PHARMACOLOGY IN SPACE MEDICINE[1,2]

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This review will deal with the possible use of pharmacological knowledge to maximize the capabilities of and to minimize the hazards to human subjects in sustained space flights. The place of drugs in manned space flight must now be carefully considered, because a number of physical and physiological consequences of space flight appear unlikely to be resolved by engineering methods alone. For other severe stresses, a partial solution provided by biomedical means should significantly reduce the mass or complexity of the life-support system required by man.

The fundamental problem is how to use known pharmacodynamic patterns to counteract functional aberrations which are produced in normal, physically fit young men by a set of interacting environmental abnormalities of unprecedented type and scope. The ideal medication is one which will completely prevent functional abnormalities; an acceptable compromise is amelioration of the abnormalities, so as to keep them within the range of physiological compensations that will permit successful accomplishment of the mission. All medication, whether it actually improves the functional status of the astronaut or merely modifies his reaction to abnormalities that are not otherwise affected, must be selected with due regard for the traditional *primo non nocere;* i.e., the drug must not, in itself, create aberrations that might bring about other penalties on the astronaut's performance.

Solution of this problem calls for fairly precise information concerning: (*a*) the functional abnormalities to be counteracted; (*b*) the drugs with the appropriate pharmacodynamic properties; and (*c*) the possibilities of doing harm with these under the peculiar conditions of space flight.

The challenge is essentially one of devising and conducting tests in which the value of drugs against foreseeable problems or emergencies can be tested in appropriate simulations and of doing this while it is still possible to include the selected agents in the training program for Gemini, MOL, and Apollo astronauts which is already well under way. The available simulations are scattered in respect to both location and administration, and systematic studies of drugs in various aspects of the space situation have not yet

[1] The survey of literature pertaining to this review was concluded in September, 1964.

[2] The followng abbreviations will be used: AET (2-aminoethylisothiuronium); g (gravity); $+g_x$ (positive transverse acceleration); $+g_z$ (positive acceleration); LD_{50} (lethal dose, median) MOL (manned orbital laboratory); PAPA (*p*-aminopropiophenone); Po_2 (oxygen pressure); and psi (lb/in^2).

been undertaken in any of them. It is no simple matter to decide on the pattern and content of a research program in any one simulation; and the problem of integrating the activities of different groups, so as to secure a serviceable approximation to the total space situation, will be a formidable one.

It is our hope that the following pages may be useful in formulating specific problems for investigation and in delineating the types of studies that appear to be urgently indicated.

Preflight Preparations

The early-preparatory stage includes experiences with simulations of various parts of the space situation. This is the time to carry out preflight tests of the astronaut's reactions to the drugs that have been potentially selected for his medicine chest. The purpose is not only to uncover the presence of unsuspected idiosyncrasies but also to provide information on effective dosages, latent periods, durations of action, and undesirable side effects under these unusual circumstances.

Throughout the entire preflight period, but particularly in its closing stages, drugs may be considered to supplement other measures designed to minimize the possibility of infectious diseases during the flight. Full use of immunological procedures is desirable. Decontamination of the spacecraft and its nonliving contents is now easily accomplished, even to the killing of spores, by exposure to high concentrations of ethylene oxide vapor (2). The astronaut will be encased in a sterilizable space suit when he lands on the moon or foreign planet. Thus, it should be possible to prevent contamination of the planet with earthly microorganisms and to preserve the heuristic value of the subsequent examinations of soil specimens for the presence of life elsewhere than on the earth. The astronaut, himself, however, presents a more difficult problem since he cannot be made germ-free by any measures presently available or in prospect. Nevertheless, it may be desirable to modify the character of his microbial population before he starts a voyage that will confine him, together with one, two, or more colleagues, in the weightless state in a closed ecological system for a period of a month or more. Of particular importance is eradication of potentially pathogenic organisms.

One obvious place to begin the process of partial decontamination is the skin, which could be freed of potentially dangerous bacteria and fungi by means of appropriate antibiotic and other medication shortly before the final countdown. The cocci and spirochetes of the normal nose, mouth, pharynx, and paranasal sinuses might be the source of trouble during the flight, and drugs capable of controlling these organisms deserve serious consideration, for use both before and during the flight. The gastrointestinal tract of a normal man may contain, in addition to the harmless organisms that make up the bulk of the stool, micrococci, bacteria of the salmonella group, and even protozoan parasites. Here, the possibility of the development of a frankly pathological state under the peculiar circumstances of a long space journey calls for consideration of prophylactic therapy by strepto-

mycin, tetracyclines, and succinylsulfathiazole. The probability of overgrowth of yeasts and of bacteria such as *Clostridium welchii* and micrococci following such therapy (3) must enter into this decision. Perhaps drugs aimed at combating the associated intestinal distention will have to be provided.

The possibility of infections due to viruses developing during the space journey is a special cause for concern because there are, at present, no very effective agents to prevent or combat such infections. Recent reports of success with amantadine against influenza (4) and *n*-methylisatin-β-thiosemicarbazone against smallpox (5) justify the hope that effective systemic antiviral chemotherapy may soon become feasible (5).

During the final stages of the preparation for orbital flight, each astronaut of the Mercury Program was kept in seclusion and shielded from exposure to infectious diseases, as far as possible without rigid quarantine which was deemed inadvisable (1). He was placed on a low-residue diet that made defecation unnecessary during the flight, and about 4 hr before the take-off he began to breathe the gas (100 percent oxygen) that he was to inhale throughout the flight. These procedures were adequate for flights up to 1 day, but will certainly be modified in future flights. It is scarcely likely that defecation can be dispensed with entirely for 2 wk or more in a space vehicle; however, it should be possible to limit the volume of intestinal wastes. Nor is it at all certain that the inhaled gas will be 100 percent oxygen at 5 psi (about 250 mm Hg) as it was during the Mercury flights. This selection had the following advantages: (*a*) it afforded the lowest possible intracapsular pressure, which minimized both the thickness (weight) of the capsular wall and the magnitude of the outboard leak of gas; (*b*) it removed the necessity for monitoring and controlling anything but the total pressure of the intracapsular gas; (*c*) it provided denitrogenation, which would be a great advantage in case of accidental, explosive decompression of the capsule at high altitude or in space (6); and (*d*) it made possible a reasonably safe compromise between the pulmonary toxicity of excessive Po_2 (7, 8, 9) and maximum protection against incapacitating hypoxia in the event of a leak or other failure of the environmental control system (10–13).

Objections to pure oxygen have included: (*a*) fire hazard, which has already been experienced in at least one attempted simulation of the space situation (14) and was found, on analysis, to be due in large measure to the absence of inert gas molecules (15, 16, 17); and (*b*) the occurrence of aggravation of the atelectasis inevitably associated with the transverse acceleration of take-off and re-entry (18); this will be considered in greater detail in the next section.

At present, it appears that no one gas mixture can be expected to satisfy all requirements of the forthcoming space flights, and a planned sequencing of gaseous environments may ultimately be employed (19). The Russians used the equivalent of air at 1 atm as the breathing medium in their orbital flights (20); but, in flights of many weeks duration, this selection has more drawbacks than advantages. Mixtures of helium and oxygen lead to diffi-

culties in communication by reason of changes in the voice (21). Diluent gases other than nitrogen and helium may be physiologically active or explosive. Finally, and regardless of the gas mixture selected, the progressive accumulation of toxic atmospheric contaminants in a nearly closed system should present a considerable problem (22). Further discussion of this topic, which now is under intensive study (23), will not be attempted here.

Blast-off and Acceleration to Orbiting or Escape Velocity

When the space vehicle is launched, the first stress an astronaut will encounter is due to the accelerative forces of the take-off. These may be expected to bring about an approximately tenfold increase in effective weight of all parts of the astronaut's body. The untoward physiological effects on the man are minimized by carefully positioning him so that the acceleration is directed from chest to back [positive transverse acceleration, or $+g_x$ (24, 25)]. Further protection is provided by a suitable semiformed couch, which supports the man in the proper position during acceleration and deceleration (24, 26). In due time, the development of engines capable of more sustained thrust will make it possible to reduce the stresses of blast-off. At present, and especially for the circumstances of escape from earth's gravitational field, the situation is marginal; i.e., the flight pattern must be such as to bring the acceleration very close to the limits of the man's tolerance without serious, prolonged functional impairment.

The mechanical measures mentioned above obviate the cerebral ischemia that would occur at much lower degrees of acceleration in the head-to-foot axis (positive acceleration, $+g_z$). However, when the transverse acceleration exceeds about $+5gz$ and is continued for more than about 30 sec, the arterial oxygen saturation begins to fall (18, 26–29). At the same time, pain in the chest, difficulty in breathing, and coughing are likely to occur. These effects coincide with redistribution of blood in the thorax so as to cause relative underperfusion of the anterior and overperfusion of the posterior parts of the lungs; at the same time, alveolar gas is displaced and atelectasis occurs in the posterior areas (24, 27). The associated pain is attributed to distortion of intrathoracic viscera; posterior displacement of the heart can be very marked in dogs (28), but correspondingly severe changes do not occur in man. The cough (in comparable exposures to $+g_x$ on the centrifuge) may sometimes be productive of bloody fluid (30, 31), indicating pulmonary edema or traumatic rupture of pulmonary vessels, or both. A rise in pulmonary artery pressure, large enough to cause pulmonary edema, occurs during $+g_x$ in the dog (28); the probability of forcing secretions from above down into the finer respiratory passages also exists, regardless of the direction of the accelerative force. That mechanical obstruction of these passages probably is involved during air or oxygen breathing is indicated by the failure of forced ventilation of the lungs to bring about prompt recovery of arterial oxygen

saturation in dogs exposed to $+5\ g_x$ and $+10\ g_x$ on the centrifuge (28). Each of these ventilatory effects should be more pronounced when pure oxygen is breathed during acceleration than during air breathing.

The dangers in this situation arise not only from trauma but also from the distracting influences of dyspnea, pain and cough, the functional deteriorations produced by anoxemia, and the decrements in performance to be expected from the combination of all these effects. The patterns of drug actions that might be helpful are those aimed at minimizing fluid in the respiratory tract and at preventing alveolar atelectasis. Avoidance of upper-respiratory infection prior to take-off is clearly indicated, and use of antimicrobial drugs to reduce the hazard of infection during the subsequent space flight deserves consideration.

Other possible means for minimizing the fluid content of the respiratory tract would be: (*a*) drugs which could combat the rise in pressure in the pulmonary circulation during transverse acceleration and thus reduce the tendency toward pulmonary hemorrhage or edema; and (*b*) drugs which depress the secretions of glands of the respiratory tract. For (*a*), a nonpressor sympathomimetic agent (e.g., isoproterenol) has been suggested (28); the ethoxy congener of methoxamine has a selective dilator action on the pulmonary circulation of the dog, but it has been disappointing when tested in man (32). Perhaps it would work better in acute pulmonary hypertension in normal young men whose pulmonary vessels have not undergone irreversible changes. These types of intervention, aimed at minimizing pulmonary vascular pressures during $+g_x$, remain to be tested in animals, and their desirability in man is at present highly conjectural. For (*b*), long-action parasympatholytic drugs are probably precluded because of unavoidable visual, cardiac, vascular, gastrointestinal, and thermoregulatory side effects.

Analgesics, antitussives, or both, might aid in combating the dyspnea, pain and cough associated with transverse G, if administered appropriately in advance. However, these symptoms are evidence that the G force involved is producing damage, and masking of the symptoms is a less rational solution than prevention. If the problem of cough, alone, remains unsolved, the necessity for utmost alertness on the part of the astronaut and the practical certainty that a narcotic antitussive, if successful, would have only an adverse influence on the concomitant anoxemia, require better nondepressant antitussives than are presently available (33).

The occurrence of anoxemia at a critical phase of a flight, which involves a series of decisions and specialized tasks, obviously is undesirable. This question is related to the choice of gas for the space capsule, which was considered in the prelaunch phase (page 385). It is worth reemphasizing that, at this phase of flight, the inhalation of a nitrogen-free atmosphere distinctly delays the return of normal arterial oxygen saturation after termination of the acceleration (18), a result attributable to aggravation of atelectasis in the

absence of inert gas (18, 34). Perhaps the temporary use of a nitrogen-oxygen mixture just before and during the stage of maximum acceleration would improve matters significantly. This remains to be tested on the centrifuge.

Clearly, there are objections to the obvious procedure of raising the Po_2 of the gas in the space capsule to combat the anoxemia of transverse acceleration, when the only gas is oxygen. Pressurized breathing of pure oxygen by the astronaut may be useful during blast-off, but the information presently available is insufficient to decide whether the gain is worth the price of discomfort, mechanical complexity, and added hazard of oxygen toxicity. The most likely benefit can be expected from the previously mentioned, transient administration of an appropriate oxygen-nitrogen mixture of high Po_2 during actual acceleration (19). The adverse influences of helium upon voice communication would be especially objectionable at this critical stage (21).

Orbit and Escape Trajectory

Once the vehicle has left the earth's atmosphere to enter earth orbit (Gemini and MOL), circum-lunar orbit (Apollo), or the earth-moon escape trajectory of a still-more-advanced flight, and the astronaut has recovered from the initial *g* stresses, he faces a protracted period of exposure to isolation and confinement, greatly restricted mobility, unusual patterns of work and exercise, peculiar arrangements for ingestion of food and liquid and for disposal of wastes, and the probability of disrupted circadian rhythms. Additional abnormalities of extrinsic origin include the gravity-free state, unusual gaseous environments, fluctuating temperatures in the vehicle and pressure suit, the constant noise of gas-circulating motors, toxic radiations of heterogeneous types and uncertain intensities, and the progressive accumulation of weightless debris. Further problems arise from the likelihood of motion sickness (due to rotation of the vehicle) and the, albeit unlikely, danger of sudden decompression by reason of structural flaw in the spacecraft or collision with a foreign object. In the face of these and other interacting conditions (19, 36, 37), pharmacological agents may ultimately provide the means to accomplish an otherwise-impractical mission.

In the first two manned Mercury orbital missions, each of which lasted a little less than 5 hr, there seem to have been no indications for any form of medication during the weightless state or immediately after the flight (1). Detailed information is not now available concerning the use of drugs in the three-day earth-orbital flights performed by the Soviet Union. However, in the final two Mercury missions (which lasted 9 and 34 hr, respectively) and in Soviet flights Vostok 5 and 6 (lasting 119 and 71 hr, respectively), each of the astronauts, after returning to earth at the close of the flight, manifested signs of postural hypotension, which was demonstrated by actual measurements of blood pressure (1, 20). The orthostatic changes may have persisted after the longer flights for at least two days (20).

If decompensation of circulatory reflexes occurs during prolonged ex-

posure to weightlessness, leading to postural hypotension on deceleration and persisting after return to the normal gravitational state, this may present one of the most formidable physiological problems of a space flight which extends beyond one or two days. This possibility has been repeatedly proposed (36, 38–42) and subjected to study under conditions of prolonged immersion and horizontal bed rest, not only to simulate aspects of the weightless state (39, 40, 41) but also to study the effects of immobilization upon disease states (43).

Orthostatic hypotension in a normal young man points to inactivation of the normal baroceptor reflex mechanism as one possible basis for circulatory decompensation. In the normal, land-bound environment, this mechanism responds many hundreds of times daily to the transient lowering of intravascular pressure in the carotid sinuses and aortic arch associated with assuming the erect position. The resulting increases in efferent sympathoadrenal discharges lead to vasoconstriction and increased cardiac activity, which sustain blood pressure in the face of hydrostatic forces produced by the centripetal gravitational influence. Much is known of the mechanisms of fainting at 1 *g* (44). In the weightless state, hydrostatic forces should not exist and changes of position should no longer lead to hydrostatically induced c
mersion of the subject in water or saline, in which case the hydrostatic pressure of fluid outside the vessels proportionately compensates for positional alterations of hydrostatic pressure within them. Decreased reactivity of baroreceptor reflex mechanisms is only one of the several mechanisms which may conceivably contribute to orthostatic hypotension following prolonged orbital flight. Severe fluid loss and decrease in blood volume may have resulted from the excessive sweating required to maintain body temperature within the space capsule; increased urinary output and other causes, including those related to the possible existence of blood volume control by receptors in the right atria (45, 46), may have further decreased blood volume (47).

If postural hypotension following exposure to weightlessness is, in fact, due to an accommodation to excessive activation of the inhibitory afferent baroreflex mechanisms and consequent inadequate exercise of the sympathetic nervous system, some form of substitution for the physiological effects of periodic standing at 1 *g* must be provided. This may be mechanical (42) or pharmacological. The practicality of a direct pharmacological substitute for gravity in this reflex system deserves special consideration in this review. Transient daily or other periodic vasodilatation by as simple an oral agent as nitroglycerine or one like isoproterenol should provide, in the weightless state, a fall in blood pressure offering the means of nonmechanical simulation of the baroreflex consequences of erect posture in a gravitational field of almost any desired intensity (45). It should be expected that even intracranial vessels would tend to be dilated by each of the agents cited, and this

would occur to a greater degree than in the normal state. Should an additional mechanism include loss of extracellular fluid volume and blood volume by way of atrial stretch or baroreflex influences upon adrenal cortical activity (48), pharmacological baroreceptor manipulation may have to be supplemented by direct administration of aldosterone to prevent the loss of sodium.

Vestibular dysfunction, disorientation, and motion sickness were anticipated from the start of the manned space flight program. However, the gravity-free state, according to the Mercury astronauts, gives rise only to pleasant sensations (1), and the present tendency is to denigrate its physiological importance (1, 49, 50, 51), but the situation in longer flights may well be different. This is particularly true if weight requirements necessitate only sparing use of gas to combat rotation of the vehicle, as probably will be the case. Thus, in any but navigational, sighting, rendezvous, or other specific maneuvers requiring precise orientation of the craft, a continuous, random slow tumbling may be the normal state. The likelihood of motion sickness upon rapid head movement under such conditions is greatly increased (25, 52). Again, the early use of drugs may offer a solution requiring far less mass than the fuel which would be required to prevent slow tumbling. The choice of drug and dose, here, will depend partly on the pattern of action desired (e.g., tranquilization or not) and partly upon actual tests of the drugs on each man for both desirable and undesirable effects.

Muscular deterioration has also been considered a likely consequence of prolonged exposure to the weightless state (39, 40, 41, 45). This prediction is based upon observations that restricted motor activity, as in paralysis, immobilization in plaster casts (43, 53), and prolonged bed rest (40, 43, 45), leads to decreased skeletal muscle tone, strength, and size. While muscle wasting can occur with disuse alone, it may prove to be further exaggerated by long-continued weightlessness. In the weightless state, mass and inertial forces will still remain, but no clear picture now exists of the degree to which weightlessness will modify the tone of postural or reciprocally innervated muscles. If a gross decline in muscle power does prove to occur in the weightless state, it is not now clear how fast this defect will develop, to what degree it can be expected to proceed, and whether the deterioration will be selective (54). There are indications that frequent feeding prevents the breakdown of body tissue in experimental subjects exposed to prolonged bed rest (40) and that brief periods of physical exercise prevent the decline of exercise tolerance in such subjects (40). It is unlikely that any reasonable system of drug administration will maintain skeletal muscle tone, but carefully designed and systematized patterns of tonic exercise appear to be desirable (55). Failure to sustain the strength of the skeletal musculature is not expected to handicap the weightless astronaut in flight, unless deterioration proceeds to an extreme degree. However, even minor deterioration will present a serious problem in the strenuous deceleration of reentry. This will be severe on return

from earth orbit and still more so on deceleration from the much higher velocities of a lunar-earth trajectory.

A decrease in strength of bone, such as the osteoporosis and the spontaneous fractures seen in elderly patients (56), has been considered as a hazard of sustained inactivity and weightlessness in space flight (39, 40, 41, 45). Normal subjects exposed to inactivity and prolonged bed rest for periods as long as 42 days do indeed show an increased calcium excretion beginning almost immediately and continuing for 2 to 3 wk after remobilizatoin (40, 43). While calcium loss from bones undoubtedly does occur in prolonged inactivity, the magnitude of this loss probably represents only about 1 percent of the skeletal mass (45). This degree of loss, if uniformly distributed, should cause no alarm either from the standpoint of bone failure in re-entry deceleration or of formation of renal calculi in the normal kidney (57). However, osteoclastic activity results in resorption not only of calcium apatite but also of the organic matrix of bone as well (58); and it is not clear whether the resorption and bony weakening occur primarily at discrete local sites of diminished mechanical stress, or whether systemic factors related to inactivity lead to a generalized resorption of bone (45). Administration of calcium can be expected to minimize removal of calcium from bone, but this will occur at the risk of nephrolithiasis. There is, as yet, no reason to believe that fluoride, deposited as calcium fluoroapatite, will interfere with bone resorption (59); sodium fluoride is toxic, high doses are required to produce a positive calcium balance, and no clear indication of protection has been seen in clinical osteoporosis (59). At present, it seems reasonable to conclude that decalcification will not be an important problem in weightless flights of only 1 to 2 wk duration. These flights will provide the in-flight laboratory experiments needed to determine whether problems of bone resorption and calcium metabolism will require special preventive measures in longer flights. From the standpoint of the kidney, drugs and dietary composition can be employed to assure acidification of the urine and thus aid in preventing nephrocalcification.

Nutrition and alimentation in brief earth-orbital flights appear to present no serious problems requiring pharmacological intervention. Important metabolites are available in body stores, but supplementation of essential minerals such as sodium, phosphorus, potassium, and calcium will be necessary as the duration of flight increases beyond that of lunar missions. Then ascorbic acid, menadione, vitamin D, essential amino acids, and even fatty acids may have to be provided to prevent deficiencies (23).

The difficulties associated with accumulation and disposition of alimentary wastes on long expeditions have prompted suggestions aimed at minimal residue diet combined with antibiotic and chemotherapeutic suppression of bacterial flora to reduce drastically the stool volume, together with inhibition of rectal reflexes to minimize the frequency of defecation (23). If serious abdominal distention ensues, appropriate medication may be required.

The converse problem, related to the probable ultimate use of synthetic

diets, is that of long sustained constipation; this may require the occasional addition of a synthetic inert dietary residue such as methyl cellulose and even capsules of mineral oil. Thus far, following only 1 to 5 days of earth-orbital flight, little reason for serious concern has been reported relative to gastrointestinal function.

Maintenance of body temperature of the space-suited astronaut will provide one of the most challenging of the engineering tasks concerned with life support in space. A rise in body temperature may result from failure of components of the suits' temperature control system. Should this occur, drugs such as salicylates and promethazine cannot be expected to aid, since the cause will be a gradient of heat from an excessively hot environment within the capsule. The rise in body temperature, which may be aggravated on the hot lunar surface (the probable temperature range at the center of the sunlit surface is expected to be 100° to 130° C) (60) or during exposure to the friction of re-entry into earth's atmosphere, may cause unexpected and undesirable modifications in the effects of drugs. For example, aspirin used to relieve headache in environmentally induced hyperthermia should have no antipyretic action and should even aggravate the respiratory-stimulant effects of hyperthermia, itself (61, 62).

The Lunar Trajectory

The radiation hazard is one of the most extensively studied, as well as one of the most obscure, of all the aspects of prolonged space flight. This has not, as yet, been a serious problem to astronauts because none of them has orbited at an altitude higher than 160 mi (266 km), which is well below important concentration of the radiation trapped in the Van Allen belts in the earth's magnetosphere. Dosage-measuring devices carried on the longest Mercury and Vostok flights indicated that the astronauts received no more radiation than they would have received on earth and certainly less than that involved in a chest X ray (1, 20).

These were earth-orbital flights, however, and space voyages that involve escape from the earth's gravitational attraction will require the astronaut to traverse the entire zone (or zones) of trapped radiation. These extend, from an altitude ranging from about 450 km over Chile to about 1400 km over Australia, out into space for approximately 55,000 km, with peak intensities at about 4000 and 18,000 km (63). Recent reports of the findings of the Explorer XVIII space probe (launched in November, 1963) give evidence of a previously unsuspected belt of intense radioactivity beginning at the outer edge of the outer Van Allen belt and terminating abruptly at about 96,000 km. This is tentatively attributed to local acceleration of electrons because of a shock wave produced by the impact of the solar wind on the earth's magnetosphere (64). Perhaps the most important aspect of this new discovery with regard to manned flight is the reminder that more distant expeditions may continue to encounter the unexpected.

In addition to the belts of trapped radiation, the spacecraft will be ex-

posed to the full effects of cosmic rays as soon as it gets beyond the earth's atmosphere, which ordinarily dissipates all but a small fraction of the high energy of these particles (65, 66, 67). The astronaut will also be exposed to continuous radiation from the sun and subject to occasional exacerbation in solar storms of great intensity (63, 67, 68, 69). The latter, at present, are at a minimum; but by 1967 or 1968 they are expected to be on the increase again, and the astronauts involved in lunar explorations must be prepared to protect themselves against sudden great increases in radioactivity from the sun with little advance warning (67, 70) and without atmospheric shielding. To this naturally occurring radioactivity must be added that which is produced by nuclear detonations in the outer atmosphere or in space.

Another facet of the radiation problem is connected with the probable ultimate use of nuclear energy to propel space vehicles. One of the major deterrents, here, is concern over the concomitant radiation hazard, which will necessitate a combination of special tactics and utilization of water, food, oxygen, wastes, fuel, and even heavy metals such as mercury and uranium as shielding (71).

These problems of protection against more-or-less unpredictable increases in radiation dosage are further complicated by uncertainties about the average dosages of radiation which are ordinarily to be expected and about man's tolerance to them under space conditions. According to one recent review (70), the present criteria for estimating radiation tolerance on earth are unlikely to apply to man in space, not only because there is now no earthly counterpart for the heterogeneous mixtures of radiation he will encounter there but also because the unique circumstances (increased *g*, followed by the gravity-free state, inactivity, abnormally high oxygen tensions, peculiar diet, and exposure without interruption for days, weeks, or months) may enhance the deleterious effects of the radiations. A twofold error in estimating the dosage, while permissible at a low (10 rad) level, is disastrous at higher (50 rad) dosage levels (70).

The present lack of definite information about the total radiation a man would acquire during a space flight lasting weeks or months, as well as about the limits of tolerance, and the anticipated recovery patterns, are emphasized in another recent review (63).

The problem of adequate physical protection of the astronauts against toxic radiation in lunar flights would be greatly simplified if it were possible to provide them with drugs that could be depended upon to protect them against intermittent bursts of increased dosage, as well as to compensate for miscalculations of radiation dosage, effectiveness of physical shielding, and human tolerance under the unprecedented circumstances.

Chemical protection against ionizing radiation appears to be the greatest challenge and opportunity for pharmacology to make an essential contribution to our space program. Although considerable progress has been made (72, 73), the drugs presently available have fundamental deficiencies from the viewpoint of an astronaut en route to or from outer space.

(*a*) The maximal protection attainable in mice and rats is of the order of 1.5 to 2 times the tolerance of untreated animals (72). The degree of protection is directly proportional to the dose; and, at the level of maximal protection, the drugs exert distinctly toxic effects (72, 73). Comparable results were obtained in monkeys, but a combination of oral and intravenous administration of several different drugs (including coma-producing doses of a barbiturate) was required (74).

(*b*) The drugs are effective only as preventives, not as curatives; i.e., they must be present in optimal concentration at the time of radiation (72, 73), since the interval between the formation of a free radical and its reaction with a tissue component is apparently not greater than 1 msec (75). No drug with specific actions on existing radiation damage has yet been discovered (72) or is likely to be. The claim that clinical radiation sickness can be strikingly ameliorated by some of these compounds (76, 77) has not been substantiated. and drugs have not been accepted for general use for this purpose (72).

(*c*) Experiments on animals indicate that none of the chemical protectants thus far tested can be depended upon to protect against repeated or continuous low-grade radiation (78, 79). Chemical protection against moderate whole-body radiation (100r to 500r) takes the form of acceleration of the recovery process, not of prevention of the acute symptoms which are diminished only slightly, if at all (72, 77).

It appears fair to conclude that full dosages of the drugs presently available would be justified only for brief, nonrecurrent exposures followed by ample time for recovery from untoward acute effects of the drugs and the radiation. Examples would be during passage through the Van Allen belts and areas contaminated with residues of nuclear detonations; exposure to radiation resulting from solar flares can now be considered too prolonged and too intense to be effectively combated by such measures alone. Certainly, use of existing drugs throughout the voyage to protect against the continuous radiations of space appears to be unjustified.

If the hope of effecting a great saving in weight of a space vehicle by substituting drugs for some of the physical shielding is to be realized, it will be by new drugs that are more effective and less toxic or by better utilization of the available drugs and devices.

Search for superior chemical protectants for use in the space environment is complicated by the diversity of effective agents and uncertainties concerning their mode of action. These questions are discussed in a recent review (72).

Several forms of chemical protection are considered to exist including: (*a*) selective transient pre-exposure attachment of a radioprotective agent such as 2-aminoethylisothiuronium (AET) to enzyme groups at the highly reactive sulfhydryl moiety, which is presumably inactivated by free radicals (72, 73); (*b*) pre-exposure administration of agents such as cysteamine, which along with other actions can apparently compete with cell enzymes for the free radicals formed from water or cellular macromolecules by ionizing radia-

tion (80, 81); (*c*) protection by replacement of damaged, naturally occurring sulfhydryl components such as glutathione (72); (*d*) protection by alteration of cell metabolism (72); and (*e*) protection by reduction of cellular oxygen tension to diminish the rate at which free radicals are formed by ionizing radiation (82, 83). Agents such as PAPA (*p*-aminopropiophenone), which produce cellular hypoxia and radiation protection by inducing methemoglobin formation or otherwise inactivating hemoglobin, have no rational place in protecting humans against radiation in space flight.

The well-established protective effect of a decrease in environmental oxygen tension against ionizing radiation deserves special attention with respect to the isolated, controlled, gaseous environment within a spacecraft. Diminished Po_2 reduces the damage and mortality of essentially all cell types which have been studied, including plant, microorganism, and tumor cells (83, 84). The 30-day LD_{50} for rats exposed to radiation while breathing 5 percent oxygen is about twice that for rats irradiated while breathing air (85), indicating that this form of protection also extends to mammals. Such a severe level of hypoxia, of course, is not recommended as a protective measure for human occupants of spacecraft. Nevertheless, the degree of protection provided by this nonpharmacological approach is noteworthy in its own right, and exaggeration of toxicity by increased oxygenation (83) has immediate importance in relation to possible extension of the protection afforded by drugs.

From the standpoint of size of the effective dose, reserpine and 5-hydroxytryptamine (serotonin) are among the most potent of all chemical protectants against ionizing radiation in mice (72, 73). The radioprotective action of pharmacologically active amines has generally been attributed to tissue hypoxia resulting from cardiovascular effects (73), but recent developments suggest that this may not be the entire story. Thus, indole derivatives, in general, are good radical-sinks (80), which may account for the fact that the rate of decay of free radicals, formed in suspensions of eye melanin *in vitro* by exposure to visible light (86), is greatly accelerated by the addition of serotonin (87). In this case, there can be no question of indirect effects through cardiovascular actions. Corresponding studies with reserpine (which contains an indole moiety) have not yet been made, but this area deserves investigation because these agents have a wider margin between effective and toxic dose than any of the commonly used chemical protectants.

Since more than one form of chemical protection appears feasible, a natural question is whether a compounding of protective effects can be accomplished by concurrent administration of the several different drug types found to reduce radiation damage. Experiments on primates indicate that the greatest degree of protection against lethal X radiation is provided by a combination of intravenous and oral administration of several thiols, together with a coma-producing dose of barbiturate (74). Subsequent studies indicate the usefulness of an AET-cysteine-pentobarbital-antibiotic combination (88). These findings suggest that astronauts might be enabled to sur-

vive otherwise-certainly-fatal episodes of toxic radiation by appropriate combinations of drugs now available, but at the cost of temporary, total incapacitation.

The impression we derive from the information now available is that adequate protection of astronauts against the radiation hazards of long journeys in space is less likely to be secured by a breakthrough in the form of greatly superior new drugs than it is by combinations of several methods, including the use of several chemical protectants to supplement well-engineered physical protection and even the transient employment of diminished oxygenation at periods of excessive radiation exposure (19, 23). The possibility that such a combination of methods may be useful is indicated by studies in which hypoxia enhanced the radioprotective effect of cystine at a level of Po_2 not, in itself, sufficiently reduced to provide detectable protection (82). This is not to say that efforts at finding better chemical protectants should be abandoned, but rather that the actions of toxic radiation on cells are so diverse and complex (73, 82, 89) that single antagonists of high potency and low toxicity seem unlikely.

Agents modifying central nervous functions can be expected to be required on each prolonged flight. During the period of days, weeks, or even months of enforced isolation and physical inactivity, some or all of the astronauts may, at times, require medication for motion sickness. Lack of need thus far should not be interpreted as indicating that the problem of motion sickness will not arise in flights of long duration. The choice of agent will depend on individual responses to test doses before the flight and on the pattern of pharmacological activity desired. The latter includes, particularly, the presence or absence of tranquilizing action, which may be considered for some of the crew members (in alternation) during much of the flight. Such medication could minimize adverse personality reactions and reduce the requirements for food, liquid, and oxygen. Perhaps the chlorpromazine congeners might also increase resistance to toxic effects of radiation (90). In any event, selection of drug and dosage schedule would have to be made in appropriate simulation experiments.

The use of tranquilizers by astronauts raises many questions, some of which could be answered in simulation experiments. In the future, long periods in transit with minimal demand for attention or action may provide a rational indication for drugs which depress emotional reactivity, even at the expense of intellectual alertness. In short flights and during critical control functions, drugs which adversely affect performance must be avoided. A small start has already been made in the direction of studying the influence of a minor tranquilizer on the performance capability of normal young men with respect to physical work (91) and their ability to carry out guidance functions under transverse g_x on the centrifuge (92). In both cases, the drug tested was meprobamate. In the centrifuge studies (92), effects of 400 mg doses of meprobamate were indistinguishable from those of placebo. In the work studies (91), the drug had no discernible effect in dosages up to 800 mg;

but at 1200 mg or more blood pressure fell slightly, and there was an increased tendency toward orthostatic hypotension. Most interesting is the fact that the only one of four types of medication (meprobamate, dextroamphetamine, secobarbital, and placebo) that definitely enhanced the performance of these subjects under acceleration stress was secobarbital (92). This drug, in the dosage used (50 mg by mouth), produced no overt drowsiness or inattention. Its beneficial effects on performance were ascribed to alleviation of anxiety or a mild elevation of the central threshold for perception of distracting nerve impulses.

Requirement for sleep may necessitate occasional use of hypnotic drugs to compensate for noise and general discomforts, as well as for disruption of the normal day-night cycle. Restful sleep without drugs has been possible in American and Russian earth-orbital flights (1), but it does not necessarily follow that sleep will present no problem on much longer journeys.

The favorable influence of a small dose of secobarbital on the capability to perform tasks similar to those of astronauts under acceleration stress (92) is interesting but not necessarily pertinent to the situation of astronauts facing the physical and mental stresses of take-off or re-entry. Nevertheless, such information is reassuring as to one aspect of the occasional use of a hypnotic to aid in the induction of sleep. If this type of medication is to be used by astronauts, it is not certain that a barbiturate is a better choice than chloral hydrate or drugs only now being explored. According to recent evidence (93–96), γ-hydroxybutyric acid and γ-butyrolactone, normal products of tissue metabolism, are capable of causing sleep of a normal physiological type with minimal side effects or sequelae, and are useful in human anesthesia. The lactone has been stated to be the active agent (96). This has recently been denied, as has the claim that the acid and the lactone are normally found in blood or brain (97). Very recently (98), the lactone has been found to produce marked and fully reversible depression of the oxygen uptake of the cat. Such an effect would be important in conjunction with the production of temporary or periodic narcosis in one or more of the crew of a space vehicle if that were deemed desirable in flights not yet planned.

The above comments about drugs that could be used to promote sleep by astronauts also apply, in general, to the intermittent use of stimulants to combat somnolence and inattention and to antagonize the depressant effects of other drugs. Thus far, the only pertinent studies are those in which dextroamphetamine was studied in respect to effects upon psychomotor performance during acceleration stress on the centrifuge (92). The findings are of limited value for reasons stated (see above). In the centrifuge tests, dextroamphetamine caused a significant deterioration in performance (increase in number of errors), a finding opposite to the improved alertness and competence attributed by Astronaut Cooper to the same drug (1) and long established for other circumstances in earth-bound laboratories (99).

The selection of antidepressant drugs should be based upon simulation studies with particular attention to the stage of the flight and the identity

and dosage of depressant drugs to be antagonized. For example, it would not be difficult to determine, in a simple simulation (50), whether ephedrine or any other central stimulant also has cardiovascular stimulant actions which are superior to dextroamphetamine in combating postural hypotension corresponding with that to be expected by astronauts after landing.

The effectiveness of different analeptics and energizers against depressant drugs could also be tested in simulations. Restoration of full consciousness after prolonged narcosis would be a special problem, particularly if it had to be done rapidly in anticipation of a situation calling for peak mental and physical performance. Since no known drugs can be depended upon to do this, appropriate timing of depressant medication will be necessary.

A great variety of other pharmacological agents may be desirable. During a voyage, there may be occasion for symptomatic medication for mild or severe pain, for antihistaminics to relieve allergies, for nasal decongestion, and for abdominal distention, diarrhea, and hyperacidity. The possible role of bacterial and viral chemotherapeutic measures is discussed elsewhere (page 384) as is the desirability of food supplements (page 391).

The additional complications of borderline temperature control, limited mobility in a nearly closed, weightless system, and long periods without bathing require consideration of a number of other peculiar possibilities. One is that the skin will possibly be constantly wet by perspiration in regions of poor ventilation, macerated by mild trauma, infected by bacteria and fungi, frozen on exit from the capsule by inadvertent contact with a shaded part of the suit, or burned by contact with suit segments imperfectly cooled. All of these problems will require anticipation and medical and pharmacological management. Agents designed to provide preventive skin care without poisoning or physical polluting of the capsule atmosphere will be required. Skin care will depend upon cleaning, toughening, bacteriostatic and mycostatic agents which will neither volatilize nor become suspended as dusts in the capsule atmosphere.

Minute particles of weightless debris, including body wastes, will probably accumulate over a period of time and must be dealt with in order to minimize the pulmonary consequences of aspirating them and the ophthalmologic irritation and infection which would follow repeated irritation and contamination of the conjunctival space. Anti-inflammatory and anti-infective agents suitable for low-grade conjunctivitis thus deserve inclusion among the supplies for prolonged flight. Blockage of the eustachian tubes in a pure oxygen atmosphere may lead to resorption of gas from the middle ear and to otic barotrauma. Even this problem may be less troublesome than the quite-likely failure of drainage of normal and pathological secretions from the paranasal sinuses and middle ears. In the weightless state, such drainage should not occur spontaneously, and if respiratory infection were superimposed, its cure in the absence of drainage might require intensive antibiotic therapy. During the critical period of re-entry, as gravitational stress is again experienced, such an ordinary biomedical event as sudden drainage of

frontal or ethmoid cells may lead to temporary, gross disability. A counterpart of this has been experienced in studies on the human centrifuge, in which situation choking on such secretions has occurred (100).

Re-Entry

The final stages of the flight will involve the most complex and difficult pharmacological decisions of the entire mission, because the need for immediate and definitive psychomotor coordination will be greater than at any other stage and so will the physiological and psychological stresses. At the same time, the physical and mental condition of the astronauts certainly will not be as good as it was when they went through the similar but lesser stresses of the take-off. Pharmacological problems here involve both: (*a*) minimizing or avoiding drug effects that might place a further burden on the astronauts at a most critical time; and (*b*) enhancement by drugs of the astronaut's capacity to carry out the highly specialized tasks on which his safe landing and eventual survival depend.

Under (*a*) must be considered residual effects of anti-emetics, hypnotics, and tranquilizers, which could be minimized and perhaps avoided by appropriate timing of such medication in accordance with preflight experience of the astronauts with the same drugs. The finding (92) that mild sedation may actually enhance the performance of tasks similar to those involved in the astronaut's re-entry indicates the necessity for further investigations of representative drug effects in appropriate simulations. If it is decided to use chemical protectants in anticipation of the return passage of the vehicle through belts of trapped radiation in and beyond the earth's magnetosphere, the effects of such medication probably will not have worn away when the accleration stresses of re-entry and landing are encountered. The pattern and magnitude of this complication will have to be determined in simulations before any recommendations can be made. Much will depend on the drugs and dosages selected. With appropriate training of the astronauts for the purpose, intravenous administration of radioprotective drugs might be employed to minimize duration of action.

The possibilities of enhancing the astronaut's capabilities by drugs on re-entry may conveniently be listed according to the time at which the drugs should be given. First would come measures intended to minimize the adverse effects of deceleration during re-entry. Here may be included antibiotic and antiviral medication, agents to obviate excess secretions in the respiratory tract, and a nasal decongestant (for the same reason). The desirability of attempting to counteract the rise in pulmonary arterial pressure during re-entry (page 387) cannot be decided without appropriate tests on the centrifuge. The same is true of the use of positive-pressure breathing and of the choice between 100 percent oxygen and a mixture of oxygen with an inert gas that will counteract the tendency of oxygen to exaggerate the atelectasis of transverse acceleration (page 387) (19). The proper timing of such interventions also remains to be determined.

Next would come drugs which will counteract deterioration of mental and physical functions, whether due to the prior use of other drugs or to the abnormal space situation (page 388). To promote mental activity, the only drug thus far tried in actual space flight is dextroamphetamine which, in the small dosage used, did not prevent othostatic hypotension on ambulation. This phenomenon may be expected to be worse after a journey of the Apollo type than ever before, partly because of the greater duration, partly because the acceleration stress will be the greatest yet experienced and the attendant pulmonary and cardiovascular disturbances (including arterial anoxemia), coming after the deconditioning effects of prolonged confinement and inactivity, are likely to lead to gross decrease in the capacity of the astronaut to bring his training to bear upon the tasks before him. Anti-emetics, narcotics, reserpine, and chlorpromazine would be expected to aggravate this situation. The radioprotective thiols remain to be tested.

Post Landing

If the landing is to be on the lunar surface, it is presumed, from simulation studies and Vostok flights (20), that no gross deterioration will have occurred in the several-day period of transit from earth to moon. In addition, the deceleration stress involved in leaving a 10,000 mi per hr lunar orbit and then decreasing velocity to zero at the instant of landing on the moon's surface is considerably less than the gravitational stress of accomplishing a landing on earth from the nearly 25,000 mi per hr velocity of the return from the moon. Since the fixed gravitational stress of standing on the lunar surface should be only about 0.16 *g* (101), the partially decompensated circulation should present less handicap on the moon or Mars than on return to earth itself.

When the vehicle has come to rest on earth, the astronauts should recover promptly from the acute gravitational and thermal stresses of re-entry, but they may recover more slowly from their exposure to prolonged weightlessness and restricted mobility. The pulmonary atelectasis of deceleration should disappear spontaneously and promptly on breathing air at sea level. Body temperature should return to normal following exit from the capsule and removal of the air-tight pressure suit. However, the presence of circulatory decompensation and orthostatic hypotension may require not only that aid be available, but also that an extended program of recompensation be accomplished. Drugs may be extremely valuable here, both in terms of support of the weakened circulation and in terms of a retraining of the circulatory reflexes and sympathetic system. The behavior of the otolith mechanism after re-entry and the possible need for re-education of kinesthetic senses on abrupt return to 1 *g* are not established, but are probably beyond specific aid by drugs.

Finally, if the vehicle should come to rest in a location in which rescue is going to be delayed or unlikely, and the astronauts must fend for themselves for a period of time in hostile surroundings, they may even need medical pro-

tection against malaria, amebiasis, and infectious diseases such as typhoid, cholera, plague, pneumonia, and meningitis. The selection of appropriate drugs and measures should not be difficult, but the astronauts may not welcome this further addition to the list of drugs which pharmacologists wish to have tested on them during their training period.

Conclusion

It should be made as clear as possible that the preceding pages are intended to propose, not a set of specified drugs to be included in the medicine chest for the forthcoming Gemini, MOL, Apollo and more remote space flights, but only a series of problems which deserve consideration for early investigation in appropriate simulations. If, at the same time, we have left the impression that the possibilities of drugs to support our space effort are both extensive and unexplored, we will have achieved our immediate purpose. The time schedule attests to the urgency of the situation better than any words of ours could do.

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