with a risk of convulsions.

Thus, in conclusion, the preference for hyperbaric anesthesia is reliance on intravenous anesthetics including Pauvlon for relaxation and reversibility, Innovar, Sublimaze, Droperidol, Valium, Ketamine and Pentothal for anesthesia/analgesia. Due to the paucity of reliable data available on the use of anesthetics at raised pressures, it is an area which could benefit from further research.

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ANESTHESIA UNDER HIGH PRESSURE

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In the 1960s hyperbaric oxygenation was widely used for certain surgical procedures (Smith et al. 1964) to increase the amount of dissolved oxygen in the blood. Among these procedures are:

1. Correction or palliation for cyanotic congenital heart diseases,
2. debridement for burns or for reconstructive surgery where blood supply is questionable,
3. debridement for clostridial infections,
4. injuries requiring immediate operation when associated with decompression sickness, cyanide or carbon monoxide poisoning, massive methemoglobinemia,
5. shock,
6. planned pulmonary embolectomy,
7. certain types of fetal distress.

With increasing use of saturation dives at ever increasing depths, an anesthesiologist may find himself dealing not only with trauma but also with operative procedures involving common surgical emergencies such as appendicitis, bleeding or perforated ulcers and incarcerated hernias. As a consultant familiar with the care of the unconscious patient, use of muscle relaxants, anticonvulsants and hypnotic-sedatives, the anesthesiologist's role may include (1) directing resuscitative and minor anesthetic procedures in an underwater habitat using distorted electronic communication; (2) at depth, providing anesthesia for major surgical procedures and (3) at times while at depth, acting as surgical assistant.

Most of the problems during surgery in a hyperbaric chamber are technical or logistic in nature and have been previously addressed to (McDowall, 1964; Pittinger, 1966; Severinghaus, 1965; Spence and Smith, 1974). They are easily overcome by the present state of technology. Pharmacologic problems, however, remain because of the general lack of information regarding the dose-response to drugs when administered to patients while under high pressure. There is also paucity of data from animal models whose physiology closely resembles man. Even if proper calibration for flow meters and vaporizers are obtained at an operational depth, there will still be reluctance in using inhalation anesthesia. In an answer to an editorial in the British Medical Journal (1975), Wisely (1976) suggested that inhalation anesthesia is "out of the question" at about 20 atmospheres. He further suggested the use of intravenous agents like althesin -- a drug mixture whose potency is

known to be reduced at high pressure (Bailey et al, 1977).

As mentioned, one reason for the reluctance to use gaseous anesthetics is the absence of dose response information on these agents. Anesthesia can be obtained by simply increasing the dose that might be needed while under high pressure. It is not known, however, if there is a parallel increase in the tolerance of other organ systems to the agent. For example, the increased MAC for halothane required to abolish response to painful stimulation under pressure may be devastating to the cardiovascular system, or as in the case with methoxyflurane, damaging to the kidneys, making either of them unsafe.

The role of intravenous agents, their increased requirements and shortened duration of action have been described (Tobey et al, 1978; Halsey et al, 1978; McCracken et al, 1979). To these we add our findings. In guinea pigs, widely variable doses of diazepam are required to induce sleep (loss of righting reflex) on the surface with long duration of action. In 3 ATA oxygen, larger doses are required with short duration of action and in 6 ATA air, the smallest doses are required with equally shortened duration of action (Nicodemus et al, 1979).

Intravenous anesthesia known as balanced anesthesia is now widely employed in most clinics. With this technique, narcotics provide analgesia, barbiturates provide loss of consciousness and muscle relaxants, varying degrees of muscle paralysis. The use of diazepam, singly, with ketamine or with narcotic could be expected to gain prominence under hyperbaria. Diazepam offers some degree of amnesia while it softens the hallucinogenic effect of ketamine (Burnap, 1974). But what of their duration of action? Most work on neuromuscular function and the effect of muscle relaxants thereof were reported by workers from Stanford University (Kendig and Cohen, 1976; Gountis-Bonikos et al, 1977). The reports are mostly on isolated nerve-muscle preparations and do not shed light on the duration of effect. McCracken (1979) has data on succinyl choline in intact guinea pigs at 31 ATA helium-oxygen. Like others, he noted increased twitch tension height. In addition, his work revealed that the duration of action of this depolarizing relaxant is not different from that of the surface control which indicates that at high pressure, there is an intact and functional pseudocholine esterase system. It should be noted that some local anesthetics are hydrolyzed by this enzyme.

There is meager information on the efficacy of anticholine esterases in the reversal of non-depolarizing neuromuscular blocks. Their muscarinic side effects also need to be studied under high pressure environment since gastrointestinal motility and the gas contents of the bowel are important considerations when environmental pressure is less than stable. Interaction between antibiotics and such other factors as low serum calcium, electrolyte imbalance, narcotics and muscle relaxants can lead to prolonged muscle paralysis. This interaction is difficult enough to unravel at 1 ATA and is totally undocumented under high pressure. More work on antibacterial efficacy of antibiotics similar to that reported by Argamaso (1967) are needed so the anesthesiologist can choose the antibiotic that does not interact with relaxants.

Narcotics, singly (Stanley et al, 1979) or in combination with other agents, e.g. Innovar, have proved adequate as primary anesthesia. Can their actions be reversed with their specific antagonists? For example, physostigmin reverses diazepam and other sedatives (Rosenberg, 1974); can one expect similar results at high pressure? Included among the antagonists of special interest to the anesthesiologist are nalline and naloxone. Balanced anesthesia requires reversal of some of its effects, certainly those effects that will prevent adequate ventilation in the patient. Mechanical artificial ventilation in a hyperbaric chamber is not easy even to those familiar with it at surface conditions.

Parenthetically, Bennett (1979) was able to abolish most of the tremors in HPNS by adding nitrogen to the inspired gas. Those intension tremors that occur with muscular movement however persisted. Pressure is known to increase twitch tension height (Kendig and Cohen, 1976) so that it is not illogical to expect jerky muscular movement during exposure to high pressure. Since muscular contraction is initiated by a train of nerve impulses (tetanus), this jerky movement of HPNS is reminiscent of post-tetanic fascilitation seen in partially curarized muscles. Kendig and her associates (1978) however have reported that repetitive impulse generation in the nerve terminal may be the basis for the hyperactivity in HPNS.

Regional Anesthesia: A large number of major surgical procedures may be performed under regional or field block anesthesia (Carter and Goldsmith, 1970). Several authors (Kendig and Cohen, 1977; Roth et al, 1976) have reported that pressure reversed the nerve conduction block induced with local or general anesthesia. Whether or not local anesthesia will work is not the concern here. We are assured that it will, since all clinical methods of bathing the nerves in local anesthetic agents constitute a gross overdose. Of greater interest to anesthesiologist is the duration of effect as might be influenced by the pressure. How long a subarachnoid or epidural block lasts depends on the effect of pressure on tissue binding, blood flow and redistribution of the drug. The other area of concern here is the change in the toxic dose. Metabolism is generally not a factor in the termination of anesthetic block. However, blood level is a factor concerned with toxicity. There are indications that induction of drug metabolizing enzymes is influenced by exposure to high pressure and different gas mixtures (Tofano et al, 1976; Geiger et al, 1977). From available information, changes in toxicity may constitute a minor problem (Small, 1970). Herold and Nicodemus (1979) found that hyperbaric air or oxygen increased the dose required to induce convulsion in guinea pigs. They concluded that the safe limits of the surface doses of lidocaine are just as safe to use under pressure up to 6 ATA air. Krenis et al (1971) presented data that subhypnotic doses of lidocaine and cocaine protected against central nervous system toxicity of high pressure oxygen. Pretreatment with subhypnotic doses of diazepam nearly double the amount of local anesthetic necessary to induce convulsion in cats (de Jong and Heavner, 1972). Herold and Nicodemus (1979) failed to show alterations in the anticonvulsant property of diazepam in guinea pigs when challenged with convulsive doses of lidocaine while in 3 ATA oxygen or 6 ATA air. Caution should, however, be exercised when diazepam, local anesthesia

and high pressure nitrogen are combined because a far greater depression can occur and may be misinterpreted as arising from other causes.

Catecholamines, Adrenergic Blockers, Vasodilators and Monitoring of Cardiovascular Function: These subjects are grouped together because of their close relationship. Although the response of animals to the stress of infection has been shown as an increased circulating catecholamines (Won and Ross, 1975), the sympathetic autonomic response of a patient should be more characterized at hyperbaric condition. A high sympathetic tone may be expected (Hammond and Akers, 1975). In addition, one of the hallmarks of balanced anesthesia is an intact and sensitive sympathetic response to surgical stimulation. Evans and Greenbaum (1970) reported that pressor response to epinephrine is unaltered in the cat at 200 ATA. However, adrenergic responses can be either alpha, represented by increased blood pressure, or beta, represented by increased heart rate with or without ventricular extrasystole. The cardiovascular dose-response to ganglionic blockers and the more specific alpha and beta blockers are largely undocumented at high pressure.

If peripheral resistance due to intensed vasoconstriction becomes unduly high in an anesthetized patient, the strain on the myocardium may precipitate acute failure. In this situation, vasodilators are indicated. Information on the efficacy of nitroglycerin and sodium nitroprusside is needed to insure their safe and rational use while under hyperbaria. Certain antihypertensive agents, e.g. diazoxide, also require testing.

Should acute heart failure develop, digitalization is the accepted mode of therapy. In the presence of factors such as electrolyte imbalance, loss of potassium due to pressure diuresis, altered catecholamine response, altered response to calcium and altered membrane physiology, rapid digitalization is a perfect setup for ventricular dysrhythmia or even fibrillation. To say that electrical defibrillation is difficult in a hyperbaric chamber is an understatement.

The key to the use of the drugs under this heading is monitoring. Technically, the problem of electrocardiography, continuous blood pressure monitoring or even cardiac output determination are surmountable. What may be required, though, is a reinterpretation of some of the changes in the vital signs especially when exposed to hyperbaric oxygen (Gutsche et al. 1966). For example, a patient may show electrocardiographic signs of cardiovascular strain, increased blood pressure and rapid heart rate in the presence of blood loss. Traditionally, hematocrit, cardiac output and peripheral resistance are determinants of oxygen delivery to the tissues. In a critical care situation at 1 ATA, a given set of readings may determine the need for more red blood cells, or if the hematocrit is normal, more fluids to improve blood flow. While under pressure, oxygen delivery could be improved or at least brought to near normal values regardless of hematocrit by simply increasing the inspired oxygen concentration. The increased amount of dissolved oxygen may be enough to meet basal requirements. More information is needed in this area for a more logical conclusion and action. To be complete, the algorithm must also include the appropriate fluid, whether crystalloid or colloid or a mixture of both plus red blood cells constitute the best course of action.

Monitoring should also include urine output. Balanced anesthesia which includes narcotic could change the antidiuretic hormone output. It is known however, that pressure reverses the antidiuretic effect of morphine (Tofano and DeBoer, 1976). To be sure, urine volume must be measured together with determination of urine pH as it may indicate adequacy of blood flow and oxygenation. By the way, does pressure or exposure to different gas mixtures alter the response of test tapes for urine pH?

Non-pharmacologic Methods: While this heading is outside the topic of pharmacology and high pressure, anesthesiologists concerned with provision of adequate anesthesia and pain relief would certainly like to know if electronarcosis is effective under high pressure. Anesthesia induced in this manner does not require uptake, distribution and metabolism or even atmospheric contamination; therefore, it appears ideal for hyperbaric work. Other modalities of pain relief that may prove useful are transcutaneous nerve stimulation, acupuncture and perhaps, in the distant future, endorphins.

To summarize, as a clinical anesthesiologist, I have tried to integrate available drug information with the problems encountered in the operating room. I tried to paint a picture in natural color. As familiar to all divers, the colors change as one takes the picture deeper into the water. We need to know both the graduations of these color changes and the final hue that the picture would take when we finally get to the bottom.

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DISCUSSION

Dr. Bove asked what the objection was to the use of nitrogen as an anesthetic?

Dr. Bennett replied that you would need a lot of molecules which means going to a very high pressure. One could use xenon, but then there is the immediate problem of decompression, (we have no xenon tables) and there is a density problem at surface pressure, which at any kind of depth will become worse. Nitrous oxide is very unpopular because it is flammable and has a potentially high risk of decompression sickness because of its solubility. What we are probably left with if it is necessary to make a choice of anesthetic is ketamine with diazepam.

Dr. Kendig commented on the interaction of temperature and pressure. Her work on model membranes and nerve preparations indicate that low temperature and high pressure often enhance each other's effects. Dr. Bennett suggested that this effect may vary across species as has been found in the HPNS work; rats and humans are more resistant to HPNS when cold, and less so when hot. The panel agreed that the confusion right now relates to the emerging realization that we are looking at multi-sided effects of both pressure and of anesthetics.

Dr. Zell asked what kinds of problems are encountered during surgery under hyperbaric conditions? Dr. Nicodemus replied that most surgery is performed at about 3 ATA with the patient breathing oxygen and the surgeon and crew breathing air. The problems are mostly technical, i.e., monitoring blood gases and bringing things to the chamber. In terms of anesthesia there should not be any problems except for contamination of the room with the vapor. Dr. Bove suggested that it is probably safe to say that down to depths of several hundred feet, anesthetic effects would not differ greatly from those at the surface. It was acknowledged that there should not be problems because anesthesia is generally an overdose anyway.

The panel engaged in extensive discussion weighing the pros and cons of various research models. It was generally agreed that there was no substitute for the intact animal model although isolated preparations do provide clues to broad categories of drugs that are likely to cause problems. Human models of drug research are almost out of the question, but it was suggested that some sort of reporting system be developed to record those cases where drugs are used in humans in the hyperbaric environment.

Dr. Bennett cited the summary of the Anesthesia session from the EUBS meeting in Luxembourg which he stated summarized exactly where we are in hyperbaric anesthesia: Little is known about:

a. The performance of respirators and evaporators at pressures above 5 bar in HeO_2;

b. The pharmacology and pharmacokinetics of the drugs that are likely to be used in anesthesia at increased pressure;

c. The secondary gas effects of anesthetics such as the variations of volume of closed body compartments, counterdiffusion, and added risk of bubble formation.

There is also the need thoroughly to evaluate intravenous anesthetic agents with the goal of regional anesthesia.

CHAPTER IV

EMERGENCY USE OF DRUGS

DRUGS IN THE HYPERBARIC ENVIRONMENT

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In considering the hyperbaric environment and its interactions with drugs, an important subject is the use of drugs in intensive care situations which arise in the hyperbaric environment. Indeed, many patients who need treatment in a hyperbaric chamber require not only high pressure or high pressure and oxygen, but in addition, significant intensive medical care as it is applied outside of the hyperbaric chamber. Thus, considerations of treatment for myocardial infarction, shock, bacterial sepsis, pneumonia, heart failure, and a variety of other diseases must be included in the discussion of drugs in the hyperbaric environment. Thus, a variety of therapeutic problems may arise in a seriously ill patient treated with hyperbaric oxygen. In each case, the disease being treated may result in a situation where the physician may be required to provide life support for the patient while he is undergoing the treatment of the primary disease, for which hyperbaric oxygen or pressure is indicated. A list of typical problems which may occur in a chamber is presented below with a discussion of drugs which may be required.

1. Seizures. Treatment of patients with arterial gas embolism or massive decompression sickness as well as gas gangrene, carbon monoxide inhalation, and a variety of other acute illnesses may require the treatment of acute seizures. In addition, oxygen toxicity may also stimulate seizures. The treatment of oxygen seizures is withdrawal of the oxygen environment. Other seizures however do require medical treatment. At the present time the drug of choice is Diazepam 10 mg. given intravenously. This is a relatively rapid acting drug and is quite successful in controlling grand mal seizures. Personal experience with this drug suggests that there are no major interactions or complications with the use of this drug in the hyperbaric environment. Other drugs that should be considered for seizures are Dilantin and the barbiturates. Although some questions arise concerning barbiturate toxicity in hyperbaric oxygen, this question has not been fully resolved and still remains open to question.

2. Cardiac Arrhythmias. In general, seriously ill patients including those treated in the hyperbaric environment are prone to a variety of cardiac arrhythmias. Many of these are relatively benign and can be tolerated without definitive therapy. Specifically, premature atrial contractions which are infrequent or isolated generally can be tolerated without treatment. Recurrent periods of atrial flutter or atrial tachycardia, however, should be treated since these arrhythmias can reduce the cardiac output and they can aggravate the state of shock or produce progressive ischemia of the myocardium. The treatment

of these arrhythmias is varied. In general, digitalis type drugs should be used orally or intravenously. The most common is Digoxin, the dose is from .1 to .25 mg orally or intravenously every 6 to 8 hours for a total dose of 1.5 to 2.0 mg. Care must be taken to know or assess renal function since this drug cannot be excreted if there is any compromised renal function. Other treatment for atrial flutter or atrial tachycardia include quinidine, procainamide and the new antiarrhythmic drug Norpace.

None of these drugs have been specifically tested in the hyperbaric environment and although there appears to be no anticipated interaction, study of their use in this environment is warranted. For ventricular arrhythmias, including frequent premature ventricular beats or recurrent ventricular tachycardia, the drug of choice is lidocaine, given either intravenously at 1 - 3 mg/minute or as a bolus of 50 to 75 mg. The use of lidocaine in many instances can be life saving and the choice of this drug for treatment of arrhythmias should not be compromised by the fact that the patient is in the hyperbaric environment. The interaction of lidocaine with high pressure and increased oxygen partial pressure is not known but practical considerations suggest that its use would be safe. However, some study in this area is warranted. The antiarrhythmia drugs, procainamide, quinidine and norpace all can be used successfully in treating premature ventricular beats and ventricular tachycardia. The same considerations as mentioned above apply in this case. In addition to the drug therapy of cardiac arrhythmias, one should consider the use of electric cardioversion in the hyperbaric chamber. In some instances, cardioversion is the only possible way of reversing a life threatening arrhythmia and suitable precautions must be taken to prevent sparks or open arcs during the use of electrical defibrillation.

3. Shock. Shock may be caused by a variety of disorders including cardiogenic where severe damage of the myocardium has occurred and the heart cannot pump an adequate forward cardiac output, neurogenic where peripheral vasodilitation occurs due to loss of vascular neurocontrol or septic where generally a gram negative sepsis has occurred and caused endotoxic shock. Other causes are severe fluid loss from dehydration and severe blood loss from acute bleeding. In all cases, the treatment of choice for shock is to return the cardiac output to normal. This can be done by improving cardiac performance with medications, by replacing blood loss or fluid loss to restore adequate circulating blood volume, by treating infection, and with the use of large dose steroids for prevention of the endotoxic effects of circulating bacteria on the circulation. There appears to be no significant contraindication to the use of replacement fluids in the hyperbaric chamber. Indeed, these are recommended in all instances of chamber treatment to prevent dehydration. In addition, the use of whole blood or blood products would appear to have no major problems or interactions unique to the hyperbaric environment. In endotoxic shock the use of large dose steroids is warranted and previous experience by a number of treatment centers suggests that steroids injected intravenously in the hyperbaric environment do not produce any major interaction. In addition to steroid medications in the shock produced by sepsis, antibiotics are also used. In vitro studies suggest that bacteria may be more

resistant to antibiotics in hyperbaric oxygen. However, standard medical indications should rule in the treatment of infection with antibiotics.

4. Allergic Reactions. It is quite possible in a chamber treatment, to experience reactions to drugs which result in urticaria or anaphylactic shock. These can be entirely unpredictable and can result from injection of almost any drug. The treatment is rapid infusion of epinephrine and large doses of steroids given intravenously. Antihistamines also play a role in the treatment of anaphylaxis or allergic responses to drugs. Even though the reaction to drugs used to treat anaphylaxis may not be entirely evaluated in a hyperbaric environment it is important to treat anaphylactic shock rapidly with all known methods and to consider interactions with the environment as a secondary problem to be dealt with as they arise. These patients may require endotracheal intubation, cardiac resuscitation and treatment of a cardiac arrest with the entire complement of drugs available for this purpose. Once again, the use of these drugs should not be compromised by consideration of interactions with the environment since they may be lifesaving and interactions can be dealt with as a secondary problem as they arise.

5. Anxiety and Pain. Many patients being treated for disorders requiring hyperbaric oxygen or pressure will experience pain of some sort or may have acute anxiety reactions. In either case, sedation and/or analgesia will be required in the treatment of these individuals. This mode of therapy is necessary to avoid injury to the patient while other therapy is underway and to protect the chamber support personnel as well. For pain, a variety of drugs are available. The most potent is morphine which can be used in the hyperbaric environment with results similar to those expected in the normal environment. Other analgesics include Talwin, Demerol, and combined analgesic-tranquilizer medications. All of these medications are sometimes useful in this environment and should be used when clinically indicated with due consideration for factors such as respiratory arrest. For acute anxiety some sedative is often necessary and at present diazepam appears to be the drug of choice. However, there are a variety of tranquilizers and sedatives which could be used in the hyperbaric environment. It is important in the use of both analgesics and tranquilizers to not compromise the neurologic status of the patient since evaluation of neurologic status may be an important component of the patient's treatment. However, when acute anxiety or severe pain is compromising treatment or endangering the individual or the support personnel, then these medications should be used.

6. Heart Failure. It is unlikely that heart failure would develop in a healthy young diver with decompression sickness, however in severe massive decompression sickness heart failure may occur because of significant pulmonary vascular obstruction, gas emboli to the coronary circulation or severe hypoxia. In older individuals being treated with hyperbaric oxygen for other reasons it is possible that some of these individuals will have compromised cardiac function and could develop progressive congestive heart failure or evidence of

acute pulmonary edema, as a result of other underlying illnesses. Acute or chronic congestive heart failure requires a variety of medications including digitalis, diuretics, morphine, and sometime xanthine derivatives such as aminophylline. None of these drugs should be withheld from the patient in the hyperbaric environment. They are often life-saving in the case of acute pulmonary edema, and to date no obvious detrimental interactions between these drugs and the hyperbaric environment are known. The patient in pulmonary edema in the hyperbaric environment may benefit from hyperbaric oxygen if the pulmonary edema is cardiac in origin and not, for example, secondary to oxygen toxicity to the lung. In cases of heart failure often times rapid diuresis is the best treatment, although other modes of treatment, including tourniquets and the previously mentioned drugs, are also important. It may be necessary to provide intensive care monitoring with arterial pressure and central venous or pulmonary arterial monitoring using a balloon tip catheter placed by flotation in the pulmonary artery. Operation of these devices should not be impaired by the hyperbaric environment if due care is exerted to appropriately balance and calibrate pressure measuring devices inside the chamber prior to the recording of pressures from the circulation. The results obtained from these measurements can be of extreme value in handling the complicated patient in heart failure and in some instances, it is possible that these patients would be treated with hyperbaric oxygen as part of their overall care.

7. Respiratory Failure. Failure of the lungs to transport oxygen into the circulation occurs from a variety of acute and chronic causes. Besides heart failure, in the acute situation, drowning, smoke inhalation, severe oxygen toxicity, shock lung, and several other disorders will produce respiratory insufficiency and chronic hypoxia. In the hyperbaric environment when oxygen toxicity is not the cause, the high partial pressures of oxygen can be used to advantage for short periods of time, however, care must be rendered in the administration of high pressures of oxygen because of the rapid onset of the pulmonary toxicity when previous lung injury has already occurred. Respiratory failure is generally treated with careful monitoring with arterial blood gases and establishing an optimal inspired gas concentration to provide adequate oxygen to the blood while minimizing the possibility of pulmonary oxygen toxicity. It may be necessary to measure arterial blood gases while the patient is in the hyperbaric chamber and if this is the case, arterial blood gases must be done inside the hyperbaric chamber or they will be inaccurate. In chronic respiratory failure, often times the patient has an elevated partial pressure of carbon dioxide in the blood and the administration of hyperbaric oxygen can be lethal because of respiratory arrest. Since in these cases careful and complex patient management is necessary, it is important to have a knowledgeable physician trained in respiratory disease to assist in the care of the individual. Drugs used in this environment include xanthine derivatives such as aminophylline, diuretics and often times antibiotics.

Management of these cases is complex and requires careful balance of drug therapy, oxygen therapy and ventilatory assistance. Prior to treating a patient of this type in the hyperbaric chamber, careful assessment of the facilities of the chamber and the support personnel should

be made to assure proper care of the patient in the presence of a variety of possibilities including the use of a respirator inside the hyperbaric chamber, the need to carefully adjust inspired oxygen concentration and the need for special instrumentation for measuring arterial blood gases under high pressure.

8. Pneumonia. Acute pneumonia is considered separately from respiratory failure since it involves a series of systemic responses which may indeed interact with the hyperbaric environment. Patients with acute pneumonia generally are given large doses of antibiotics and consideration should be given to interaction of antibiotics with the hyperbaric environment, or alterations in bacterial septability due to the hyperbaric environment. Choice of antibiotics is made on general clinical indication and not necessarily based on interactions with the hyperbaric environment. In addition to the infectious process which must be dealt with, the patients with pneumonia often are hypotensive because of septicemia, may have high temperatures which increase metabolic rate and may be more susceptible to acute oxygen toxicity. Temperature lowering medications are indicated in this instance, and treatment of seizures and convulsions due to high temperature is best done with diazepam, as is the treatment of other types of seizures in the hyperbaric environment. Once again, the hyperbaric oxygen environment may be beneficial to patients with acute pneumonia since it is possible to provide adequate or improved oxygenation of the blood with the high partial O_2 pressure. However, it is also more likely that these patients will develop acute oxygen toxicity because of the already present pathologic process in the lung and due consideration must be provided for this possibility.

9. Hypertensive Crises. Many acutely ill patients who have underlying chronic hypertension are susceptible to having marked blood pressure elevation during acute stress. In this case, it would be desirable to provide therapy to lower blood pressure since the elevated blood pressure simply adds to the overall stress state of the individual and impairs recovery. Blood pressure lowering agents are varied and numerous and, in general, there is little known interaction of these agents with the hyperbaric environment. An exception is the possibility of Reserpine enhancing cerebral oxygen toxicity and this drug or combined drugs containing Reserpine should be avoided in the hyperbaric environment.

10. Anticoagulation. The use of anticoagulants in the hyperbaric environment is generally uncommon, however, it has been advocated that anticoagulation be used in cases of severe decompression sickness and this possibility may arise. To date there is no evidence that there is interaction of anticoagulants with the hyperbaric environment and these drugs should be used if indicated. The major problem with anticoagulation, if used acutely, is bleeding from either an internal or external site and there should be precautions taken so that the patient on anticoagulants does not sustain even minor trauma by contact with the hyperbaric chamber or chamber fittings. If anticoagulation becomes excessive and bleeding develops in the hyperbaric environment, then, reverse of the anticoagulation is important. The classic reverse agent

for heparin, protamine, would be the drug of choice in anticoagulation induced by heparin. In prolonged coagulation induced by anti-vitamin K agents, the best means of reversal, if time allows, is infusion or injection of vitamin K. However, in acute situations, fresh frozen plasma is necessary to rapidly reverse bleeding due to anti-vitamin K agents. In either case, a reversal of anti-vitamin K induced anti-coagulation should not be compromised because of considerations of interactions with the hyperbaric environment but the use of either of the drugs as indicated should be done when necessary.

CONCLUSION

The methods of treatment of an acutely ill patient in an intensive care setting have been developed over many years and well established methods for care of these patients with a variety of illnesses and system or organ failures is now possible. The use of life support equipment, a variety of drugs, invasive and non-invasive measurement techniques all have led to improved survival in the acutely ill patient. In the hyperbaric environment, when treating severe diving injuries or severely ill patients from non-diving diseases, there should be no hesitation in providing a full battery of intensive care medications, diagnostic and therapeutic procedures as needed in care of the patient. Thus, consideration should be given to proper instrumentation in the hyperbaric chamber to deal with the acutely ill patient requiring special care and a full complement of drugs designed for use in the intensive care environment should be available in the hyperbaric chamber. These drugs at least at this time, do not have major complicating problems when used in the hyperbaric environment either under increased pressure or under increased pressure with hyperbaric oxygen, however, specific details of all drugs have not been evaluated and although several have been evaluated, there is much work needed to further examine the possibility of interactions with the hyperbaric environment.

DISCUSSION

Dr. Kendig began the discussion by asking how far behind (technically) was the typical recompression facility as compared to an intensive care unit of a major hospital center? The panel agreed that in most chamber facilities the available equipment was technologically 50 years out of date. However, Dr. Bove suggested that if you did nothing else but hook up an electrocardiogram and check rhythm and rate you would have a fair amount of useful data to help during a crisis. Most of the panel felt that the principal goal of chamber therapy was:

a. To keep the diver alive;
b. Keep fluids up;
c. Get through decompression;
d. Send the diver on to an intensive care unit.

It was noted that in treating the critical care patient (septic/neurogenic shock) it would be extremely difficult to tease out the effectiveness or safety of a drug under hyperbaric conditions. Dr. Bove commented that, first of all, you don't have time; secondly, you are titrating everything so that you are continuously changing administration rates to get effects and the perception of differences in drug effect is lost in the multiple use of drugs and in the changing administration rates.

Dr. Hunt noted that vasodilators were not discussed and posed the following question: "Suppose you have a person with severe decompression sickness, hemoconcentration, and high right side pressures due to bubbles. Do you use fluids and push the pressure higher or use vasodilators?" Dr. Bove replied: "The problem is that the treatment of complicated circulatory collapse is multifaceted. There are times when in spite of the fact that the patient has a low blood pressure you want to give him peripheral arterial vasodilators because tissues are under-perfused and acidotic. Getting rid of the under-perfusion and the acidosis will improve the picture. Those decisions are complex, as you know, and I think I would not like to see that patient managed by a single physician, trained mainly in hyperbaric medicine. In the chamber, these patients require a team effort with multiple physicians with different expertise, and yes, vasodilators would be used in some instances. Especially when your monitoring suggests the patient has had enough fluid or more fluid than he needs and his fluid output is down because of cardiac insufficiency. Then you vasodilate, reduce the heart load to get better perfusion, being willing however to accept a slight reduction in blood pressure while you are getting better perfusion. The whole issue gets very complex."

A question was raised about the possibility of adverse reactions to epinephrine in the hyperbaric environment. Dr. Bove responded: "At this point we don't know for sure, but you have to give the

[illegible]

Dr. Linaweaver commented on the necessity for humidification of gases (O_2, etc., because most of them are ultra dry, and reported that symptoms from dry gas are often misdiagnosed as pulmonary O_2 toxicity. The panel unanimously recommended the humidification of O_2, especially when used in treatment tables.

Dr. Nicodemus asked if we need be concerned with the neuromuscular side effects of antibiotics especially when combined with muscle relaxants. The reply from Drs. Bove and Hardy was that these side effects would probably only occur at very high pressure. However, it would be important to know whether renal perfusion was adequate, since in kidney failure the half-life of the drug is significantly increased.

Dr. Linaweaver commented on two areas of emergency that were not covered: these are thermal injuries and electrical shock injuries other than electrocution. "These are relatively common injuries because the majority of underwater diving work is welding and burning and cutting and there have been at least two deaths as a result of electrical accidents in bells causing burns and, unfortunately, asphyxiation. I think they would have survived their burns had they not caught on fire. The usual desire to spread some petroleum substance on a burn should be contraindicated in a hyperbaric atmosphere where fire potential would be increased (i.e., as you get shallower and a higher PO_2."

There was a protracted discussion and controversy over the routine use of steroids in the treatment of decompression sickness. Dr. Linaweaver expressed his concern that because of medico-legal aspects the diving medical officer was forced to use steroids when there was no real evidence to indicate their use or efficacy. He suggested that a formal recommendation be made cautioning against the routine use of steroids in DCS therapy. Dr. Bove felt that since standard neurological literature recommends that steroids be given any time there is a suspected incidence or possibility of cerebral edema, we are stuck with this procedure. However, as the devil's advocate, Dr. Bove suggested that a pulse dose of steroids is well accepted as a relatively benign process that won't cause problems with the patient. Dr. Yorosmarti agreed with Dr. Linaweaver and commented that steroids were never meant to be used for cases of decompression sickness over 5 hours old. Steroids were originally used for air embolism cases as a prophylactic to prevent cerebral edema, not to treat edema. At this point dexamethasone is being used in many cases where it was never intended to be used, and this practice is questionable. Dr. Linaweaver cited that the rationale for using steroids is to prevent cerebral edema and the most effective medication available is HBO.

Dr. McIver asked whether steroids are useful in spinal cord [illegible]. Dr. Bove replied: "If you look at basic mechanisms, the

capillary membrane is injured in acute bubble diseases. Dr. John Hallenbeck's work suggests that the bubbles release mediators in the blood which communicate with the cell walls and make the capillaries break down. We have done permeability studies at Temple and we also find widespread changes in vascular permeability with bubble disease. We know there are permeability changes that occur throughout the vascular system in decompression sickness. The endothelium is damaged because something released in the blood is altering vascular endothelial permeability. There are several basic studies in the literature which say that when that process occurs, the administration of steroids will stabilize the endothelium and stop the process. So, if you want to go back to basic mechanisms, there is some justification for the use of steroids - to stabilize the leaking endothelium membrane and perhaps prevent further leakage or further spread of this permeability problem. How you convert that information into patient care is another problem. But if you wanted to argue that permeability changes occur and that steroids may reverse or stop these changes, you can justify their use."

The panel unanimously agreed that the area of steroids should be considered a high research priority to determine:

a. Whether steroids are effective in the treatment of DCS;
b. When they should be given;
c. How long after the insult they are indicated;
d. Comparative evaluation of different steroid preparations.

CHAPTER V

NEW DIRECTIONS FOR DRUG RESEARCH

NEW DIRECTIONS FOR RESEARCH

ON

DRUGS IN THE HYPERBARIC ENVIRONMENT

Investigation of the interaction of drugs and the hyperbaric environment has been somewhat limited. Furthermore, the studies that have been reported in the literature have focused on isolated portions of the problem, resulting in minimal information from which one can derive sound medical decisions. This chapter presumes to suggest the direction in which research efforts should be focused in the near future to produce such a data base.

The workshop panel took the position that large-scale screening of drugs under hyperbaric conditions is not a productive approach, and that research efforts should be concentrated on understanding basic mechanisms, which ultimately would clarify the requirements for treatment and the drug of choice. Some drugs, however, were specified for evaluation of their safety and efficacy of use in the hyperbaric environment.

In the attempt to define clear lines of research, the workshop panel encountered several major factors that made recommendations difficult:

1) The problem of targeting specifics because the interaction of drugs in the hyperbaric environment is a diffuse area;

2) The fact that hard data is very limited at all levels and for humans is almost nonexistent;

3) The difficulty in setting research priorities because of the very different populations requiring treatment with drugs (e.g. sport, commercial, and saturation divers; injured divers requiring emergency treatment; and persons requiring hyperbaric therapy).

The principal conclusion of the workshop panel was that, in fact, very little is known about the interaction of drugs and the hyperbaric environment; therefore, there was no sound basis for clinical recommendation until further information is available. The panel recommended that an integrated, systematic research approach be substituted for the shotgun techniques that have been used in the past. Allowing for the limited research dollars and the enormity of the issue under discussion, the panel recommended the following research areas, in order of priority, as the most logical approach to the problem.

RECOMMENDED RESEARCH AREAS

A. Basic Mechanisms

The highest priority was given to the continuance of studies aimed at a basic understanding of the mechanisms of anesthesia, the pathophysiology of nitrogen narcosis, and further investigation of oxygen toxicity, decompression sickness, and high pressure nervous syndrome.

The sentiment of the workshop panel was that once an understanding of basic mechanisms was available, classes of drugs that should interact with the pathophysiology of these hyperbaric disorders could be more readily identified, and that this approach was more scientifically sound than wholesale screening. Subsequent research would deal with the identification of pharmacological substances for the prevention of nitrogen narcosis, oxygen toxicity, and decompression sickness.

In the area of oxygen toxicity, where considerable work has been accomplished with sodium succinate and gamma-amino butyric acid (GABA), it was suggested that continued work should focus on reducing side effects that make the use of these compounds questionable. In the area of prevention of decompression sickness (e.g. SMAF, migristine, antibradykinen, and antiplatelet-aggregating substances), further support was recommended and research on prostaglandins is suggested as a principal area of new research.

B. Models of Research

Considerable discussion was given to the controversy as to whether data from isolated preparations and data from small animals had any value in determining pressure dose-response curves for humans. The workshop panel was divided about the advocacy of one model over the other, considering that single cell, isolated preparations, and small animal research have been invaluable in the evolution of understanding basic mechanisms and the prohibitive nature of human research. For evaluation of specific substances for safety and efficacy in humans, however, large animals having physiology similar to the human are deemed more appropriate. Therefore, concurrent research protocols should be encouraged at all levels (i.e., isolated preparations, small/large animals, and humans). Furthermore, it was recommended that within these various models some standardization of valid end-points be accomplished, which would facilitate integration of resulting information.

C. Evaluation of Emergency Drugs

Because the practitioner must deal with the application of drugs in the treatment of injured or sick divers and because there is no hard evidence upon which vital decisions can be made in these instances, a number of specific classes of drugs were recommended for evaluation to determine whether interactions occur in either hyperoxic

or hyperbaric environments. Those classes of drugs recommended for evaluation (in air, oxygen, and helium-oxygen) are as follows:

1. Antiarrythmics (e.g. Lidocaine, Quinidine, Propranolol)
2. Xanthine derivatives (e.g. Aminophylline)
3. Catecholamines
4. Vasodilators
5. Antibiotics (especially the Mycin family; e.g. Neomycin, Gentamicin, etc.)
6. Barbiturates
7. Steroids (e.g. Dexamethasone, Hydrocortisone)

There was considerable controversy over the use of steroids, especially in the treatment of decompression sickness. In terms of future research, the evaluation of the efficacy of steroids (e.g. dexamethasone) in the treatment of decompression sickness was considered among the highest priority items.

RESEARCH AREAS IN HYPERBARIC ANESTHESIA

In the same circumstance as the emergency physician, the hyperbaric anesthesiologist is placed in the position of working on intuition and being severely restricted in terms of the kinds of techniques he may utilize in the hyperbaric environment. Evaluation of the following research areas was delineated as being of critical importance in providing a data base for hyperbaric anesthesia:

1. Local and regional anesthetics for interaction and changes in potency
2. Intravenous anesthetics for interaction and changes in potency
3. Analgesics (esp. Endorphins) for efficacy
4. Prototypes for vagal and neuromuscular blockers
5. Diuretics
6. Beta-blockers
7. Ganglionic blockers
8. The use of nitrogen as an anesthetic
9. The potential use of gaseous anesthetics (e.g. Halothane)

PHYSIOLOGICAL/BEHAVIORAL EFFECTS OF DRUGS COMMONLY USED BY DIVERS

Another area of concern where the practitioner could use a better data base is that of the routine requests by divers for medications to relieve common everyday problems (e.g. upper respiratory congestion, motion sickness, etc.). This research area would focus on evaluating both physiological and behavioral aspects of commonly

prescribed/abused drugs. Of particular interest would be drugs producing changes in cardiovascular physiology, which would predispose the diver to hyperbaric disorders, and drugs producing changes in cognitive and neuromuscular functioning (CNS changes), which would significantly increase the risk of diving.

The workshop panel recommended the following substances for evaluation because of their acknowledged widespread use by divers:

1. Decongestants (oral and nasal)
2. Antihistamines
3. Motion sickness preparation
4. Alcohol
5. Oral contraceptives (esp. for changes in predisposition to decompression sickness)

GENERAL RECOMMENDATIONS

A need was identified for a centralized data collection base for integrating information concerning the use of drugs in the hyperbaric environment. At present there is no facility in the U.S. where reports of diving accidents from treatment centers can be sent for review by competent medical personnel. The workshop panel recommended that the Undersea Medical Society set up a committee (possibly as a subcomittee of the Medical Therapeutics Committee) to collect and review accident reports from treatment centers for efficacy of treatment and to establish a feedback mechanism for information on the therapeutic use of drugs in the hyperbaric environment.

A second recommendation along these same lines, was to publish more clinical case histories in Undersea Biomedical Research (UBR) and PRESSURE which would include detailed drug therapy.

As for answering the questions this workshop posed, relatively few concrete solutions evolved. What this panel did accomplish was to clearly define the problem, and to make specific recommendations as to how the problem might be better investigated and ultimately resolved.

ADDENDUM

ANNOTATED SUMMARY TABLES

As mentioned in Chapter 5, no drug has been proven to be reliably safe and effective in the hyperbaric environment. With the acknowledgement of this fact, the following summary tables were prepared in an attempt to provide "best guess" information based on the knowledge available.

Drugs have been categorized using the British MIMS system, and typical compounds and clinical effects are listed. Statements concerning the use of these drugs in divers are based on comments by the participants, but do not necessarily represent a consensus of the panel. Again, these comments are made with an awareness that there is limited hard data to support specific recommendations; therefore, general comments are presented with the philosophy that to err on the conservative side is a reasonable approach to this problem.

The reader will note that in many instances no comments have been listed. It is anticipated that as research in the near future progresses, these blank spaces will be filled in and all comments may become more specific.

The information in these tables is offered for the use of physicians involved in the treatment of divers. However, because of the experimental nature of the subject, we do not accept the responsibility for any decision or action based on these comments.

ALLERGIC DISORDERS

SUBCLASS	EXAMPLES	CLINICAL EFFECTS	COMMENTS
Anti-allergic drugs	Diphenhydramine hydrochlor. Clorpheniramine maleate Diphenylpyraline hydrochlor. Cyproheptadine hydrochlor. Promethazine hydrochlor. Triprolidine hydrochlor.	Block most smooth muscle responses to histamine Antagonize histamine actions of increased capillary permeability and edema Stimulant and depressant effects on CNS	All antihistaminics are CNS depressants capable of causing drowsiness. They are contraindicated when driving automobiles or operating complicated machinery and should be used most cautiously prior to diving and should be avoided by subjects who experience excessive drowsiness with them. There appears to be a need for a short-acting ,safe, antihistamine for use under pressure.

CARDIOVASCULAR SYSTEM

SUBCLASS	EXAMPLES	CLINICAL EFFECTS	COMMENTS
Cardiac Disorders	Inderal Digitalis Quinidine Procainamide Beta-adrenergic blocking agents	Supress cardiac arrhythmias Supress automomic response	Divers should not use these drugs routinely. Use in emergencies should not be limited by hyperbaric environment.
Anginal drugs and coronary vasodilators	Nitroglycerin Sodium Nitrite Amyl Nitrite	Generalized vasodilatation Decreases blood pressure	Diseases for which these drugs are used contraindicate diving.
Peripheral vasodilators	Xanthines Alpha-adrenergic blocking agents	CNS stimulation Increased cardiac output Peripheral dilatation	May result in unstable blood pressure with postural changes.
Antihypertensives	Reserpine Methyldopa Hydralazine Thiazide diuretics	Sedation Decreases blood pressure Block sodium reabsorption	Drugs which block sympathetic responses will reduce exercise capacity needed for diving.
Vasoconstrictors and Migraine treatments	Ergot alkaloids Angiotensin	Contraction of vascular/ uterine smooth muscle Hypertension Vasoconstriction	
Anticoagulants and Antithrombotics	Heparin K vitamins Fibrinolysis Plasmin activators	Neutralize thrombi Dissolve thrombi and emboli	May have a place in the therapy of Severe cases of decompression sickness.

CENTRAL NERVOUS SYSTEM

SUBCLASS	EXAMPLES	CLINICAL EFFECTS	COMMENTS
Analgesics/ Antipyretics	Non-narcotic Anti-inflamatory Aspirin Indomethacin	Anti-inflamatory Mild analgesia Fever reducing	All of these drugs may cause occult gastrointestinal bleeding and exacerbate existing peptic ulcers. All inhibit prostaglandin synthesis and hence impair platelet function and possibly hemostasis.
	Others Acetaminophen Phenacetin	Mild analgesia Fever reducing	Phenacetin may induce mild sedation and euphoria, and has renal toxicity. Aspirin and Acetaminophen have been shown to be relatively safe for use in hyperbaric conditions (Walsh and Burch, 1979).
	Narcotic Morphine Codeine Levorphanol Phenazocine Pentazocine Meperidine Propoxyphene	Analgesia Depressed respiration Sedation and narcosis Euphoria Constipation Pinpoint pupils (usually)	Narcotic analgesics are CNS depressants with the potential to impair cognition and depress respiration. They may be additive with inert gas narcosis. Pinpoint pupils may impair vision at low levels of light. It should be remembered that many non-prescription, proprietary drugs may contain small amounts of narcotic analgesics, especially cough syrups and some analgesics such as aspirin in combination with codeine or propoxyphene. Excessive use prior to diving carries the potential of dangerous interactions with the hyperbaric environment.
Antianxiety Minor Tranquilizers	Benzodiazepines: Chlordiazepoxide Diazepam Others: Meprobamate Hydroxyzine	Relieve anxiety Depress CNS (depression is dose dependent)	Generally these drugs cause drowsiness, lethargy, ataxia, and confusion. Hypotension and syncope may also occur. These adverse effects could be fatal in the water. Person who requires tranquilizers for anxiety is probably a poor candidate for diving. Short acting benzodiazepines might be considered for insomnia in a long saturation dive.
Hypnotic/ Sedatives	Barbiturates Methaqualone Chloral Hydrate	Depress CNS Induce sleep	Safe diving requires an alert, responsive individual, therefore, these drugs are generally contraindicated for divers.

CNS (CON'T)

Antipsychotic Major Tranquilizers	Phenothiazines: Chlorpromazine Promazine Butyrophenones: Haloperidol	Relieve anxiety and thought disturbances	These drugs produce significant biological changes. Side effects which would endanger a diver include: sedation, hypothermia, hypotension, reduction of seizure threshold, cardiac arrythmias, etc.
Anti-Depressants	Tricyclic Antidepressants: Amitriptyline Desipramine Monoamine-Oxidase Inhibitors: Phenylzine Tranylcypromine	Psychostimulants (CNS)-stimulants Anticholinergic	Tricyclics cause dry mouth, blurred vision, tachycardia, and cardiac arrythmias. MAO inhibitors have been shown to interact synergistically with high nitrogen pressures (Thomas & Walsh, 1978). Tricyclics have a slow onset and are unlikely to be of use even in an emergency.
CNS Stimulants and Anorexiants	Amphetamines	Increase alertness Inhibit fatigue Suppress appetite Mood elevation	Dizziness, excessive sweating, euphoria, anxiety and panic. Amphetamines have been shown to interact synergistically with increased pressures of air as shallow as 50 fsw (Walsh, 1974; Thomas, 1973).
Antiemetics	Phenothiazines Anticholinergics Sedatives Antihistamines	Relieve nausea, vomiting	For motion sickness the antihistamine group are the only acceptable drugs for divers. Dimenhydrinate and diphenhydramine have been evaluated in U.S. Navy divers and shown to be relatively safe for use (Walsh & Burch, 1979) although drowsiness may cause decreased cognitive abilities.

EAR, NOSE AND OROPHARYNX

SUBCLASS	EXAMPLES	CLINICAL EFFECTS	COMMENTS
Local reactants on the nose	Ephedrine hydrochlor. Xylometazoline	Nasal mucosal decongestion	Nasal decongestants have only mild side effects. A possible disadvantage is that with repeated applications symptomatic relief is short-acting and rebound congestion could result in reverse squeeze for the driver on surfacing.
Oropharyngeal preparations	Betadine gargle Phenol Nystatin	Germicidal Local anesthetic Bacteriostatic Fungicidal	
Aural preparations	Triamcinolone acetenide Chloramphenicol eardrops Gentamicin Neomycin Steroid/Antibiotic combinations		

EYE

SUBCLASS	EXAMPLES	CLINICAL EFFECTS	COMMENTS
Anti-infective preparations	Tetracyclines Sulphacetamide Chloramphenicol Neomycin Gentamicin	Anti-bacterial	
Anti-inflammatory and Anti-allergic preparations (steroid and non-steroid)	Betamethasone Sulphacetamide Hydrocortisone Prednisolone Dexamethasone	Sodium retention Anti-inflammatory	Steroid eye drops should not be used in saturation.
Glaucoma	Dichlorphenamide Acetazolamide Adrenaline Guanethidine Pilocarpine Phenylephrine Neostigmine		
Mydriatics and cycloplegics	Atropine sulph. Cyclopentolate hydrochlor. Homatropine hydrobromide. Hyoscine hydrobromide Phenylephrine hydrochlor.	Mydriasis Cycloplegia	
[illegible] and [illegible]	Hypromellose Phenylephrine hydrochlor. Amethocaine hydrochlor. Florescein sodium Lignocaine hydrochlor.		

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GENITO-URINARY SYSTEM

SUBCLASS	EXAMPLES	CLINICAL EFFECTS	COMMENTS
Diuretics and Antidiuretics	Clopamide Hydrochlorothiazide Frusemide (Lasix) Hydroflumethiazide Acetazolamide Triamterene	Increase sodium excretion Potassium depletion Decreased blood pressure	
Urinary Anti-infectives and Antispasmodics	Penicillins Trimethoprim Sulphonamides Gentamicin Nitrofurantoin	Anti-microbial Antiseptic	
Local and systemic drugs for vaginal and urethral conditions	Nystatin Amphotericin Sulphonamides Candicidin	Anti-bacterial Anti-fungal	
Drugs acting on the uterus	Oxytocin Ergometrine maleate Salbutamol Hyocine Butylbromide	Stimulates uterine and mammary gland smooth muscle	
Spermicidal Contraceptives	Nonoxynol-9 Benzethonium chloride Di-isobutylphenoxy-polyethoxyethanol	Spermicidal	

GI (ALIMENTARY SYSTEM)

SUBCLASS	EXAMPLES	CLINICAL EFFECTS	COMMENTS
Antacids	Maalox Gelusil Mylanta Sodium Bicarbonate	Supress peptic activity Raise pH of gastric contents	For divers, especially commercial divers, these drugs are appropriate for short-term use only.
Gastrointestinal sedatives, antacid-sedative combinations and other ulcer healing drugs	Donnatol Librax Probanthine Cimetidine	Antispasmodic Local anesthetic Decreased gastric acid secretion	Librax contains chlordiazepoxide, a tranquilizer which may cause drowsiness and ataxia. It also contains clidinium HCl, an anticholinergic agent which may produce dryness of mouth and blurring of vision. These effects could reduce the efficiency of a diver.
Laxatives, Purgatives and Lubricants	Stimulant cathartics (castor oil) Saline cathartics (Magnesium sulfate) Bulk-forming laxatives (Methylcellulose) Emollient laxatives (Mineral oil)	Increases intestinal motility Increases volume of intestinal contents Distention Lubrication	
Drugs acting locally on the colon and rectum	Anthraquinone Phenolphthalein	Large bowel stimulation	
Antidiarrheals	Lomotil Donnagel Novaflor Paregoric Laudanum	Constipating	Laudanum, Paregoric and Lomotil all contain narcotic analgesics capable of causing depression of the Central Nervous System with drowsiness and sedation. They should be used most cautiously before diving.
Pancreatic Preparations	Pancreatin Pancrelipase Vidkase	Replacement therapy for pancreatic insufficiency	Conditions requiring these drugs contraindicate diving.

HORMONES

SUBCLASS	EXAMPLES	CLINICAL EFFECTS	COMMENTS
Gonadal hormones and related synthetic compounds	Ethinylestradiol Progesterone Estradiol Mestranol	Maintain normal structure and blood vessels in women Reduce bowel motility Alter production and activity of many enzymes Alter composition of plasma lipids	
Oral Contraceptives	Estrogen/Progesterone combinations	Depression of ovarian function Breast stimulation	
Corticosteroids and related drugs	Betamethasone Prednisolone Cortisone Dexamethasone Phenylbutazone	Sodium retention Anti-inflammatory	Possibly useful in therapy of cerebral edema, severe spinal DCS and severe shock.
Trophic hormones and related drugs	Corticotrophin Tetracosactrin Chorionic gonadotrophin	Stimulates adrenocortical secretion and growth Induces ovulation	
Hyper- and Hypoglycemics	Insulins Phenformin Chlorpropamide Tolbutamide	Reduction in blood glucose	Divers should not routinely use these drugs. Conditions requiring chronic therapy with these drugs contraindicate diving.
Thyroid and Antithyroid drugs	L-thyroxin Carbimazole Potassium perchlorate		Divers should not routinely use these drugs.
Other Hormones	Oxytocin Salcatonin Parathyroid hormone Lypressin	Stimulates smooth muscles of uterus and mammary gland	

INFECTIONS AND INFESTATIONS

SUBCLASS	EXAMPLES	CLINICAL EFFECTS	COMMENTS
Antibiotics	**Tetracyclines** ***Penicillins*** **Sulphonamides** ***Cephalosporins***	Anti-bacterial action *Diverse side effects*	Antibiotics appear effective under pressure. However, increased resistance of staph. aureus has been shown (Wild, J.R., 1977, Schiamm, N.A. and Daily, O.P., 1972) and other resistance might be suspected.
Anti-tuberculous drugs	**Ethambutol** **Isoniazid** **Rifampacin**	Tuberculostatic Dryness of the mouth Epigastric distress Urinary retention	Peripheral neuropathy (parasthesias) is a common toxic effect which could be misdiagnosed as DCS. In addition, these drugs may lower threshold for O2 convulsion which is a factor to consider in DCS treatment.
Anti-fungals	**Miconazole** **Griseofulvin** **Amphotericin** **Nystatin** **Tolnaftate**	Inhibit growth of pathogenic fungi	Griseofulvin has been used operationally with commercial divers with success in prevention of chronic relapsing fungal infections of the skin.
Anti-amoebics	**Chloroquine phos.** **Metronidazole**		
Anti-malarials	**Chloroquine phos.** **Pyrimethamine** **Dapsone** **Chloroquine sulph.** **Proguanil hydrochlor.** **Hydroxychloroquine sulph.**	Chemosuppression of malaria	

INFECTIONS (CON'T)

Anti-helminics and other Anti-infestive drugs	Bephenium Piperazine hydrate Dichlorophen Thiabendazole Mebendazole	Eradicate helminic parasites in the intestinal tract or tissues	
Anti-virals	Methisazone Amantadine hydrochlor.	Inhibit viral replication	Amantadine has been used where influenza threatened a deep saturation dive with apparent success and absence of side effect at 32 ATA (McIver, NSMC).
Vaccines	Diptheria Polio (oral) Smallpox Rabies Rubella Tetanus Typhoid Typhus Yellow Fever Cholera Double Vaccines Triple Vaccines	Induce active immunity to infectious agents	In dealing with commercial divers in offshore status, polio vaccine should not be given prior to proceeding to a closed offshore community because of the risk of infection to a susceptible non-immune.

METABOLISM

SUBCLASS	EXAMPLES	CLINICAL EFFECTS	COMMENTS
Carcino-Chemotherapeutic drugs	Thioguanine Cyclophosphamide Chlorambucil Procarbazine Mercaptopurine	Cytotoxic action Nausea and vomiting Immunosuppressive action	Conditions requiring these drugs contraindicate diving.
Immuno-suppressants	Azathioprine Antilymphocyte-immunoglobulin	Cytotoxic action Bone marrow depression	
Gout	Sulphinpyrazone Probenecid Allopurinol	Increased urinary excretion of uric acid Inhibits uric acid synthesis	These drugs mask potentially complicated symptoms should they occur under pressure This condition contraindicates diving.
Drug Dependance	Citrated calcium carbimide Disulfiram (Antabuse)		Persons addicted to alcohol or drugs should not be diving.

RESPIRATORY SYSTEM

SUBCLASS	EXAMPLES	CLINICAL EFFECTS	COMMENTS
Bronchospasm relaxants	Epinephrine Isoproterenol Theophylline Aminophylline	May cause dryness of mucous membranes Causes increased heart rate Cause arrhythmia	Monitor heart rate and blood pressure during their use. Response unpredictable under pressure, may be exagerated.
Expectorants, Cough suppressants, Mucolytics and Decongestants	Actifed Dimetapp Phenergan Sudafed	May cause dryness of mucous membrane, arrhythmia, increased blood pressure	Action synergistic with nasal decongestants.

SURGICAL

SUBCLASS	EXAMPLES	CLINICAL EFFECTS	COMMENTS
Anesthetics, general and local	**Mepivicaine hydrochlor.** **Lidocaine hydrochlor.** **Enflurane** **Methoxyflurane**	Pain relief during surgical procedures All are capable of CNS action, excitement initially, followed by depression. May cause respiratory depression	When used, resuscitative equipment must be available. Special equipment required for general anesthetics, may contaminate the atmosphere. Increased dose requirement under pressure. Do not exceed recommended maximum doses for local anesthetics. When local anesthetics are combined with sedatives, greater depression may occur, especially under high N2 partial pressure.
Surgical Anti-bacterial preparations	**Povidone-iodine (betadine)** **Clorhexidine gluconate** **Hexachlorophane** **Neomycin sulph.** **Benzalkonium chloride**	Skin disinfection	n.b. Iodine sensitivity.
Mucolytic, Proteolytic and other enzymes	**Trypsin** **Chymotrypsin** **Bromela in concentrate** ***Urokinase*** **Streptokinase**		
Plasma Expanders	**Dextran** **Gelatin** **Polygeline**	Improves circulation and blood flow to organs May cause allergic response May complicate typing and cross-matching of blood.	Check hematocrit before and after it's use. Monitor blood pressure/venous pressures. Do not overload circulation.
Neuro muscular blockers	**Suxamethonium** **Curare** ***Pavulon***	Cause general muscle paralysis Causes apnea	Their use requires knowledge of artificial respiration by mask. May require tracheal intubation. May require reversal of action of choline-esterase inhibitor.

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20. ABSTRACT *(Continue on reverse side if necessary and identify by block number)*

It is interesting to note that the goals set before the workshop meeting were very completely answered by the presentations and discussions of the workshop; they were:

1. To summarize current knowledge on the effects of drugs in the hyperbaric environment, including basic and applied research, and clinical application. ...

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2. To provide clinicians with the best information available concerning use of drugs by and for diving personnel.

3. To recommend new directions for research to resolve major problem areas.

There were five major sub-divisions of the workshop report. The first one deals with the interaction of drugs and pressure covering such activities as the interaction between hyperbaric pressure and drugs on nervous tissues to behavioral effects of drugs in the hyperbaric environment.

The second section covers clinical aspects of drug treatment.

The third was a very interesting presentation dealing with anesthesia under high pressure.

The fourth covers emergency use of drugs and the

Fifth deals with new techniques of drug research.

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