AEROSPACE PROBLEMS IN PHARMACOLOGY AND TOXICOLOGY

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The recent rapid advances in aerospace technology have brought about an increasingly complex chemical environment in which man must operate effectively in the research laboratory, in the giant governmental and industrial field complex, and in the relatively new environments of space and deepest oceans. Chemists and materials engineers are spawning new chemicals and new uses for old chemicals at a rate infinitely faster than toxicologists, pharmacologists, and industrial hygiene and industrial medicine personnel can cope with the many-faceted problems presented by these compounds. The second generation of ballistic missiles and boosters, characterized by increased range and quick reaction capability, required the development of new high energy storable propellants. The Department of Defense, the National Aeronautics and Space Administration, and the Federal Aviation Agency, as well as many private and industrial concerns, have been instrumental in sponsoring a great deal of research in the areas of propellants, fuels, oxidizers, and other chemicals of use. Unfortunately, the price for increased energy content has been increased reactivity and biological activity. Consequently, propellant toxicology has become one of the major areas for Air Force research in toxicology. To understand and properly evaluate the health hazards peculiar to a certain propellant, or indeed any chemical compound, its pharmacological properties must be investigated, the pathways of metabolism, absorption, distribution, excretion, the type and magnitude of pathology established, and diagnostic and therapeutic methodology must be developed. Based on these parameters, tolerance criteria can be recommended for personnel who handle and are in contact with these compounds under any and all use conditions.

Another major area of research concerns environmental pollution that results from large scale and extended propellant and motor test operations. In this instance, other byproducts of propellant usage become increasingly important. Combustion products, motor exhausts, chemically treated wastes, and reaction products with the environment all possess potential toxicity to animal and human life, vegetation, and soil microflora. The most important

implication is pollution of community air and water around large scale industrial R & D operations. The sources for such pollution are either acute (large spills, transportation accidents, waste disposal, test firing of motors) or cumulative (venting and flare-off of propellant vapors, routine decontamination procedures, long term operations). Evaluation of the environmental pollution profile of a specific propellant operation requires both controlled experimental laboratory studies and on-site field investigations using mobile analytical laboratories.

The third most important area is the environmental toxicology of closed systems such as space cabins. Here, long-duration continuous confinement to an atmosphere contaminated by a bizarre mixture of trace contaminants is further aggravated by the exotic configuration of reduced pressure and oxygen-rich atmospheres. Since the volume is small, interaction of the environment and crew becomes critically important since both contribute their own contaminants to the total atmosphere. The reduced pressure enhances evaporation of volatile ingredients from all sorts of cabin materials and equipment. In studying this complex crew-environment interface, a drastically new approach in both experimental design and facilities has been required.

Since this is the first review article of its kind and encompasses a many-faceted problem area, it will only be possible to highlight pertinent areas of research, define some of the philosophy involved in pursuing the research areas, explain how the problems have been attacked, and at the same time bring forward pertinent data of interest to all who are handling or blessed with the responsibilities of the medical aspects involved. Almost all of the work has been performed in government laboratories or in for-profit, not-for-profit, or educational institutions under government sponsored contracts and grants. For this reason, most of the information is detailed in one-of-a-kind reports many of which are not yet published in journals. Further, meager information in many areas requires that much of the review be synoptic rather than a critical appraisal of the subject.

Toxicology of Propellants and Other Chemicals

Two major problem areas are peculiar to aerospace operations. The first is the type of exposure that is usually encountered by Air Force personnel. Contrary to the industrial type of exposure during the production of propellants, where daily low level frequent exposure occurs and industrial Threshold Limit Values (TLV) are applicable for protective purposes, most of the field operations are characterized by short duration, high level infrequent exposures that are generated by test activities or by accidental release of propellants. Under the latter circumstances, TLV's are meaningless and become extremely difficult to live with. In the past few years, much research effort has been expended in characterizing tolerance to high level, short duration exposure, and in establishing Emergency Exposure Limits (EEL) for missile operators.

The establishment of scientifically valid and safe EEL's requires extensive animal experimentation, highly specialized inhalation facilities, and the application of psychopharmacological principles in addition to the classical pharmacological and toxicological methods. The philosophy of emergency exposure is predicated on three cardinal assumptions: (*a*) nobody will be intentionally exposed to high concentrations of propellant vapors under ordinary circumstances; (*b*) if exposed, subjective and objective symtomatology may occur but pathology should be reversible; and (*c*) while discomfort and pathology are tolerable, performance of the operator must not be impaired. On the basis of animal and any human exposure data available, EEL's are recommended by either the American Conference of Governmental Industrial Hygienists or by the Committee on Toxicology, National Research Council of the National Academy of Sciences.

Hydrazine.—This propellant is generally used in combination with 1,1 dimethylhydrazine as a missile propellant. Because of its low vapor pressure, health hazards usually stem from skin or eye contact and absorption. The compound has been reviewed by Krop in 1954 (1); however, new attempts have been made to determine the mechanism of action since there is no known therapy for exposure. The compound is a strong convulsant in high doses but may be a central nervous system depressant in lower doses. Animals may die acutely of convulsions, respiratory arrest, or cardiovascular collapse within a few hours of an acute exposure by any route of administration, or may die 2 to 4 days later of liver and kidney toxicity (2–4). The great bulk of the recent work has been centered around the metabolic effects of the compound on either the CNS or the liver. Hydrazine has been known for a long time to depress the blood glucose concentration (5). This blood glucose depletion, in dogs, has been associated with depletion of glycogen stores in both liver and muscle during the first 4 hours following intravenous injection of hydrazine (6). In fasted animals, hydrazine elevates plasma free fatty acid concentration (7, 8) and increases liver total fatty acid content (9) while speeding hepatic secretion of triglycerides into the blood (10). If blood glucose is kept high by using nonfasted or carbohydrate fed rats, free fatty acid levels are not increased in the plasma of hydrazine injected animals. Amenta and associates have shown that hydrazine inhibits the formation of carbohydrate from amino acid precursors (11, 12) and also interferes with glycogen formation in the liver following glucose administration (13). Most of the work reporting accumulation of lipid in the liver and kidney following single or multiple doses of hydrazine has been done in the rat (9, 14–16). Patrick & Back (16) have shown that while the rat showed minimal fatty changes in the liver to multiple high daily doses of hydrazine, the monkey was much more susceptible and exhibited marked increase in SGOT and serum bilirubin with lipid accumulations of the liver, myocardium, kidney, and skeletal muscle. Massive liver necrosis was observed in one animal and all exhibited loss of appetite, vomiting, lethargy, and severe weakness.

Hydrazines and hydrazides have been shown to inhibit amine oxidases (17); however, little work has been reported on the effects of simple hydrazine on the metabolism of amines in intact animals. Reed and co-workers (18) showed that hydrazine strongly inhibited oxidation of putrescine-1, 4-^{14}C (1, 4-diamino butane), and methylamine-^{14}C to $^{14}CO_2$ by intact rats. Hydrazine was not found to be an *in vivo* monoamine oxidase inhibitor but appeared to have strong diamine oxidase suppressive activity. The compound also inhibited the metabolism of L-glutamic-1-^{14}C, the oxidation of large doses of L-alanine-1-^{14}C to respiratory $^{14}CO_2$ and almost complete inhibition of GABA-1-^{14}C conversion to $^{14}CO_2$. About the same time, Medina (19) showed that rats injected with hydrazine had a significant inhibition of brain glutamic acid decarboxylase and GABA-transaminase with an increase in GABA itself. A direct relationship between the metabolism of GABA in whole rat brains and the convulsive action of the hydrazines could not be shown. These studies were the basis for a group of investigations on the effects of a number of hydrazines and hydrazones upon systems involving pyridoxal phosphate and related Vitamin B_6 congeners with the idea of proving a causal relationship between cofactors of GABA transaminase and toxicity. Unfortunately, none has been found and pyridoxine or pyridoxal phosphate do not protect against hydrazine convulsions (20). Though Roberts and coworkers have found that arginine, L-glutamate, L-alanine, alpha-ketoglutarate, and oxalocetate protect against hydrazine convulsions in the mouse, there is little evidence that liver changes or other metabolic effects are reduced (21–23). The therapy for hydrazine intoxication remains to be discovered.

1,1 Dimethylhydrazine (UDMH).—This propellant has been given special attention because of its use in multiton quantities and its high volatility with a great potential for exposure due to accidental spill. The acute toxicity of UDMH is approximately the same in all species tested and by whatever route of administration (4, 24–27). The mouse, rat, dog, and monkey all show clonic-tonic convulsions and death by respiratory arrest. Intravenous injection of 1 to 50 mg/kg UDMH caused no immediate effect on carotid blood pressure, respiration, or EKG of the anesthetized dog. It did not effect the pharmacodynamic activity of acetylcholine, histamine, epinephrine, or norepinephrine, nor did it alter responses caused by faradic stimulation of the peripheral or central end of the cut vagus. Pentobarbital sleep times were not altered in mice but the onset of seizures and death in metrazol-treated mice was hastened (27).

The absorption, distribution, and excretion of UDMH were studied in rats, rabbits, cats, dogs, and monkeys by use of ^{14}C-tracer and colorimetric methods (28). UDMH was rapidly absorbed into the blood regardless of route of administration and quite rapidly excreted by the kidneys. Simultaneous tracer and colorimetric studies indicated 30 to 50 per cent of the compound was excreted unchanged in cats and dogs in 5 hours. The compound is

not preferentially concentrated in any tissue (29). Mitz and associates identified six compounds by paper chromatography in rats and dogs following injection of ^{14}C-UDMH. Three major components were present in urine. One was the glucose hydrazone of UDMH (3 to 10 per cent), 50 to 60 per cent was unreacted UDMH and 20 to 25 per cent was unidentified but suggested to be a hydrazone of higher molecular weight than acetic acid (30). In radio-respirometry studies Reed and coworkers (31, 32) found that UDMH-^{14}C methyl groups were rapidly metabolized to $^{14}CO_2$ in the rat. At low doses of UDMH, 30 per cent of the ^{14}C appeared as respiratory $^{14}CO_2$ in 10 hours and approximately 50 per cent of the activity appeared in the urine in 2 days. Like hydrazine, UDMH strongly inhibited oxidation of putrescine-1, 4-^{14}C and methylamine-^{14}C in rats; however, the metabolism of varied doses of L-glutamic acid-1-C^{14} was not inhibited by UDMH as it was by hydrazine (18).

In direct contrast to hydrazine, UDMH is not an hepatotoxic agent, and increases rather than decreases blood glucose in dogs and monkeys (16). Further, it reacts differently than does hydrazine on CNS enzymes such as GABA-transaminase, being only a weak inhibitor (19). Reeves reported that pyridoxine and pyridoxamine exhibited a protective effect in preventing seizures in UDMH intoxicated monkeys (33). Back and co-workers (34) found marked species differences in the protective efficacy of pyridoxine and pyridoxamine. Pyridoxamine was the drug of choice in the rat but the mouse, dog, and monkey were best protected by pyridoxine. In fact pyridoxamine had little effect in the monkey at doses eight times that of pyridoxine. The only manifestation of intoxication not abolished by pyridoxine in dogs and monkeys was emesis. The use of strong antiemetic agents such as prochlorperazine have not been effective even at doses causing marked depression in the dog or monkey (3). Effects of UDMH on learned behavior in the monkey indicate that doses of one-third to one-half the lethal dose do not produce marked changes in performance even though emesis may be present (35, 36). However, cats have shown CNS effects at doses well below convulsive levels. Cats with implanted brain electrodes showed UDMH capable of aborting performance when the basal forebrain inhibitory area was stimulated (37, 38). Later studies indicate that UDMH increases intracortical neural excitability and acts primarily at axodendritic synapses of somatosensory cortex pyramidal cells. Therefore, sensory-motor feedback appears important to the production of seizures (39). Other studies in the cat, using locomotor performance as a measure of CNS effects, show predictable changes in performance at doses 1/8 to 1/3 of that necessary for changes in monkey performance (40).

Methylhydrazine (MMH).—This monopropellant is used extensively as the attitude control fuel for many of our current space craft. It is about three times more toxic acutely than UDMH and also causes marked changes in liver and kidney function. The liver and kidney changes are confounding

because they appear to be species specific. MMH causes marked kidney changes in the dog, producing hematuria, and relatively few changes in the liver, while monkeys appear to have little or greatly reduced kidney involvement (41). In addition, recent experiments performed by Dr. G. D. Taylor in the laboratory of these reviewers have shown that blood glucose decreases markedly within an hour following a dose of 15 to 30 mg/kg MMH in the monkey. Glucose levels may decrease to levels as low as 20 mg per cent. This finding makes a difference therapeutically and may account for some of the differences we find with pyridoxine treatment between UDMH and MMH. Pyrodoxine alone is not sufficient to abort convulsions and death in monkeys exposed to 30 mg/kg MMH. Glucose administration is also necessary to protect against death.

We have found that MMH is not handled markedly differently from UDMH as about 40 per cent is excreted unchanged in the urine. However, the mouse, rat, and monkey excrete twice as much as the dog in the first two hours. Tissue distribution of ^{14}C showed the highest concentrations in the liver, kidney, bladder, pancreas, and blood serum (42). Some 20 to 25 per cent appears to be excreted in the respiratory gases as CO_2 and some gas has been identified as methane by use of ^{14}C-MMH (32).

Performance decrement has been found in the monkey at doses of 2.5 to 5.0 mg/kg. Decrements occur within 1 to 3 hours and animals return to baseline between 3 and 30 hours in the absence or presence of clinical symptoms such as vomiting (43). Again, as with UDMH, MMH at doses of 2 to 4 mg/kg in the cat causes performance decrement (44); convulsions were delayed or prevented in cats trained to suppress movement through use of a special EEG conditioning technique (45).

The boranes.—The first toxicity tests on borane compounds such as diborane, pentaborane, and decaborane were performed in the early 1950's by Svirbely (46), Comstock & Oberst (47), and Krackow (48). The symptoms of exposure are marked CNS depression, catatonia, muscular fasciculations, and occasional convulsions. Merritt (49) has an excellent review that covers results up to 1966. Delgado & Back (50, 51) have shown that the EEG changes seem to be localized in or near the hypothalamus. In addition Reynolds & Back (52) had shown that primate performance using trained monkeys was markedly changed for long periods of time following single doses of 2 to 4 mg/kg decaborane. Animals given single doses of 2 mg/kg spaced over a period of 4 months showed no accumulative effects since performance returned to normal in 96 to 177 hours following exposure. The reason for the decrement of performance is now obvious in light of the work of Weir and coworkers (53), and Merritt, Schultz & Wykes (54, 55) who independently found decaborane to be a potent catecholamine depressing agent. Von Euler & Lishajko have used decaborane to study catecholamine uptake in rabbit heart (56) and release rates of noradrenaline granules in splenic as opposed to adrenal medulla adrenergic neurons (57).

Of interest is another property of decaborane that we have studied quite by accident in our laboratory. One of the monkeys (the only female) used in our performance studies spontaneously lactated during exposure. We then exposed eight female monkeys and six female dogs to 4 mg/kg decaborane. All monkeys lactated in 24 to 72 hours after injection and lactation lasted from 9 to 40 days while only 2 dogs lactated. Multiple doses of decaborane were needed to get this response from a nonpregnant goat (58).

Oxidizers and other fuels.—Most of the propellant oxidizers are strong pulmonary irritants and are not systemically active. However, a few of the newer oxidizers contain fluorine. Since the subject of fluorine toxicity has great national importance and many communities are upset with regard to placing fluorine in drinking water, the Air Force must look at all aspects of the use of fluorine-containing compounds. Of interest, then, is the compound trifluoroamine oxide, NF_3O (AMOX). Lee (59) has studied the toxicological and metabolic aspects of this compound and has contributed greatly to some new aspects of the metabolism of fluorine of which we were not aware in the literature heretofore. The acute inhalation toxicity of AMOX appears to be due to severe pulmonary irritation as evidenced by edema formation and extensive pulmonary hemorrhage. The LC_{50} of AMOX for adult male rats at the end of 7 days after acute exposure for 4 hours, 60, 30, and 15 minutes was 24.2, 87 to 104, 119 to 149, and 202 to 240 ppm, respectively. The acute inhalation toxicity of AMOX was greater for mice; the LC_{50} for a 4-hour exposure being 17.5 ppm. Of marked interest was the finding that the total fluoride concentration of the thyroid increased quickly after AMOX administration and reached a peak level at the seventh day, at which time the concentration was 17 times higher than that of blood. The concentration of fluoride in the thyroid returned to the normal range of the control rats about 4 to 6 weeks after AMOX administration. As expected, both the femur and teeth of control rats contained high concentrations of total fluoride. After AMOX administration, concentrations of fluoride in femur and teeth increased and reached peak levels at about 1 to 7 days. The total fluoride disappeared gradually from the femur and teeth, and concentrations in these two tissues returned to the normal levels of the control rats about 2 weeks after administration. The majority of the administered fluoride following AMOX was excreted in the urine. An average of 61.1 per cent of the administered fluoride was excreted in 7 days, with 33.6 and 20.2 per cent of the dose excreted during the first 2 days, respectively. These rats excreted a total of 9.7 per cent of the administered fluoride in the feces in 7 days.

The interesting phenomenon of fluoride concentration in the thyroid was pursued further. Since the thyroid preferentially held increased amounts of fluoride for two weeks following administration, it was necessary to learn whether fluorine concentration physiologically affected thyroid function. Van Stee treated intact and thyroidectomized growing rats daily for 60 days

with thyroxine, potassium iodide, sodium fluoride, or AMOX. Treatment with sodium fluoride or AMOX at molar equivalent doses with respect to fluoride had no effect on thyroid function (60).

A summary of the EEL's and TLV's of most of the current propellant materials is shown in Table I (61, 62).

TABLE I

EMERGENCY EXPOSURE LIMITS (EEL) AND INDUSTRIAL THRESHOLD LIMIT VALUES (TLV) FOR PROPELLANTS

	EEL Minutes			TLV Hours
	10	30	60	8
		(ppm)		(ppm)
Oxidizers				
Chlorine trifluoride	7	3	1	0.1
Fluorine	15	10	5	0.1
Hydrogen chloride	30	20	10	5
Hydrogen fluoride	20	10	8	3
Nitrogen dioxide	30	20	10	5
Oxygen difluoride	0.5	0.2	0.1	0.05
Tellurium hexafluoride	1	0.4	0.2	0.02
Nitrogen trifluoride	—	100	50	10
Bromine pentafluoride[a]	3	1.5	0.5	0.1
Chlorine pentafluoride[a]	3	1.5	0.5	—
Perchloryl fluoride	50	20	10	3
Fuels				
Pentaborane	8	4	2	0.005
Hydrazine	30	20	10	1
1,1 Dimethylhydrazine	100	50	30	0.5
Methylhydrazine[a]	90	30	15	0.2

[a] Tentative

Halogenated fire extinguishing agents.—The toxicity of fire extinguishing agents and their pyrolysis products has been an area of concern to both civilian and military pilots for many years. In the wake of the tragic Apollo fire and subsequent altitude chamber fire at Brooks AFB, a significant amount of interest has been generated in fire suppression systems for use in closed or semi-closed systems such as an airplane. Further, recent civilian aircraft crashes have shown that lives could have been saved if fire could have been adequately handled. A review of the toxicity of a number of halogenated compounds was made by Engibous & Torkelson (63) showing that most of the candidate agents were pyrolized to compounds of, for all practical purposes, equal toxicity but that there was at least a 49-fold difference

between the undecomposed vapors of the least and most toxic compounds, i.e., carbon tetrachloride and trifluorobromomethane ($CBrF_3$).

The toxicities of the pyrolysis products of two currently used extinguishants, CH_2ClBr and $CBrF_3$, were compared for single 15 minute exposures. The LC_{50} value of 2300 ppm for pyrolized $CBrF_3$ produced a hydrogen fluoride concentration of 2480 ppm consistent with the reported LC_{50} value for a single 15 min exposure of rats to this gas. CH_2ClBr pyrolysis products were found to have a LC_{50} of 465 ppm. This response appears to be one to a mixture of hydrogen chloride, hydrogen bromide, and bromine (64). In addition to decreased toxicity, $CBrF_3$ appears to be one of the most satisfactory agents for use in oxygen-rich situations (65). $CBrF_3$ has been shown to sensitize the heart of the dog to the effects of epinephrine (Haskell Laboratories, personal communication from Dr. G. J. Stopps). Van Stee & Back have shown that exposure of dogs and monkeys to 10 to 80 per cent $CBrF_3$ causes cardiovascular and central nervous system effects which increase in severity with concentration. The compound causes a decrease in blood pressure, spontaneous cardiac arrhythmias, and possibly ventricular fibrillation. Epileptiform seizures were seen in 50 per cent of the dogs exposed to 50 to 80 per cent $CBrF_3$ while conscious. Conscious monkeys become lethargic but do not convulse (66). Recent work by Carter and co-workers (67) indicates that significant performance changes are seen in trained monkeys exposed to greater than 20 per cent concentrations of $CBrF_3$. No visible signs of CNS depression or analgesia accompanied the loss of ability to perform on conditioned performance tasks. This work is compatible with that of Dr. C. H. Hine, who studied the effects of doses of 5 to 16 per cent $CBrF_3$ in human subjects. A majority of these subjects exhibited signs of beginning inebriation or analgesia and most would have become unconscious at levels of 15 to 25 per cent if allowed to remain exposed.

Space Cabin Toxicology

Introduction.—From the inception of contemplated space flight, the Air Force has been vitally interested in research directed toward providing a safe and habitable environment in the hostile conditions of space. The idea of safely sustaining men in a closed system for long periods of time is not particularly new or unique. The United States Navy has been confronted with this problem for many years and has performed many successful missions requiring prolonged periods of submergence in the nuclear-powered submarine. Approximately 40 years of research effort have been necessary to obtain the underwater capabilities of today's submarine with regard to atmospheric control. Fortunately, the experience and data compiled on submarine habitability problems have direct application to space cabin function. One soon realizes, however, that although the problems are essentially alike in the two systems, environmental control problems in spacecraft will be greatly accentuated by both the external and internal environments of the

vehicle. Just as with the submarine, one can anticipate that short manned space missions from 1 to 30 days will present no major difficulties with regard to trace concentrations of toxic contaminants. The only major toxicity hazard for short missions would be of an acute nature only, such as a leaky refrigeration or attitude control system, an accidental spill of some noxious material, or complete failure of the air filtering system. Generally, astronauts could protect themselves from these mishaps by closed-circuit breathing of pure oxygen or, if necessary, by aborting the mission. The cardinal problems, then, would appear to be associated with greater than 30-day missions and also with missions which could not be easily aborted.

For long-term missions, then, one faces the problem of the possibility of intoxication from trace contaminants generated by various space cabin chemicals and materials. In fact, long-term space flights may require closed ecological systems for supplying a habitable environment. This may add chemical, algal, bacterial, and perhaps fungal subsystems to the craft. Since the space cabin will operate at between 5- and 14-psi pressure, the problems of boil-off from common substances such as paints, varnishes, adhesives, plastics, oils, solvents, and even metals may become enhanced. Zero-gravity conditions present problems with particulate matter, such as dusts and aerosols, which tends to agglomerate into larger aggregates and to be harmful to both man and filtering systems.

The factors that can aggravate the contaminant concentration are far more numerous than those than can alleviate the problem. The limited volume of usable atmosphere in space systems allows for very little latitude in air pollution control. Air purification and life support equipment are being heavily taxed with increasing mission profile and can, per se, change the total contaminant picture by incomplete processing of toxic materials (68). The state-of-the-art in environmental toxicology does not allow valid predictions of human tolerance to any toxic materials for prolonged continuous exposure (69). Moreover, the bizarre mixture of any contaminants always carries the threat of potentiation of toxic effect by individual constituents within the mixture (70, 71). Exotic environments such as low barometric pressure, single gas oxygen atmosphere, and the multitude of physiological and psychological stresses are still unknown quantities that can have a profound influence upon man's resistance to chemical insults. Similar to our air pollution problems on earth, freak coincidences of relatively harmless factors could lead to severe biological embarrassment. It is also obvious that the problems on nuclear submarines are far less serious than in spacecraft environment. Finally, truly uninterrupted 90-day continuous exposure to contaminant concentrations not exceeding the Threshold Limit Value has resulted in 100 per cent mortality of animals with certain chemicals (72).

Until 1964, the question of whether a man could safely live in an environment of 100 per cent oxygen at 5 psi for longer than 30 days was unanswered. It had been known for quite some time that pure oxygen by itself

was toxic when breathed for 1 to 2 days under sea level pressures. It was also surmised that oxygen toxicity might cause certain changes in the presence of other trace contaminants that were also irritants. This, in effect, would enhance the toxicity of these contaminants. Data that proved or disprove these synergistic effects have been unavailable until just recently. When toxicologists were asked to provide information regarding the toxic effects of contaminants in an oxygen-rich environment for long continuous periods of time, it was soon evident that there were no data available, and also no equipment at hand with which to gather such data. Consequently, scientists of the Toxic Hazards Division, Aerospace Medical Research Laboratories, started work in this unique field of trace contaminant toxicology.

Toxic Hazards Research Unit.—A Toxic Hazards Research Unit (73, 74, 75) has been designed, constructed, and is currently operating to study the toxic hazards of trace contaminants at reduced atmospheric pressure. This unit was designed by Dr. Anthony A. Thomas, Director of the Toxic Hazards Division, Aerospace Medical Research Laboratory. This unique inhalation exposure unit has the capacity to perform toxicological research on a large number of animals at simulated atmospheric compositions of typical space cabin conditions, that is, at reduced atmospheric pressures (5 to 14 psi) and in either single (oxygen) or mixed gas (oxygen/nitrogen) atmospheres. The primary mission of this relatively new facility is to study the effects of truly uninterrupted, prolonged continuous exposure to various trace contaminants under a single gas oxygen atmosphere. The unit is capable of performing experiments continuously for 2 weeks to more than 1 year.

The research unit consists of 8 inhalation exposure chambers (Thomas Domes). Each dome is 12 feet in diameter and 9 feet in height. Glass paneling permits unrestricted visual and photographic observation of animal or human activity in any direction. This greatly facilitates the use of trained animals for psychopharmacological evaluation. Behavioral and biological instrumentation can be placed within the domes. Forty pairs of shielded cables are available for transmission of monitoring signals. Each dome may be elevated from its base to aid in loading and unloading of equipment and animals and also to provide a quick escape mechanism in case of fi
mishap. Daily servicing is accomplished through a vertical airlock system. This allows for undisturbed exposure conditions.

All vital systems including vacuum pumps, air compressors, air conditioning, and electrical power generators are present in duplicate to act as back-up in case of failure of any individual unit. The system is a dynamic flow configuration
dome through a single diffuser pipe, and the flow proceeds to an O-ring located in the floor of the dome, is filtered, and is exhausted to the outdoors. The dynamic flow system prevents pile-up of contaminants and volatile animal excreta and is maintained at a constant five complete changes per hour.

All entries into the domes by humans are monitored by an intercommunication system which is backed up by a loudspeaker system. Three persons are necessary to operate each dome during entry for emergency purposes. In case of accidents, a person either inside or outside of the dome can "dive" the test chamber to atmospheric level, and the dome can be immediately lifted (10 seconds) for rapid escape. An automatic and manual water deluge system is available in case of fire.

One of the domes has been equipped with 12 behavioral units for use in testing performance changes of monkeys exposed to selected contaminants. Each of the 12 units consists of cages equipped with a performance panel and the necessary solid-state programming equipment, located outside of the dome, to present the animal with the proper tasks. The programmer and accessories are attached to each unit within the dome via cables and connectors which can function at altitude without leaking or presenting a fire hazard.

One of the domes has been equipped to test the inhalation toxicity of space cabin materials, using rodents as the test animals. The dome is used as an environmental envelope containing a completely closed system in which the rodents are continuously exposed to recirculating trace contaminants. The contaminants are gassed-off in ovens maintained at 154°F and in 100 per cent oxygen or in a mixed gas atmosphere, as required. The materials flow into a cage system containing the rodents and back through the ovens after being scrubbed for carbon dioxide and excess water vapor. Materials to be tested are placed in the ovens roughly in the amounts in which they will be used within a space cabin and under conditions which might be expected to give maximum surface area. Early screening is performed using groups of materials. If toxicological signs are observed, as evidenced by decrease in body weight of the animals or other gross signs of toxicity, further tests are done to determine which material or materials in the group are responsible.

To test the absolute composition of the atmospheres in the Thomas Domes, a battery of highly specialized analytical instrumentation is available. This includes a Time-of-Flight mass spectrometer and necessary accessories to sample gases, liquids, and particulates simultaneously. In addition, gas chromatographs with flame ionization, thermal conductivity, and electron capture detectors, as well as infrared spectrometers, spectrophotometers (visible and ultraviolet), and spectrofluorophotometers are available as necessary to evaluate environmental species. These instruments are also used to provide fingerprinting of gas-off products from single materials exposed to 100 per cent oxygen in a container evacuated to 5 psia, or to air under ambient conditions.

The U.S. Air Force mission is to provide both fundamental experimental data on space cabin toxicology and a quick reaction capability in the toxicological qualification of space cabin materials. A joint U.S. Air Force-Na-

tional Aeronautics and Space Administration research effort has been exploring the following fundamental and practical questions:

(*a*) Does 5 psi, single gas, oxygen atmosphere cause pulmonary irritation or functional impairment during long-term 14-day to 1-year exposure?

(*b*) Will a 5 psi, single gas, oxygen atmosphere influence tolerance to toxic materials, especially to pulmonary irritants and systemic poisons?

(*c*) Will a 5 psi, mixed gas, 70 per cent oxygen-30 per cent nitrogen atmosphere influence tolerance to toxic materials?

(*d*) Should space cabin materials be screened for toxic properties singly or in mixtures?

(*e*) Are there differences in gas-off properties of space cabin materials at 5 psi, in single versus mixed gas atmospheres?

(*f*) What are the chemical gas-off profiles of compounds exposed to single and mixed gas atmospheres for 30, 60, and 90 days?

Oxygen toxicity.—The facility has been in constant use since September 1964. During this time, one of the domes has been devoted to the problem of studying the effects of 100 per cent oxygen at 5 psia on monkeys, dogs, rats, and mice. The purpose of the tests was to explore the suitability of this atmosphere for long mission durations and to differentiate the effects of contaminants from the effects of contaminants and oxygen combined. The longest continuous exposure in space cabin toxicology research was completed on 4 December 1965. The animal complement consisted of 40 mice, 65 rats, 8 beagle dogs, and 4 rhesus monkeys and the exposure lasted 236 days. Examination of the animals by pathological and clinical observation showed that this environment was, for the most part, innocuous (76, 77). Other experiments that were run for 16 and 90 days, from which tissues were taken for electron microscopy studies, indicated that there were some changes at the cellular level which tended to revert to normal with time.

Experiments using 100 per cent oxygen at 760, 720, 700, 650, and 600 mm of mercury were performed for comparative purposes. It was found that toxicity decreased as total pO_2 decreased. In addition, the manner in which toxicity became evident changed as the altitude increased. Animals exposed at 760 mm Hg pressure succumbed to the environment within a 3-day period and died from pulmonary edema and hemorrhage; those exposed to 700 or less mm Hg pressure showed marked decrease in mortality and evidence of pulmonary fibrotic change rather than primary hemorrhagic changes (78).

Psychopharmacological testing, using 12 trained monkeys at 5 psia, 100 per cent oxygen for 90 days, showed no decrement of performance to either continuous or discrete avoidance tasks (79). The foregoing studies clearly indicate the feasibility of applying 5 psi oxygen atmospheres for at least 90-day mission durations in orbital systems.

Effects of 5 psi, 100 per cent oxygen upon toxicity.—Studies were performed for 14-day periods using either ozone, nitrogen dioxide, or carbon

tetrachloride as the toxic contaminant (80) (Table II).

TABLE II

CONTAMINANT TOXICITY AT 5 PSI, 100% OXYGEN

Continuous Exposure			Cumulative Mortality			
Duration	Concentration	Compound	Mice	Rats	Dogs	Monkeys
90 day	100%	Oxygen	3/40	9/40	0/4	0/4
14 day	630.00 mg/m³	CCl_4+O_2	39/40	0/50	0/8	0/4
	80.00 mg/m³	CCl_4+O_2	0/40	7/50	0/8	0/4
	100%	Control O_2	0/40	8/40	0/2	0/2
14 day	84.6 mg/m³	NO_2+O_2	40/40	37/50	7/8	4/4
	38.00 mg/m³	NO_2+O_2	5/40	0/50	0/8	2/4
	17.00 mg/m³	NO_2+O_2	0/40	0/50	0/8	0/4
	100%	Control O_2	0/40	0/40	0/4	0/4
14 day	14.7 mg/m³	O^3+O_2	—	—	6/8	0/4
	7/8 mg/m³	O^3+O_2	33/40	45/50	2/8	0/4
	3.92 mg/m³	O^3+O_2	0/40	0/50	1/8	0/4
	1.96 mg/m³	O^3+O_2	0/40	0/50	0/8	0/4
	100%	Control O_2	3/20	2/20	0/4	0/4

Comparative results indicate a number of interesting and important bits of data. It is quite evident that there are species differences to various concentrations of these compounds. That is, the dog is more susceptible to the pulmonary irritant effects of ozone than is the monkey and the reverse appears true for NO_2. All animals exposed to 2 mg/m³ ozone survived under 5 psi 100 per cent oxygen conditions. The Threshold Limit Value (TLV) for an 8-hour day for man is 0.2 mg/m³ ozone. The TLV for NO_2 is 9 mg/m³ and 65 mg/m³ for CCl_4. The pulmonary irritants are less toxic at 5 psi, 100 per cent oxygen than in ambient air. Further, 70 per cent O_2–30 per cent N_2 at 5 psi appears to be less effective than 100 per cent oxygen. In contrast, the systemic poison, CCl_4, did show slightly more toxicity at altitude than on the ground. This may be explained by early reversible liver changes seen during 2-week exposure to oxygen (81) and increased susceptibility of liver to CCl_4 under these conditions.

Further experiments such as these and others designed to study the long-term effects of pulmonary irritants and increased oxygen pressure plus altitude on lung and other tissues are necessary. The morphometric evaluation of lung tissue as well as electron microscopic findings together with cellular and subcellular metabolic function are steps in the right direction for the total study of mechanisms of toxicity (82–89).

Other comments.—Work studying the long-term effects of exposure to trace contaminants under different conditions of altitude and oxygen ten-

sions have really just begun. It has recently been shown that combinations of oxygen pressure and reduced total pressure affects the red blood cell osmotic fragility of rats (90); however, other parameters of physiologic function on a long-term basis have yet to be studied, and the vast area of the effects of drugs under the conditions of space have hardly been touched (91–96).

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