Drugs in aerospace medicine

Primary variables of aerospace are altitude, radiation, motion, thermal extremes, and weightlessness. With respect to drug studies, only the first four have been explored directly. Secondary variables include the general nonspecific stress of the aerospace situation and operational performance considerations. These have been studied with respect to pharmacologic questions. Finally, another variety of compounds has been tested under one or more aerospace variables. Therapeutic and prophylactic usefulness for conditions unrelated to environmental stress have made this broad group of drugs available for inclusion in this review.

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Pharmacodynamics has been the least area of consideration in aerospace medicine's concern with pharmacology. The toxicology of pharmaceutic compounds and therapeutic usage have been the areas of primary attention. This has often been the case on the assumption that drug action would not be altered when the drug and its object were in an altered environment. To attest to the fact of this oversight, there are innumerable studies about the effects of drugs on complex performance tasks such as those required of an astronaut during a mission, but seldom have these studies considered environmentally induced alterations in the subject or drug. These could very likely interact and cause an "unexpected" drug action.

Problems encountered in evaluation of drug action on man are well known. They have been aptly summarized to show the extreme complexity of factors to be considered.[64] Add to this the other complex variables which exist in any aerospace venture, and the problem becomes almost hopelessly compounded. Little wonder, then, that the potential value of drugs in aerospace situations is still of secondary interest. It has been more fruitful and predictable to deal with manipulations of immediate external environmental conditions.

Even so, considerations of pharmacologic interest have been present in aviation and space medicine, practically from their very inception. In 1923, pilots' intolerance to orthostatic stress was noted to be affected by prior ingestion of chocolate but not by coffee.[82] In 1924, Bauer[6] cited and rejected De Brichambaut's suggestion that Adrenalin, pilocarpine, or amyl nitrite might be used therapeutically in pilots developing "unreasonable fear." There was also early interest in the possibility of pharmacodynamic alterations. The effect of digitalis on

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cats and pigeons was found to be enhanced by altitude.[53] On the basis of this study, the recommendation was made that digitalis dosage should be reduced from one fourth to two fifths of the sea-level dose on progressing to 3.3 Km. (10,000 feet). Later, the fact that aerospace conditions could affect pharmacodynamics became dramatically apparent as new drugs and new aircraft were developed. Thus in 1939 reference was made to correspondence in British literature which appeared as early as 1937 that certain drugs could interfere with the normal oxygen-carrying capacity of blood.[27] In operational considerations it was flatly said that sulfanilamide reduced the flyer's eupoxic ceiling by 1.7 Km. (5,000 feet). In commercial and military flights of relatively short duration it has been safer to rule against the use of any drug by aircrew.[22] In wartime, and under some stressful peacetime operations, use of drugs has been sanctioned for economic considerations but not without occasional untoward results.

During a recent crisis a 38-year-old reconnaissance aircraft commander was admitted to the psychiatric section of a military hospital. He was taking 1,800 mg. chlorpromazine which required augmentation with occasional 75 mg. intramuscular doses to control his agitation. The referring flight surgeon described the onset of illness as an abrupt, severely acute reaction but the possibility of a drug-induced process was not mentioned, probably not considered. There were paranoid, schizoid, and manic elements to the patient's illness which were severe but which cleared completely over the course of six weeks. Reconstruction of the onset was then possible. Situational stress factors had been maximal, typical of combat situations. The patient's premorbid personality had been cyclothymic. To help him maintain alertness and maximum efficiency during his missions, the patient's flight surgeon had prescribed phenmetrazine without allowing the usual observation period prior to flying which is prescribed under "normal" conditions.

It is possible that various environmental elements associated with the nature of the pilot's flying missions may have contributed to this "unexpected" drug action. Similar reactions implicating phenmetrazine have been reported when aerospace environment conditions were absent. This does not obviate the possibility of transient hypoxia or local anoxemia in either situation, and it may be that such a factor alters the pharmacodynamics of phenmetrazine to produce an "unexpected" reaction. The possibility is remote but it is the nature of the problem of drug actions in aerospace situations. Now, on the eve of extended-duration space flights, renewed interest is developing in possible drug uses from very practical considerations. In earlier days scurvy was a primary hazard of extended sea voyages which was resolved by the simple expedient of taking along citrus fruit. Drugs may likewise obviate hazards of extended space missions. At the very least it will be necessary for the space traveler to have some drugs for use in emergency. It is also necessary that these drugs should act in such an environment at least as predictably as they do on earth.

Environmentally induced pharmacodynamic alterations

Thermolability of compounds such as ascorbic acid presents the simplest example of an environmentally induced alteration in drug action. A clear-cut constant relationship obtains between drug and one variable. But when a physiologically active system is interposed between a drug and an environmental factor, direct relationships become obscured. The physiologic system, constantly interacting with drug and environment, presents not just another variable but a multiplicity of them. Hays[45] gives a particularly cogent framework for considering such questions to avoid the danger of undue simplification. Venturi[98] made a formidably extensive review which illustrates such gross simplification. He used the pharmacologic concept of antagonism-synergism in comparing hypoxia to various

drugs. And he evolved the generalization that hypoxia is synergistic with respect to actions of antimalarials, sulfonamides, antihistamines, and hemopoietics while antagonizing the action of diuretics.

A much more sophisticated and useful approach was used by Margolis and associates.[63] They observed the effect of hypoxia on known antagonism between various pairs of drugs. This report is one of two reviewed which illustrate a general pharmacologic principle with respect to an altered environmental condition. Their results indicate that classic drug antagonism for several pairs of drugs is obviated under conditions of lowered oxygen tension. In some cases, the noxious effect of a drug seems to be potentiated by its otherwise usual antagonist. Drug pairs were tested on mice and included: Nembutal-pentylenetetrazol, histamine-diphenhydramine, atropine-physostigmine, Nembutal-amphetamine, Nembutal-succinate, morphine-amphetamine, morphine-pentylenetetrazol, morphine-caffeine, atropine-strychnine, caffeine-Neo-Synephrine.

The other studies pertaining to this section of the review have been aimed toward elucidating specific drug environment relationships. Carpenter and Nedzel[13] found that an increase in atmospheric pressure increased the toxicity of morphine for mice. They attributed this to increased capillary permeability and found they could conversely reduce toxicity by administration of levarterenol. Nedzel[67] subsequently used reduced atmospheric pressure in a similar experiment. Morphine toxicity was reduced in this setting, particularly when eupoxic conditions prevailed, but also even in the presence of hypoxia.

The specific question of environmental alteration on drug action was more critical in earlier days of the air age. In this respect, strychnine toxicity was found to be increased by altitude more for some species than for others.[65] Variables of altitude as well as of temperature were found to be related to the action of dinitrophenol in several species.[90] Drug-treated animals showed increased vulnerability to hypoxia while drug toxicity was markedly reduced by administration of 100 per cent oxygen. The action of dinitrophenol was blocked by ambient temperatures of 2 to 6° C. This was not related to drug absorption and the inhibiting effect was attributed to cold ablation of nervous-reflex activity.

Interference with acetylation of sulfonamides during their detoxification offered a ready explanation for increased toxicity of such compounds at altitude.[27] However, Crema[21] showed that hypoxia did not influence acetylation of the drug when tested in guinea pigs. Similarly, another parameter which relates to drug action, concentration in the blood, was directly explored for quinacrine and chloroquine.[16] Acidosis and "anoxia" were exclusively induced in dogs to measure the influence each condition had on drug concentration in plasma as opposed to tissue levels. Respiratory acidosis to a degree of blood pH 6.9 increased drug concentration twofold in plasma without affecting tissue levels. An alteration of the tissue-plasma partitioning membrane by the acidotic state was hypothesized to explain these results. "Anoxia" itself as an isolated variable did not have this effect on drug concentration. Thus in hypoxic states the concentration of drug is variably related to and is an expression of acidosis secondary to the hypoxia and not to reduced oxygen concentration itself. Jailer, the author of the foregoing ingenious study, then derived the general principle for considering alterations of drug action by hypoxia, namely, if concentration of a given drug depends on metabolic processes in a given species, hypoxia *will* exert an effect on drug concentration.

Loehning and co-workers[55] devised a well-controlled study based on the fact of almost universal coca addiction among Andean natives. Using rats and purified cocaine, they found direct relationships between different doses and different altitudes on the animals' ability to gain weight. In this experimental situation, cocaine inhibited weight gain to a greater degree

than inhibition observed as a function of altitude alone. However, extrapolation from rats and cocaine to humans and coca leaf is a big step. Even if a controlled study could show comparable results in humans, it could still be that the habit has survival value by the very fact that weight gain is inhibited. The degree of spontaneous motor activity in mice is inversely related to ambient altitude.[88] Meprobamate and chlorpromazine similarly affect such motor activity. When drug and altitude were combined, even further diminution in spontaneous motor activity was observed.

Drugs and effects of altitude

In its broadest sense altitude is the primary variable of aerospace conditions. Specific altitudes produce secondary variables, such as thermal extremes, radiation, and weightlessness. To achieve altitude, motion is necessary, which is in itself another secondary variable. It is necessary to isolate these to approach an orderly study of their effects. As long as such arbitrary delineation is firmly defined, the danger of unwarranted generalizations may be minimized. Thus effects of drugs on complex task performance must be studied under altitude variables before conclusions can be applied to operational performance predictions. Conversely, to find that a drug is an effective prophylactic for motion sickness in passengers has little value except for passengers if it may interfere with optimum performance of crew members.[50, 86, 89]

The closed ecologic system has displaced drugs from a central role in prophylaxis for the extremes of altitude stress. Drug studies under variables of altitude still have secondary importance. This applies not only to elucidation of drug action, but to elucidation of physiologic and pathophysiologic mechanisms which would otherwise remain obscure,[45, 81] and there may still be areas of primary importance for drugs as summarized by Pogrund.[73] The concept of necessity for a "back-up" system to subserve primary systems in the event of failure must also be considered. Thus a drug which would allow even momentary protection from effects of rapid decompression could, in so doing, allow for correction of a malfunction.

Hypoxia. The many relationships between hypoxia and drugs have received more attention than those concerned with other altitude variables. Perhaps this has to do with the fact that oxygen deprivation itself may also be viewed as an induced chemical modification. Since this has to do with metabolism, dietary factors become involved and must be considered as variables to be controlled in drug studies. Relationships between vitamin factors and hypoxia tolerance have been identified,[14] and similar relationships exist between basic foodstuff and hypoxia tolerance.[26] Interestingly, a free-choice diet is second only to a high-carbohydrate diet in affording maximum possible dietary protection against hypoxia.

Earliest considerations for pharmacologic agents to protect against hypoxia were quite logically the convulsive, respiratory stimulants. Twelve such agents* were tested on mice in conditions of acute, severe hypoxia.[29] Full subconvulsive doses of apomorphine, camphortetrazol, potassium cyanide, and strychnine were most effective in reducing the LD_{50} of the acute experimental exposure to reduced oxygen. Whereas such a dose of coriamyrtin was ineffective, this agent proved effective in lower doses while pentylenetetrazol also showed some effectiveness in lower doses. Methylene blue was tested in human subjects at altitude to show increased oxygen saturation of blood and increased performance proficiency.[9] Procaine and diethylaminoethanol offered no protection in rats at 5.0 Km.[15] But in the same experiment para-aminobenzoic acid showed definite protective properties. More specifically, ortho- and meta-isomers were compared, the protective action of the compound was related to the position of the amine radical.

*Apomorphine, caffeine, camphor, camphortetrazol, cocaine, coriamyrtin, coramine, epinephrine, pentylenetetrazol, picrotoxin, potassium cyanide, and strychnine.

Diuretic agents have been tested because of their shifting of the oxyhemoglobin dissociation curve. Premedication with ammonium chloride in human subjects (30 Gm. over two days) produced increases in arterial oxygen saturation and arterial pO_2. Protective effects persisted for two to three days following ingestion of the drug.[5] Cain and Dunn[12] presented a comprehensive review of experiments based on this principle as an introduction to their recent study of acetazolamide in dogs. Using minimal doses in an attempt to isolate renal from erythrocyte component effects, they found ". . . a real gain in arterial and most probably tissue pO_2 levels . . . ."

The relationship of a drug to hypoxia has been considered secondarily for other compounds, since the potential aerospace usefulness of any drug is limited by this factor. In the wake of reported usefulness in German pilots,[24, 41, 51] this question was explored regarding amphetamine prior to World War II. Several parameters of critical human function were considered in this series of investigations using amphetamine in eupoxic and hypoxic states. It did not affect respiratory or psychomotor functions in hypoxia although there was sustained elevation of systolic blood pressure, and the fall in blood pressure which might occur with severe hypoxia was obviated. More recently, Hauty, Payne, and Bauer[43] studied relationships between dextroamphetamine and hypoxia in fatigued human subjects. Although the validity of their conclusions is compromised by the extremely complex experimental design, they found that dextroamphetamine did not prevent the work decrement attributed to hypoxia and fatigue. Significant improvement was related to restoration of a eupoxic state.

Positive and negative aspects of antihistamine medication will be discussed in another section. Effects of several such agents on respiratory response in hypoxia were studied in dogs.[10] None of them interfered with the normal response.

Dysbarism. Abrupt reduction in atmospheric pressure presents a hazard of aerospace and undersea operations. The manifestations of its effects on biologic systems are extremely varied and there are individual factors in susceptibility. Depending upon the site of difficulty, pain is almost invariably present. Analgesic agents to relieve pain while physiologic adjustment takes place have been examined for usefulness.[87] Agents which increase peripheral blood flow have been tested on the assumption that this will also increase the rate of gaseous nitrogen excretion.[99] Neither class of drug proved to be effective in preventing dysbarism for human subjects decompressed to an altitude of 12 Km. Experiments on rabbits indicate promising usefulness for an analeptic through effectively increasing pulmonary ventilation without increasing respiratory rate.[4*] Bradykinin given to mice resulted in an exaggeration of dysbaric effects providing a rationale for the preventive use of antagonists to this compound.[18] These "anti-inflammatory" agents provided varying degrees of protection.† Endogenous bradykinin may well be implicated in the pathophysiology of this syndrome. And this may explain the very great individual variations in susceptibility to decompression. Thiourea was given to mice prior to abrupt decompression; they were much less able to withstand the effects of decompression.[37]

The expansion of intestinal gases during decompression is a special, relatively mild manifestation of dysbarism. Freedman and Mulligan[35] administered methyl polysiloxane to a large number of volunteers and found that it does not reduce the incidence of "gas pain." Under more severe conditions of decompression, however, methyl siloxane reduced the decompression mortality of rats.[56] The protective effect of this compound was explained on the basis of its ability to lower the resistance to flow of gas emboli.

*Diethylamide-N-crotonil-ethyl amine-butyric acid and diethylamide-N-crotonil-propylamine butyric acid.

†Amidopyrine, 1-(N-methyl-piperidyl-4)-3-phenyl-4-benzyl-pyrazolone-5, and 2-(4 phenyl-1-piperazyl)-cyclohexanone hydrochloride.

Drugs and effects of motion

Motion as an important element of the aerospace environment is the least unique to that setting. For experimental purposes this variable may be studied separately under nonflight conditions more easily than others. Certainly other altitude factors can influence reactions in adaptations to motion, but fortunately it still stands as the one factor that can be most readily isolated from the rest. Two aspects of motion are particularly important in aerospace: (a) force as well as direction of acceleration on man's capacity for effectively withstanding its effects; and (b) random, arrhythmic properties of motion which may produce the familiar acute "motion sickness."

Acceleration tolerance. Schmidt[81] has stated that drugs cannot impart resistances de novo. They may only enhance or diminish such qualities in biologic systems in which some capacity for such alteration is already present. In man, widely varying individual capacities exist for tolerance to acceleration. Maximum capacities in some individuals are incredibly high, so it may be assumed that such tolerance could be produced in the less tolerant. This would be of importance in combat situations in which sudden and maximal accelerations are necessary. Greiner[12] has discussed other studies and historical aspects underlying the rationale of using drugs for increasing acceleration tolerance. He selected metaraminol as most nearly possessing ideal qualities for such an agent i.e., chiefly vasoconstrictive but venoconstrictive as well, effective orally, persisting for 2 hours following administration, should not increase cardiac automaticity, and should not induce central nervous system effects in doses producing the desired vascular effects. Metaraminol was tested in human volunteers as a sole agent and in combination with pressure suits. Though effective, it was less effective than pressure suits alone, while combined use was not significantly better than the suit alone.

Animal experiments have shown varying degrees of promise in other drugs. The results of two such studies on rats indicate greatest promise in 2-dimethyl-aminoethyl-p-chlorophenoxyacetate.[74, 83] Polis[74] inferred that this drug facilitates hypothalamic mechanisms for maintaining cerebral circulation. He presented evidence to indicate an indirect rather than direct action of the drug on this elusive center. Schock[83] compared this drug to acetylcholine and other related compounds for effectiveness in increasing acceleration tolerance.* In contrast to Greiner's concept that acceleration tolerance is primarily dependent on cardiovascular mechanisms, Schock relates it to functions of general adaptation mechanisms. Epinephrine and norepinephrine were shown to have positive effects on tolerance when tested in rabbits.[80]

Motion sickness. This topic has received pharmacologic attention second only to hypoxia. However, the importance of controlling motion sickness in aircrew members is almost negligible since only insusceptible individuals remain long as crew members. Drugs may be used to help the flight student "over the hump." However, there is indication for controlling motion sickness in commercial air passengers and even more in combat troops being airlifted. Adverse effects of anti–motion sickness medications are inconsequential for passengers during flight but extremely hazardous for crew members who must maintain optimum wakefulness and proficiency. Whether motion sickness will present a major problem in space operations remains to be seen; some think it may.[73]

The number of drugs which have been used in attempts to prevent motion sickness is greater than for any other categories discussed in this review. Robbins[76] has written a comprehensive review of these drugs and their pharmacologic properties. Belladonna alkaloids and barbiturates were among the first classes of compounds to be studied.[54,

*Dimethylaminoethanol, the parent compound, compared favorably. Sodium p-chlorophenoxyacetate, sodium dichlorophenoxyacetate, acetylcholine chloride, tripelennamine, and promethazine hydrochloride showed no significant effect. Metamphetamine reduced acceleration tolerance.

[60, 102] With the advent of dimenhydrinate (Dramamine), there were initial, highly optimistic reports of usefulness.[86, 89] But these studies were severely criticized by Tyler[95] who pointed to his earlier experience with hyoscine. He felt he had shown equal if not greater usefulness for hyoscine. The test of time seems to have borne him out. In a recent comprehensive review, Wood, Kennedy, and Graybiel[102] stated that hyoscine was the most effective anti-motion sickness drug. On the other hand, its over-all usefulness is limited by its side effects.

From his study on Navy aviation cadets, Lilienthal[54] concluded that the major action of hyoscine was directed more against physiologic than psychologic factors in motion sickness. Actions of antihistaminic compounds have been only partially identified. The propensity of the group to produce drowsiness typified by diphenhydramine (Benadryl), has been attributed to the $-CH_2-CH_2-N\langle^{CH_3}_{CH_3}$ radical which is also present in dimenhydrinate, the anti-motion sickness prototype. Simon[86] points to a need for additional proof that anti-motion sickness action is not one of sedation in this group of compounds.

An additional problem in motion sickness is that of treatment after vomiting has begun. Chinn, Hyde, and Milch[17] used hyoscine intranasal spray with good results. Not only did this route deal with the problem of administration despite the emesis, but it also proved to be more effective than oral or sublingual routes as a preventive measure.

Cramer and Dowd[20] have reported a more ambitious approach to studying effects of drugs on motion sickness than those presented thus far. Cyclizine (Marezine) was administered to decerebrate and decerebellate cats. Observations were then made on drug modification of responses when the receptive nerve or single vestibular cells were electrically stimulated. Since no differences were noted between treated and untreated animals, the authors concluded that the site of action for cyclizine could not be in the receptor portion of labyrinthine functions. The most recent efforts to provide protection against motion sickness are those in Malvin's[61] studies which have not yet been concluded. His approach eliminates the problems of side reactions by using agents which are endogenous in man. His preliminary report indicates great promise for the combined use of methionine and pyridoxine as prophylactic premedication to rough flight.

Drugs and effects of other aerospace hazards

Radiation. Pogrund[73] has thoroughly discussed pharmacologic approaches to radiation protection. He categorized these compounds according to mechanisms of action as follows:

1. Lowering tissue oxygen tension, e.g., malononitrile, Pitressin, epinephrine.
2. Enhancing the recuperative power of the hemopoietic system, e.g., sulfhydryl compounds.
3. Other ancillary actions exemplified by a variety of miscellaneous compounds, e.g., chlorpromazine, thiouracil, corticosteroids, etc.

Oxygen toxicity. Inhibition of physiologic enzyme systems by high oxygen tensions is a dramatic example of a limiting factor to be considered in the use of drugs when oxygen toxicity is a potential hazard. Mullinax and Beischer[66] have reviewed this problem. The authors also stress that there is wide interspecies and intraspecies variability of susceptibility to the effects of high oxygen tensions. It has already been mentioned that such differences comprise a particularly fertile soil in which to cultivate drug studies. For instance, Kann and associates[49] have recently reported on the protective action of vitamin E on mice exposed to high oxygen tensions for periods of three hours against hemolytic anemia and convulsions while in vitro erythrocyte lytic sensitivity to hydrogen peroxide and ultraviolet light was found to be diminished.

Thermal extremes. Vitamin E has also been shown to have protective properties against extremes of ambient temperatures.[100] It also has protective properties in other situations, e.g., hyperoxia, hypoxia, and radiation exposure. In all of these oxidation processes are enhanced and the antioxidant qualities of vitamin E suggest that this may be its mode of protective action.

One of the deleterious effects of hyperthermia in rats is increase in cardiac output which ouabain has proved effective in controlling.[70] Under conditions of microwave-induced hyperthermia, this action of ouabain represents a reversal since, in the normothermic animal, ouabain induces an increase in cardiac output.

Alterations of visual efficiency. In common with altitude factors, certain drugs induce alterations of visual efficiency.[32, 50, 75] For this reason, the usefulness of hyoscine in preventing motion sickness is said to be severely limited.[50] In this study, Keil found significant reductions in visual acuity in half of his hyoscine-treated subjects. Dark adaptation is a process of singular interest in which the combined use of vitamins A and E has led to improvement[32] although used alone, neither substance has such a beneficial action.

Reductions in orthostatic tolerance. Cardiovascular reactivity of man in aerospace must be maximally maintained. Altitude conditions themselves are well known to be specifically hazardous. The sedentary nature of the pilot's work compounds the problem. Many factors such as this will bear upon man's ability to thrive in the weightless state. A particularly useful illustration of the role of drugs in this area is the study reported by Ganslen and collaborators.[36] Effects upon orthostatic tolerance in altitude situations will be another parameter of great importance in future drug studies.

Drugs and the complex stress of aerospace operations

In the previous sections some specific aspects of stress peculiar to aerospace operations have been discussed even though none of these acts alone at any one time. When man's efforts in aerospace are viewed as the over-all complex interaction which it is, drug actions may also be related in a nonspecific way. Although artificial, it is useful to think in terms of two broad categories of man's general functions, psychologic and physiologic. Yet there are problems such as fatigue which defy attempts at breakdown between emotional and physiologic factors. Also, a particular kind of skill is required of the pilot who must maintain homeostasis under drastic environmental changes. Psychomotor functions thus provide another delineated area in which to study man's adjustment to aerospace and the effect of drugs on his so doing.

Physiologic aspects. Obvious relationships between oxygen availability and general metabolism were considered quite early in studies of aerospace applied physiology. One study based on altitude acclimatization as affected by cocaine and expressed in body weight changes has already been mentioned.[53] The role of thyroid activity was one of the earliest to be entertained.[37, 98] Goldsmith, Gordon, and Chariapper[39] extended the usefulness of looking to thyroid functions by considering gonadal interactions as well. They discredited exogenous estrogens as being of any importance.

Instances of concern with nutritional factors other than those which have already been mentioned were found in the following reports: A study involving chronic altitude exposure known to produce polycythemia in rats showed that vitamin A supplementation inhibited this response.[19] Other investigators have singled out thiamin among the group of B vitamins as having particular importance in the general resistance of rats to diminished atmospheric pressures.[14] A thiamin-deficient state provided for greater resistance than deficiencies of niacin, pyridoxine, and pantothenic acid. When the same thiamin-deficient animals were provided excess quantities of the vitamin, tolerance to reduced pressures was clearly diminished.

Selye's concepts of general adaptation to stress have found application in studies of man's adaptation to multiple stresses of aerospace. Pharmacologic and physiologic principles blend to become indistinguishable from one another. Thorn and his associates[93] reported one of the earliest studies in which altitude tolerance varied according to adrenocortical hormone therapy. These investigators developed a method for standardizing LD_{50} determinations in rats subjected to acute altitude exposure. Using preparations which were then available, they found that therapy with adrenal cortical extract in oil "greatly increased" survival rate. This was not the case for desoxycorticosterone acetate, 17-hydroxycorticosterone, sodium succinate, or the control, bland sesame oil injection.

In 1957 McGuire[57] considered the question of corticoids on stress tolerance in an extensive review with aerospace connotations. His primary concern was with the evidence he collected to show that exogenous corticoids suppress physiologic activity of the adrenal cortex. McGuire's review is recommended for further specific references on this very complex aspect of drugs in aerospace. Of other studies on this question two recent ones deserve some comment. Berry and Smythe[7] reversed the usual process by administering cortisone to mice already accommodated to altitude conditions. Mobilization of carbohydrate was pointedly less in altitude-exposed, fasted animals than in sea-level controls. This study was based on the fact that such altitude exposure increases susceptibility to arsenite poisoning which was felt to be due to greater lability of carbohydrate reserves in that situation.

The second study by DeBias and Paschkis[23] who studied hormonal factors in relation to administration of various neuropharmacologic agents* provides a bridge on which to proceed toward emotional aspects of aerospace stress tolerance. They used rats exposed to reduced barometric pressure. All animals were adrenalectomized, one group remained untreated, another received steroid supplement alone (intramuscular cortisol sodium succinate), a third group received the test neuropharmacologic agent alone, and the final group was given both cortisol and test agent. Another set of experiments using the same design, was conducted on animals which had had thyroidectomy as well as adrenalectomy. From this complex but well-controlled design, none of the test agents emerged as capable of protecting the adrenalectomized animal from the stress of reduced barometric pressure. Supplementary cortisol in the dose used was also ineffective in adrenalectomized animals, but did protect those animals that also had thyroidectomy. A point of significance from this study was that, in other similar experiments, the agents tested had shown protective capabilities when heat, cold, or formalin injections had been used as stressor agents. The authors suggested that adaptation to stress of reduced barometric pressure is subserved by different mechanisms than those underlying adaptation to other types of stress.

Psychologic factors. The rapid developments in psychopharmacology indicate that some "catching up" on the dynamics of these compounds is needed,[96] but because the safety factor is of particular importance in aerospace research, use of such drugs in this area has been limited. These safety factors are subordinated to mission requirements in time of war. Thus, since World War II, studies on psychic stimulants are nearly as numerous as those on hypoxia and on motion sickness. Graf[40] devoted an entire chapter to this topic in the USAF Surgeon General's published study of German aviation medicine. Many compounds were specifically cited including amphetamines, phenylmethylamines, xanthines, pentylenetetrazol, vitamins, cola, and cocoa. Graf succinctly summarized conclusions from his review as follows: "There is not a single drug which can bring the human

*Dibenzyl-β-chlorethylamine hydrochloride, azamethonium bromide, chlorpromazine, oxyphenonium bromide, and dextroamphetamine sulfate.

organism to that level which it reaches by normal training, proper nutrition, and adequate sleep, i.e., a life in a physiological balance between professional strain and recreation." Other reviews on the general topic of enhancing human performance capabilities have led to similar conclusions.[72, 91]

There are two studies on stimulants which have attempted to deal with the problem of extrapolating from experimental to operational conditions. Using amphetamine, dextroamphetamine, desoxyephedrine, caffeine, and caffeine-amphetamine to study the effects of performance under altitude conditions Adler[1] used symptomatology to indicate degree of adaptation to altitude. In general, drug-treated subjects had fewer symptoms at altitude than placebo subjects, but individual variations, especially in "placebo effect" and frequency of untoward effects, were striking. In addition to complex performance, parameters of adaptation expressed in flicker fusion frequency tolerance, auditory acuity range, pulmonary vital capacity, and pulse rate were also included in the foregoing study. These showed no clear-cut drug influence under altitude or control situations.

McKenzie and Elliott[59] simulated the fatiguing demands of tactical air missions to explore the feasibility or usefulness of amphetamine and secobarbital (Seconal) as adjuvants to greater pilot effectiveness. The complexity of adaptational variables is best illustrated in the operational background considerations which led to this study. For in addition to fatiguing effects of monotony, movement restriction, altitude, and long hours, the use of secobarbital indicates concern with man's "physiologic clock" as an important though poorly understood variable. "Placebo effects" were again individually noted while performance enhancement by dextroamphetamine was also again substantiated. Administration of secobarbital as a hypnotic for preflight sleep was found to have deleterious effects on performance between 10 and 22 hours following ingestion, and the usual response to dextroamphetamine during the twelve-hour simulated mission was found to be delayed in subjects who had been given secobarbital for preflight sleep. Since the subjects used in this study did not have body fat determinations, it is difficult to rule out continued, subhypnotic action of the drug throughout the period of time in which they were tested.[84]

Amphetamine compounds have proven usefulness in counteracting certain effects of fatigue, but the unpredictability of their action in individual cases has severely limited this general usefulness. Other compounds have been tested in attempts to obviate the hazards of amphetamine medication. Pregnenolone methyl ether was given to crew members immediately following completion of a prolonged mission.[85] Subjective responses reported in questionaires showed that this drug had no beneficial effect on negative affective states following arduous work in flight. A more optimistic note was found in the Italian literature wherein adenosine triphosphate and co-carboxylase were simultaneously used for treatment of "operational fatigue."[78] The author treated twenty jet aircraft pilots who complained of early or mild fatigue. He found dramatic improvement following repeated use of these compounds. Unfortunately, no placebo controls were used and it is possible that improvement was a reflection of the increased, concerned attention received from the flight surgeon in the study.

Other studies have examined the potential usefulness of the newer tranquilizer drugs.[11, 25, 30, 58] There is uniform agreement that all such drugs should not be used by aircrews. McGuire and Leary[58] studied meprobamate (Miltown) and promazine (Sparine) for effects on stress tolerance in man. Five different stress situations were used, subjects serving as their own controls. Diminished tolerance to stress was clearly shown from the use of both drugs, more from promazine than meprobamate.

The stress of reduced barometric pressure itself was used in assessing possible efficacy

for reserpine.[30] Rats were exposed to chronic altitude conditions and treated with reserpine. This drug was chosen because of its action in "blocking neurocirculatory effects of the hypothalamus on the hypophysis with respect to ACTH and gonadotrophic hormone." Reserpine itself was found to have stressor effects similar to those of the chronic altitude situation. Animals given the drug and exposed to the stress as well showed an exaggerated acclimatization response. Rather than protect against the stress of altitude or enhance the ability of the rats to adapt, reserpine acted as an added stress factor.

Thus far, then, tranquilizing agents have not been useful in aerospace conditions although several authors still point to potential future usefulness.[51, 73, 81] In a simulated space mission study which prompted hallucinatory and illusory phenomena similar to the examples cited by Pogrund[73] phenomena also similar to those reported by subjects taking LSD were found. The amenability of LSD intoxication to treatment with chlorpromazine is well known. It is possible that there is indication for use of chlorpromazine in prolonged situations of isolation and sensory deprivation.

Pharmacotherapy of aircrews

The health and welfare of flying personnel is an item of major importance in both military and commercial aviation. The clinician is hard pressed to provide treatment to such personnel for the innumerable, relatively minor illnesses which he so readily treats with drugs in the general population. A short-lived condition usually poses no problem. If a drug is indicated, there are adequate provisions for allowing such treatment while the patient is restricted from flying. There could be situations, however, which would tax manpower availability and much effort has been spent in exploring the aerospace hazard potential of effective therapeutic agents. Use of antibiotics in the early stages of general or localized infectious processes serves as a ready illustration. Because many such drugs have been used or considered for use in this way, there should be some "fallout" information regarding the pharmacodynamics of these compounds in aerospace situations. Drug therapy of aircrews has been the object of several reviews, notably those of Oberst and Ely,[68] Cutting,[22] Evrard,[31] and a symposium by Ashe[3] which was followed by several specific discussions.[8, 11, 44, 91] The most striking hazard of drugs is reduction of the oxygen-carrying capacity of the blood. This has been discussed in the section on hypoxia but these reviews emphasize this point for some compounds not yet mentioned, such as the common coal tar analgesics.

The ubiquity of allergic disorders applies to flying personnel and poses a particular problem of treatment.[44] Treatment of allergy raises the issue of parenteral desensitization, and careful guidelines for this sort of treatment have been developed for the occasional necessities of aircrews. Even when individuals may be grounded for treatment which is incompatible with flying safety, effects of withdrawal from drug prior to resuming flying must also be considered. This situation has been specifically illustrated in the case of chlordiazepoxide.[25]

Few studies are being conducted on the actions of ordinarily useful drugs in aerospace environment. Rigid policies restricting use of drugs by the flyer have, perhaps, diminished the concern necessary for exploring this question, and it is certainly safter to ground the temporarily ill flyer if replacement is available. However, such studies must be continued. There is a dearth of literature on action of the broad-spectrum antibiotics, which may be extremely useful to the combatant flyer if they pose no hazard in his special environmental situation.

The chemoprophylaxis of malaria provides the most cogent vignette of concern for and study of drug action on aircrews. It virtually grew out of World War II experience, so that in 1949 Chinn, Ferber, and Flickinger[16] reported on the toxicity of chloroquine, chlorguanide, pentaquine, and

quinine in human volunteers exposed to altitude conditions. Laboratory determinations showed a 10 per cent decrease in oxyhemoglobin and hematocrit levels for subjects taking pentaquine and quinine combinations. Clinically, this was reflected in a marked diminution in time of useful consciousness as a test for hypoxia tolerance. Jailer's[46] study on quinacrine and chloroquine blood concentrations as a reflection of acidosis has already been mentioned. Despite these definitive studies, there is continued interest in the malaria problem. Wittmer[101] explored other parameters, such as psychomotor performance at altitude, for chloroquine-primaquine combinations which are negligibly toxic in aerospace. Recent discoveries of chloroquine-resistant Plasmodium strains makes studies on other compounds essential.

Methodology for drugs in aerospace

The usefulness of information on drug action derived from most of the studies reviewed here is limited. For the most part, the limitation is an expression of lack in methodology.

Pletcher[71] has discussed human factors which may be implicated in aerospace accidents. Unfortunately drugs have been more often implicated in pathology than in successes of aerospace ventures, but from such pathology something is to be learned about drug action and areas of drug usefulness. The pathologist conducting an accident investigation is particularly concerned with developing methods for the detection of drugs in biologic specimens.[34] Malvin's[61] current study is directed toward developing techniques for detecting methionine concentrations in salivary secretions.

The Louis H. Bauer lecture which is given annually before the convention of the Aerospace Medical Association was devoted to pharmacology in 1961. In this talk, Schmidt[81] traced the historical development toward "space pharmacology," emphasizing that the important contributions have been in methodologic developments. In an article to which extensive reference has already been made, Pogrund points to a new area which will pose problems of methodology. He anticipates potential usefulness for diuretics and smooth muscle stimulants in situations of prolonged weightlessness. Kline and Clynes[51] have gone to the ultimate extreme in proposing abandonment of the closed ecologic system. Drugs have a central role in their proposed development of "cyborgs" ("self-regulating man-machine systems"). Methodologic considerations of the use of drugs in such systems are key issues.

Of the studies which have been cited here, the following represent major contributions in methodology: Chryssanthou's[18] use of identifying bradykinin as a factor in dysbarism, then testing effects of antagonists on incidence of this disorder; Cramer and Dowd's[20] attempts to isolate the locus for action of anti–motion sickness compounds; Crema's[21] study of known drug alterations during metabolism as affected by altitude conditions; Malvin's[61] unique use of virtually atoxic compounds to combat motion sickness with attempts at correlating effectiveness to drug concentrations; and Margolis'[63] previously cited ingenious approach.

There are other methodologic approaches which should be useful to future investigators. Taylor, Hunter, and Johnson[92] have applied learned observation to develop a measurable physiologic index of motion-sickness vulnerability. Margaria[62] has developed methods for measuring five parameters of neurophysiologic function which are sensitive to stress such as that induced by hypoxia. He has tested for the effects of various neurotropic drugs with these sensitive methods, which have opened a wide area of applicability for aerospace pharmacology. To date these remain untapped. Pearson[69] deduced that motion sickness and spatial orientation sensitivity may have underlying physiologic factors in common. It would then be important to know that use of drugs for motion sickness would not at the same time cause spatial disorientation. He found that none of the

drugs which he tested had deleterious effects on this function.* This study serves as an excellent example of the sort of methodologic reasoning which must take place in considering drugs for use in aerospace.

Specific regard for methodology was the basis of two presentations of note. Rosenstein[77] recognized the problem of using fatality rate in animal studies designed to measure hypoxia tolerance, but such an end point has limited practicality in extrapolation. He then developed a test of endurance based on various levels of reduced atmospheric pressure which still permitted animals to live. The effects of sodium salicylate on the endurance of rats in this system were measured to reaffirm known effects of this drug on oxygen metabolism. The methodologic system proved its sensitivity for adequate statistical compilations. Jovy, Bruner, and Klein[47] designed a system for specifically testing drug effects on psychomotor performance. They obviated much of the extraneous complexity which has beset other methods that have been used for studying this important parameter.

A sampling of abstracted reports from Russian literature is included at this point for comparison with the foregoing on points of primary emphasis.[2, 33, 38, 48, 79, 94] There seems to be little variation in concern for drugs to protect against environmental hazards. Effects of drugs on hypoxia and acceleration tolerance have been investigated, but unlike studies in this review, increased attention is being given to biologic compounds such as serotonin, heparin, glutamic acid, and ascorbic acid. It also follows on the Pavlovian tradition that "conditioning," akin to our less restricted concept of adaptation, plays a greater role in Russian considerations. In one study, the protective effect of dibazol against hyperthermia was compared to and combined with "training adaptation" in exposure to heat. This study suggested that such "adaptive training" had positive cross-over effects between exposure to heat and to hypoxia.[2] This is somewhat opposed to the conclusion of DeBias and Paschkis[28] that separate mechanisms underlie adaptation to stresses of heat as opposed to reduced barometric pressure.

*Dextroamphetamine sulfate, meclizine, cyclizine, promethazine, and a scopolamine-diphenhydramine combination.

Conclusion

Many far-flung, extremely varied considerations enter aerospace medicine and make it apparent that much like military medicine in World Wars I and II, it has ushered in a force for speculation of substantial proportions.[98] This force makes it imperative that every bit of related knowledge be considered by those who would pursue research. This applies particularly to aerospace pharmacology.

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