If a major bronchus has been entirely occluded, there are the usual signs of an obstructed lobe or lung, such as dullness to percussion, diminished fremitus, absence of breath sounds and usually some degree of mediastinal displacement.

Past experience has shown that only about 3 percent of foreign bodies in bronchi are coughed up spontaneously, the remainder having to be removed by bronchoscopy [28, 29]. Since bronchoscopy is a highly skilled procedure which is unlikely to be performed in space in the foreseeable future, appropriate supportive therapy will have to suffice until an astronaut returns to Earth. With a suitable broad spectrum antibiotic, the septic sequelae should be adequately controlled. As will be discussed under acute chemical inflammation of the lower respiratory tract, steroid therapy might be of some value in treating cases with fulminating laryngotracheobronchitis due to vegetal foreign body.

Even in cases of profound sepsis, the prognosis for complete recovery following removal of a foreign body which has been in a bronchus for a prolonged period of time is fortunately excellent. Jackson and Jackson point out that 95 percent of cases of foreign body of other than vegetal origin completely recover [30]. This figure and the unstated poor prognosis of cases of vegetal foreign body would no doubt be bettered by therapy given immediately as indicated.

Acute Chemical Inflammation of the Lower Respiratory Tract

An acute non-specific inflammation of the lower respiratory passages of an astronaut might occur if he inhales an irritant gas or chemically-irritating particles or droplets which are small enough to be inhaled beyond the nasal or oral regions of his respiratory passages. It might also result from the aspiration of chemically-irritating particles or droplets. Possible contaminants fitting into the first category are gases formed by the chemical breakdown of metals, plastics, and other materials by spilled acids and alkalis. Examples in the second category are: chemical dusts, expecially if powdered chemicals are used on board spacecraft; fumes and smokes formed by the pyrolysis or combustion of plastics, metals and other materials; and chemical mists which might be formed if acids or alkalis are sprayed into the spacecraft cabin atmosphere. Of major concern in the third category is

vomitus, the aspiration of which is considered particularly prone to occur if an astronaut vomits into the helmet of his space suit. It is pointed out that the hydrochloric acid content of vomitus is highly irritative. As well, if food particles are present in the vomitus, they can produce primary obstruction of respiratory passages and possibly further chemical irritation. The following discussion deals with the general aspects of chemical inflammation of the lower respiratory passages. Although it is considered possible that some contaminants might be absorbed from the respiratory passages and produce specific toxic effects, such effects can be described only after the hazards and their toxicology have been better defined.

A chemical which enters the lower respiratory tract can induce various respiratory protective reflexes such as coughing, apnea, glottic closure, adduction of the vocal cords and bronchospasm. These reflexes act to exclude the irritant from the deeper respiratory passages, especially the delicate alveolar cells. The stimulating action of an irritant is determined by its cytotoxic nature, by its solubility in water and, of course, by the amount of irritant entering the respiratory passages. Intense stimulation may be effective in temporarily excluding an irritant from, and so minimizing the toxic effects of the irritant in the lower respiratory passages. Unfortunately, however, these reflexes are not so efficient when a large volume of a highly irritating fluid such as vomitus is aspirated [20].

After gaining access to the lower respiratory passages, a chemical will produce toxic effects in specific regions of or throughout the passages. This will depend mainly on the amount of the irritant and its physical properties. An irritant gas with a high solubility in water will be extracted by the moist surfaces of the upper respiratory tract and high up in the lower tract, whereas an irritant gas with a low solubility will penetrate deep into the tract producing toxic effects on bronchioles and alveoli. The characteristics of deposition of inhaled particles or droplets in the lower respiratory passages in the weightless environment have been discussed previously. The distance of penetration of an aspirated liquid into the lower respiratory tract will depend mainly on the amount of liquid that enters. An aspirated particle can lodge in various regions of the lower respiratory passages. The more soluble it is, the more immediate and diffuse will be its chemical

action, all other cytotoxic factors being equal.

The inflammation produced by a chemical in the lower respiratory tract is characterized by vasodilatation, congestion and subsequent transudation of plasma through hyperpermeable capillary walls in the involved tissues. This edema fluid distends interstitial tissues and accumulates in the respiratory passages, interfering with the ventilation of the lungs and, if the alveoli are involved, impairs diffusion of respiratory gases across alveolar membranes and perfusion of alveolar capillary beds. Inflammation of the laryngeal and bronchial tissues is usually accompanied by some degree of laryngospasm and bronchospasm, which assist in blocking air flow. Chemical necrosis of tissues may occur, with debris and hemorrhage contributing further to impairment of lung function. Then, as a common and often serious sequel, secondary bacterial infection of damaged lung tissues can occur.

In the light of the above considerations, it is obvious how widely variable the clinical manifestations produced by a chemical irritant in the lower respiratory passages of an astronaut could be. The entry of an irritant into the lower respiratory passages can produce signs and symptoms such as apnea, partial or complete blockage of air entry, stridor, violent coughing, retching, a severe burning or stinging pain in the throat, larynx and trachea, a feeling of substernal pressure, wheezing, dizziness and anxiety. If the larynx is severely involved, laryngospasm and rapidly-occurring interstitial edema of its tissues can seriously compromise air flow, with severe dyspnea, cyanosis and possibly fatal asphyxia coming on within minutes after exposure. Signs and symptoms of acute chemical laryngotracheobronchitis, such as dyspnea, coarse rales and rhonci, cyanosis and the coughing of a copious, possibly blood-stained frothy sputum,can appear over a period of minutes to hours and cause death. Acute chemical pneumonitis usually begins rapidly, either immediately or after a relatively asymptomatic period of up to several hours. If the edema is severe, there is dyspnea and the coughing of a copious frothy sputum which might be blood stained. This edema may lead to cyanosis, right-sided heart failure, "shock" and death [47]. Severe necrosis of tissues in the lower respiratory passages can result in fatal hemorrhaging. Surviving

chemical inflammation and damage of one specific or all regions of his lower respiratory passages, an astronaut could develop a secondary bacterial infection over a period of many hours or days. This could manifest as laryngotracheobronchitis, bronchopneumonia, empyema or lung abcess, and could lead to his demise.

The diagnosis of chemical inflammation of the lower respiratory tract is, in most cases, obvious from the history and physical findings alone. It is important to remember that acute pulmonary edema can occur in an asymptomatic individual up to several hours after being exposed to a chemical irritant. If possible on board the spacecraft, chest x-rays could be of some assistance in diagnosing pulmonary edema in its pre-clinical and clinical stages, and secondary complications.

Experimental and apparent clinical success, especially in treating chemical inflammation of the lower respiratory tract due to aspirated vomitus, has been achieved with steroids (4, 11, 20, 22, 31, 32). The exact mode of action of these drugs is unknown (4, 32). Further research is apparently required to definitely establish their effectiveness in treating chemical inflammation in the lower respiratory passages from all causes. The standard method of treatment is the administration of a suitable steroid, such as hydrocortisone sodium succinate, intravenously as soon as possible after an incident. Depending on response to the first dose and the seriousness of the inflammation, repeat doses of such a drug can be given either intravenously or intramuscularly over a period of time. After the acute phase of the inflammation has passed, a suitable oral steroid preparation, such as methylprednisolone, should be taken in decreasing doses for several days.

Other therapeutic measures are taken as dictated by sound clinical judgment. A tracheostomy is a life-saving measure which should be performed as soon as possible in cases with laryngeal edema of rapid onset. It is also effective in cases with severe involvement of the lower respiratory passages, by allowing less obstructed ventilation of the lungs and providing a portal for the removal of copious secretions and possibly blood. Positive pressure oxygen will combat not only hypoxia but also pulmonary edema. Bronchospasm can be relieved with a suitable bronchodilator drug, such as

aminophylline, administered intravenously or intramuscularly. Nebulized isoproterenol might also be used for bronchodilation. Rapid intravenous digitalization will be required in cases with right heart failure, and may be undertaken as a prophylactic measure in potentially serious cases. "Shock" should be treated with a suitable vasopressor, such as metaraminol, administered intravenously. Analgesia and sedation might be indicated. Therapy with a suitable broad spectrum antibiotic might be commenced in serious cases even before manifestations of secondary infection appear.

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3. Aronovi
4. Bannist
5. Boettne
6. Boies,
7. Bunker
8. Busby,
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CHAPTER 9

URINARY CALCULUS

Many authors have postulated that bone will undergo partial reabsorption in the weightless environment [20, 25, 30, 42, 58, 62, 71]. They have also pointed out that the resulting excessive excretion of the products of bone reabsorption might be conducive to urinary calculus formation. Accordingly, it is thought necessary to consider urinary calculus a potential medical problem of prolonged space missions until appropriate studies in space prove otherwise. This chapter presents information considered pertinent to the occurrence of urinary calculus in space.

Weightlessness and Bone Metabolism

Bone is a living tissue and, like most other tissues in the body, is constantly undergoing the simultaneous processes of formation and destruction [84]. In bone formation, a matrix of protein and mucopolysaccharide is first produced by osteoblastic cells. Then calcium and phosphorus, mainly in the form of apatite crystals, is deposited in this matrix. Bone reabsorption is due to osteoclastic cellular activity, which is apparently responsible for the breaking down of both matrix and bone crystals [62]. By means of formation and reabsorption processes, bones are remodeled in response to the functional demands which muscular pull, other mechanical stresses, and presumably gravitational forces place on them. This fact was recognized by Julius Wolff in 1868, and has become known as Wolff's law: "Every change in the form and the function of bones, or in their function alone, is followed by certain definite changes in their internal architecture, and equally definite changes in their external conformation ....." [103].

If stresses on bones are sufficiently increased by physical activity, for example, the physicochemical processes of bone formation in the stressed bones will outdistance those of bone reabsorption, and hypertrophic changes will occur. Conversely, if the stresses on bones are decreased to a significant degree, atrophic, or osteoporotic changes will result from reabsorptive processes predominating over formation processes. The osteoporosis

which occurs in an extremity which becomes paralyzed, or is immobilized for a period of time for therapeutic purposes, is a classical example of the effect of decreasing the mechanical stresses on bone.

In accordance with Wolff's law, the state of equilibrium of bone metabolism is influenced by the forces of compression, tension, and shear exerted by weight bearing and muscular activity. One would expect, therefore, that removal of the forces normally exerted by weightbearing, as will occur in the weightless environment, will alter this state in weightbearing bones. Reabsorption processes will exceed formation processes in these bones until bone metabolism, as influenced now by only the forces of muscular activity, returns in time to a state of equilibrium. If the degree of osteoporosis produced by the excessive bone reabsorption is severe and localized, weightbearing bones could become more prone to fracture [20, 84]. However, even more important from a space operational standpoint is the possibility that the urinary output of calcium and other products of bone reabsorption could lead to urinary calculus formation, and the extremely incapacitating symptoms therefrom, during a space mission [26, 30, 42, 58, 71, 91, 92].

In various attempts to predict what effect weightlessness will have on bone metabolism, observations made on immobilized patients and healthy experimental subjects have been referred to repeatedly [8, 20, 28, 52, 101, 102, 104]. The classical experiment of Deitrick and co-workers [28] illustrates immobilization carried to one extreme. Four healthy young men were immobilized in plaster casts from waist to toes for six to seven weeks. They were placed on constant dietary intakes for several weeks prior to and during immobilization. Pertinent to considerations in this chapter are that immobilization brought about a prompt increase in urinary and fecal calcium excretion, which reached a plateau over a period of four to five weeks. At this time, the urinary calcium output was between two and three times its pre-immobilization level. The serum calcium tended to rise in this study, leading to the suggestion that during immobilization, the increase in calcium excretion and hypercalcemia may actually reflect an increase in bone reabsorption [100]. Immobilization also led to an increase in urinary

and fecal phosphorus excretion. The urinary phosphorus excretion began to rise during the first week. It reached a peak which coincided with that of increased nitrogen excretion in the second to third week, decreased somewhat, and then reached a second peak at the sixth to seventh week, when the urinary calcium excretion was at its highest level. Pertinent to considerations of urinary calculus formation is the observation that urine pH rose slightly so that, as will be discussed below, the solubility of calcium phosphate in the urine would have been decreased.

Recently, more practical immobilization experiments have been directed at maintaining recumbent, healthy, young subjects at an optimum level of physical fitness by having them intermittently perform a variety of appropriate exercises (8, 20, 96). Hopefully, such exercises, which will undoubtedly be necessary to compensate for decreases in normal physical activity during space missions, should eliminate the effect of muscular inactivity on bone metabolism. Accordingly, if subjects remain recumbent, the effects of weightlessness on weightbearing bones should be fairly well simulated in these experiments.

Throughout a 30-day bed rest study reported by Brannon and co-workers (20), 18 healthy young subjects performed one of three exercise routines, and six subjects performed no exercise except for being allowed to sit and turn about in bed. All subjects were on constant dietary intakes throughout the study. Since bed rest did not produce an increase in the urinary calcium output in either the exercise or non-exercise groups, the impression was gained that only a small amount of exercise is necessary to preserve muscular integrity and prevent bone reabsorption in a physically fit, normal individual who is confined to bed. Similar studies by Vogt and co-workers (96), in which specific isometric exercises were found to prevent reabsorption of the os calcis, suggests that appropriate exercises might even effectively protect weightbearing bones from reabsorption.

In contrast to the above findings, Birkhead and co-workers (8) failed to prevent bone reabsorption with various exercise regimens in their bed rest study. In this study, eight subjects remained recumbent for 24 days. All had a constant dietary intake during this period. Exercise was performed

on a bicycle ergometer for one hour daily by two subjects in a lying position and two subjects in a sitting position. Four subjects sat in a chair for eight hours daily.

From the studies mentioned above, it is apparent that the relative contributions of muscular activity and the stresses of weightbearing to the maintenance of normal bone integrity still remain undetermined. All exercises which involve the gravity muscles and weightbearing bones simulate weightbearing forces to some degree. For this reason, it is unlikely that the specific effects of weightlessness on the skeletal system will ever be simulated. Whedon [100] pointed out that we do not even know the exact manner in which mechanical stresses exert their effects on bone mass. He postulated that these stresses may act through the medium of muscular pull on periosteal surfaces and, in weightbearing, more directly through bone structures and columns, or by combinations of these two and perhaps other factors. On the one hand, muscular pull would seem to be the most important factor maintaining normal bone integrity, since slow rocking in a Sander's oscillating bed was effective in preventing the alteration of calcium balance of normal immobilized subjects [101] but not of severe poliomyelitis and paraplegic cases [104]. On the other hand, Abramson [1] showed that osteoporosis in paraplegics was effectively reduced by weightbearing, hence providing evidence for weightbearing as a factor.

Therefore, it appears that during space missions, efforts should be directed not only at maintaining an optimum level of muscular activity, but also at attempting to simulate the stresses of weightbearing on bone. Carefully selected exercises should prevent loss of muscle integrity, and the bone reabsorption associated with it, in an astronaut who has his physical activity reduced during a space mission. Such exercises, which should maintain stability about weightbearing joints and the fitness of postural musculature, will also contribute to keeping the risk of injuries from mechanical forces in space (Chapter 14) to a minimum. It is thought that an almost if not completely adequate simulation of weightbearing stresses on the musculoskeletal system can be accomplished in space by means of selected exercises and possibly the application of appropriate mechanical forces to the body.

This is an area which certainly requires intensive investigation.

Urinary Calculus Formation

Although weightbearing forces on the skeletal system might conceivably be adequately simulated in space by various measures, it is believed that at the present time, excretion of the products of bone reabsorption, if only to a minor degree, should be anticipated during prolonged space missions. Since one or more of a number of factors other than bone reabsorption could initiate or enhance the formation of a urinary calculus in an astronaut, they too must be taken into account when considering the prevention of urinary calculus in space. It should be remembered that some of these factors are actually potential side-effects of space operations and, either singly or in various combinations, might be capable of initiating calculus formation even though bone reabsorption might not be occurring.

Components of a Urinary Calculus

The principle component of a calculus formed in a normal urinary tract in space will probably be basic calcium phosphate principally in the form of either apatite ($Ca_{10}(PO_4)_6(OH)_2$) which is its solid phase about a pH of 6.6, or brushite ($CaHPO_4 \cdot 2H_2O$) which is its solid phase below a pH of 6.6 [33, 34, 36, 77]. If a urinary tract is infected with urea-splitting organisms, such as Proteus, Staphylococcus albus and rarely members of the colon group of bacteria, ammonia will be formed. Because of alkalinization and ammoniation, a calculus which develops in this case will probably be composed of apatite and calcium magnesium ammonium phosphate; the latter occurs at a pH of 7.1 when the calcium to phosphate ratio in the urine is below the normal mean, and is also known as triple phosphate or struvite [35, 36, 40, 77]. It is readily apparent that a calculus consisting of layers of these different crystalline materials can be produced if conditions under which calculi are formed in the urine vary.

The other component of all urinary calculi is organic matrix. It is apparently composed of constant amounts of mucoprotein and mucopolysaccharide, and is evenly distributed throughout a calculus [19]. As will be pointed out below, the role of matrix in calculus formation has received

much debate in the past few years.

Basic Mechanisms of Urinary Calculus Formation

The mechanisms underlying the formation of a urinary calculus remain essentially undefined. Current thought in this area has been reviewed by Boyce and King [17], Howard [51], Holt [50], Flocks and Bush [40], Fleisch [39], and many others [10, 41, 43, 69, 72, 77, 89].

Many investigators in this area have held the view that organic matrix is required as a framework for calculus formation, while crystal deposition appears to be a secondary phenomenon. Evidence for this was given by the observation that even though concretions of matrix material with little inorganic salt content do occur, the converse is not true [12, 17]. Fleisch [39] pointed out that if no matrix is formed, no calculus can build up, the maximum mineral deposit then being well known "urinary sand".

Boyce and co-workers [17, 18, 19] have suggested that the matrix is formed from the aggregation and molecular reorientation of uromucoid, a mucoprotein-mucopolysaccharide conjugate. Uromucoid is the largest single component of the normally excreted urinary bicolloids, and notably is one of the bicolloids which is markedly increased in patients with urinary calculus disease [14, 15, 16]. In a normal state, it is believed that there is some binding of calcium and phosphorus by uromucoid molecules, but little tendency for the molecules to aggregate [17]. Accordingly, some factor would have to alter the binding capacity of uromucoid molecules, so permitting molecular aggregation and orientation to form the structural characteristics of the calculus matrix [17]. The oriented molecules would then act as templates or epitactic stimuli for apatite or other crystal formation depending on chemical conditions in the urine [17].

The origin of uromucoid remains unknown, however. Because of the high molecular weight of its constituents, Boyce and King [17] have suggested that it is of urinary epithelial origin, either from the renal tubules or the transitional epithelium. The hypothesis that the mucoprotein and mucopolysaccharide moieties from the reabsorption of bone matrix are excreted in the urine and reform under the proper ambient conditions in the urine

into uromucoid or a similar substance remains to be substantiated [50, 87]. This mechanism could explain the origin of the matrix in urinary calculi attributed to excessive bone reabsorption. Comparison of the urinary calcium excretion rates of idiopathic calculus formers with healthy non-calculus forming individuals has indicated that under all dietary regimens employed, 24-hour calcium excretions of stone formers exceeded that of controls [13, 17, 60, 64, 88]. Accordingly it has been suggested that hypercalciuria *per se* should be considered a possible stimulus leading to the increased production of uromucoid [14, 40]. It is of interest to note that some of the calculus-formers whose urinary calcium excretion was reduced by diet still formed stones. These stones were described as non-opaque, pure matrix-material stones which contained no calcium.

How hypercalciuria might stimulate the production of uromucoid in the urinary tract is a question to be answered. To confuse the issue, it has been repeatedly pointed out that prolonged hypercalciuria is not always associated with urinary calculus formation [2, 49, 67, 69, 77]. Boyce and Garvey [12] found evidence that an organic matrix may form if the urinary tract epithelium is irritated by precipitated crystalloids. This possible irritative mechanism might also explain the origin of the matrix in the calculi which have been attributed primarily to infection of the urinary tract. In the case of infection, the bacterial and epithelial debris produced by the infection might actually act as the nuclei initiating stone formation [40].

Finally, it has been postulated that uromucoid might be excreted by the kidneys as the result of abnormalities, which have apparently been seen histologically in the renal connective tissue matrix [3]. The possibility that increased calcium transport through the kidneys might produce histologic changes has doubtlessly been considered. A possible relationship between uromucoid production and physiological "stress" has been suggested [4].

Research has, however, led other investigators to believe that organic matrix is not a crucial element for urinary calculus formation, but rather an incidental inclusion in calculi. In a number of experiments, Vermeulen and co-workers [61, 93, 94] have induced the crystalline deposition of

calculus minerals on a wire loop placed in a great variety of modified urine media. Their artificial calculi often assumed many of the structural characteristics of authentic calculi. This was found to depend on the curious phenomenon of "habit modification", or the influence which other constituents of the urine had on the growth and reworking of the calcium phosphate crystalline mass. Surprisingly, the artificial calculi also contained a matrix-like component. Their experiments also demonstrated that the matrix arises by incorporation of non-dializable urinary constituents into the developing concretion, for when a medium of urine ultrafiltrate was used in place of whole urine, no such matrix component was present. These observations were interpreted as evidence that urinary calculus formation is a crystallization phenomenon and that organic matrix is a nonessential component resulting from protein adsorption onto crystalline surfaces, an occurrence well known to crystallographers. It was suggested that matrix may, however, act by modifying crystal habit and also serve as a barrier to dissolution of a developing calculus.

An adequate explanation for the initiation of urinary calculus formation has also not been given. It has been suggested that the stimulation of uromucoid agglomeration and molecular orientation might depend on the presence of a suitable nidus, or nucleus, such as an agglomeration of calcium phosphate crystals, desquamated urinary tract epithelium, bacteria, or some mixtures of these entities [12, 40, 87]. The hypothesis that urinary calculi can originate as microscopic calcific deposits in the renal parenchyma is supported by animal experimentation and the finding of such deposits, especially in patients with hypercalciuria and proven urinary calculus formation [2, 22, 78, 93]. Animal experiments have also indicated the possible significance of an inadequate dietary intake of vitamin A in producing keratinization and excessive desquamation of urinary epithelium, which can then serve as a nidus for calculus formation [25, 32, 40, 46]. This might explain the unusually high incidence of urinary calculus disease in the citrus areas of Florida and California, for citrus fruits are

high in alkaline ash, and low in protein and vitamin A [41].

Factors Influencing Urinary Calculus Formation

Since the mechanisms underlying the formation of a urinary calculus are not understood, the reasons for the known or postulated effectiveness of the various preventive measures to be discussed below can often not be adequately explained. The use of such measures has been derived from the recognition of the many factors which influence urinary calculus formation. Pertinent to considerations of urinary calculus formation in space are various factors concerned with the urinary output of the products of bone reabsorption, the solubility of calculus crystalloids in the urine, the excretion of uromucoid in the urine, the solubility of uromucoid in the urine, and the deposition of crystalloids in the calculus matrix. Other factors which bear mentioning are urine stasis and foreign bodies. It will become apparent that many of these factors can be implicated in more than one way in urinary calculus formation.

The high incidence of urinary calculus formation associated with recumbency is well documented [40, 53, 59, 76]. It must be pointed out, however, that urologists generally attribute this to some renal complication attendant on recumbency, such as urinary infection, a congenital anomaly of the drainage system or perhaps drug-induced injury of the kidney [11]. The authors quoted above were unable to differentiate clearly between urinary tract infection, and no attempt was made to look into the use of potentially nephrotoxic drugs, such as streptomycin, which were administered to a number of the patients studied [11]. Presumably, an excessive excretion of reabsorbed calcium and phosphate, and possibly bone matrix breakdown products, could still initiate and support calculus growth in the normal urinary tract of a recumbent individual. Any contribution which urine stasis and sedimentation of precipitates makes to the formation of a urinary calculus in a recumbent individual would, of course, not occur in space. However, although it must for the present be assumed that excessive bone reabsorption associated with weightlessness will be conducive to urinary calculus formation, the above and other considerations in this

chapter indicate that in the absence of other contributing factors, the risk of urinary calculus disease from bone reabsorption per se in space will be extremely low.

Disorders which cause excess urinary calcium excretion must be taken into consideration here, for they would probably enhance any calculus-forming tendency predicted for the weightless state. Particular emphasis is placed on screening out potential astronauts who have idiopathic hypercalciuria.

Dietary factors which affect the amount of calcium excreted in the urine must be considered. There is no evidence that a high oral calcium intake has any significant effect on the urinary calcium of normal human beings [17]. On the other hand, it appears that in order to produce a significant lowering of the urinary calcium output, dietary and even therapeutic measures would have to be so rigorous that they would be impractical in space [17, 50, 65]. The fact that the intestinal absorption of calcium and the amount of it subsequently excreted in the urine is directly influenced by the dietary level of vitamin D should be remembered in selecting the diet of an astronaut [17]. It might also be necessary to take into account the amount of vitamin D production in the astronaut due to his contact with ultraviolet light in his space environment. Interestingly, animal experiments have shown that vitamin A will counteract the hypercalciuric effects of hypervitaminosis D, so that an optimum level of vitamin A in the diet of an astronaut should also be assured [24].

The urine of normal people is often, although not always, supersaturated to a minor degree with calculus-forming salts. Various factors, such as ion concentration, pH, complexors, solubilizors and crystallization inhibitors, fortunately make degrees of supersaturation in urine much more than if these salts were dissolved in water [39]. Precipitation probably does not occur due to the fact that the ion concentration required to start forming first crystals is much higher than the concentration necessary for already existing crystals to grow further [39].

The concentrating effect of a low urine output tends to promote crystallization [36]. Inadequate fluid intake, and hence an inadequate urine

production, has been implicated as a cause of the seemingly high incidence of urinary calculi in individuals exposed to high environmental temperatures during the summer months [21, 75]. The high incidence of urinary calculus observed in flying personnel has also been attributed to dehydration, exposure to high environmental temperatures and voluntary restricted fluid intake [55]. However, this conclusion may be invalid since the study and control populations were, respectively, high and low incidence groups by virtue of their ages [50].

It has been well demonstrated that the pH of the urine is an important factor affecting crystallization [33, 36, 69, 77, 82]. From *in vitro* studies of the various factors which influence the solubility of calcium phosphate, Elliot and co-workers [33, 36] concluded that average urine specimens which have a pH consistently over 6.6 will be saturated with calcium unless the urinary calcium output is less than 50 mg per 24 hours. This calcium output value is approximately one-quarter to one-third of the 24-hour output value of normal individuals [13]. Based on similar studies by Meyer [68], it has been stated that calcium phosphate will remain dissolved only as long as the pH of the urine is 5.6 or lower [87]. This "critical" pH corresponds to maximum average 24 hour urinary calcium output values of approximately 525 and 825 mg (assuming a 24 hour urinary output of 1500 ml) in the two urine specimens studied by Elliot and co-workers [36]. Moreover, for normal urine volumes, this solubility-pH relationship of calcium phosphate is such that at a pH of 6, the calcium phosphate of the urine is at least two times, and at a pH of 7, eight times supersaturated. The contributions to calculus formation of a diet-induced alkalinization of the urine and of infections of the urinary tract by urea-splitting organisms which alkalinize the urine are readily apparent, the latter having been well substantiated clinically [32, 40, 77].

Since urine is normally often supersaturated with calculus-forming crystalloids, numerous investigators have searched for excreted substances which could be responsible for keeping these calculus-forming salts in solution. Butt [21] suggested that protective colloids are present in the urine, and that some derangement in these colloids was responsible for calculus formation. His hypothesis has not been proven, however [16, 37, 95]

A great deal of interest has been focused on the possible solubilizing role of citric acid in the urine. Citric acid chelates, or binds calcium ions to form a soluble complex [44]. The high incidence of urinary calculi in patients being administered the carbonic anhydrase inhibiting drug, acetazolamide, has been attributed to a concomitant decrease in the concentration of citric acid in the urine [63]. However, it is pointed out that the concentrations of many other substances in the urine change on administration of this drug. The low urinary citric acid levels which have been found in patients who are chronic calculus formers have been attributed to impaired renal function or the utilization of citric acid by organisms infecting the urinary tract secondary to the calculus disease [26, 48, 54, 64, 69, 85]. Experiments indicate that urinary citric acid excretion fails to be increased by a diet-induced increase in urinary calcium excretion [64]. Thus, even if urinary citric acid is important in preventing calculus formation, a possible increase in its excretion to compensate for a urinary hyperexcretion of calcium would appear to be inadequate. If a therapeutic increase in urinary citric acid excretion is contemplated, it is important to note that ingested citric acid (1.5 to 2.5 percent of ingested citric acid given in doses of 2 to 20 gm) has little if any effect on the level of citric acid in the urine [56, 83]. Moreover, even though food and ingested alkalis such as sodium bicarbonate increase urinary citric acid excretion, they would not be useful since the resulting alkalinization of the urine would markedly decrease the solubility of the calculus crystalloids in the urine [9, 64, 105]. Finally, it is noted that recent evidence suggests that citrate may play a less important part in maintaining certain salts in solution than has been thought hitherto [21, 95, 106].

As mentioned previously, factors concerned with the excretion of a calculus matrix-forming substance in the urine are inadequately defined. It has been suggested that the matrix might form from the excreted mucopolysaccharide and mucoprotein products of bone reabsorption, or mainly from uromucoid, the increased production of which might be stimulated by hypercalciuria per se, by irritation of the urinary tract by precipitated

crystalloids or infection of the urinary tract, by pathological abnormalities in the renal connective tissue, or by physiological "stress" (3, 4, 12, 40, 51, 87). The only therapeutic measure directed specifically at the production of matrix material was justified by the finding that increased amounts of uromucoid are released in the urine due to a disorder in the renal connective tissue (3, 17). Anti-inflammatory agents, such as aspirin, corticosteroids, corticotropin, and phenylbutazone, were given to chronic calculus-forming patients. The potential usefulness of such a measure has not been established, however. Moreover, there is no evidence that such a connective tissue change, which could be treated with such drugs, accompanies hypercalciuria in "normal individuals".

The factors which affect the solubility of uromucoid in the urine also remain undefined. Undoubtedly the urine volume produced will influence the solubility of uromucoid as well as crystalline calculus components.

Intense interest has been focused recently on factors which appear to influence the deposition of crystalloids in the calculus matrix. Based on the fact that bone and renal calculi both consist of crystalline and matrix phases, it has been speculated that the identification of urine constituents which affect crystal deposition in bone might afford added insight into the genesis and growth of calculi within the urinary tract (89). Despite the presence of similar calcium and phosphorus concentrations in urine specimens, it has been found that the urine from most patients with renal calculus disease mineralizes, in vitro, a test substance of hypertrophic bone cartilage from rachitic rats, whereas urine from most normal subjects does not (51, 70, 89, 90). Studies designed to identify constituents which might account for this lack of matrix mineralization by urines of "normal" individuals have demonstrated that there are a variety of dialysable substances in the urine which, if present in adequate concentrations, will prevent the mineralization of rachitic cartilage (7, 51, 70, 89). Although it is thought likely that there are as yet unidentified urine substances which are of importance in determining mineralizing propensity, the inhibiting effects of trace metals such as zinc, manganese, cadmium, cobalt, chromium, and vanadium have been proven (6, 7, 89). The most

potent of these inhibitors are zinc and manganese [89]. Magnesium has been found to enhance the inhibitory effect of the trace metals and also alone, in a sufficient concentration, to be inhibitory [70, 89]. It is thought that these elements inhibit mineralization by blocking matrix or crystal templates which are necessary for calcium phosphate crystal formation [6, 39, 89].

Possibly acting in a similar fashion to the trace metals, pyrophosphate has been found to inhibit mineralization of rachitic cartilage and to markedly increase the solubility of calcium phosphate in solution [39, 89]. It has been demonstrated that urinary pyrophosphate is diminished in many patients who are chronic calculus formers [39]. To test the possible therapeutic benefits which might be derived by increasing the concentration of this compound in the urine, several investigators have been administering oral sodium or potassium orthophosphate, which is excreted in the urine as pyrophosphate, to chronic calculus-forming patients [6, 51, 79, 89]. This effect is apparently accompanied by a fall in calcium excretion and an increase in citrate excretion, both of which might also be expected to reduce the tendency for stone formation to occur [79]. Although there is insufficient confirmatory data at the present, the results of such treatment have reportedly been encouraging, for apparently no patient given orthophosphate sufficient to ensure consistent excretion of a non-mineralizing urine has formed new urinary calculi or has increased the size of pre-existing calculi. The effect of pyrophosphate on the urinary pH which, as previously stated, exerts a profound effect on calcium phosphate solubility has not been stated [6].

It has not been postulated whether pyrophosphate or the trace metals mentioned above could play a role in preventing uromucoid agglomeration to form the matrix of a urinary calculus. Further research in this area will, no doubt, give added insight into the mechanisms involved in urinary calculus formation, and possibly substantiate the effective clinical usage of other non-toxic inhibitors. Such research is certainly pertinent to considerations of the possible requirements for therapeutic measures directed at the prevention of urinary calculus in space. Since there is now good experimental evidence that chronic calculus-forming patients, and possibly even individuals

with a calculus-forming tendency have an absence of factors concerned with protection from matrix mineralization, a test of astronaut candidate urines for mineralizing propensity might be considered, if only for experimental purposes.

Other factors which influence urinary calculus formation and should be mentioned here are urinary stasis and the presence of foreign bodies in the urinary tract. It is thought that urinary stasis promotes the precipitation of calculus crystalloids by allowing crystalloid concentrations in certain portions of the renal collecting system to rise above critical levels [40]. Sedimentation of precipitates in various parts of a normal urinary tract should not occur in a weightless environment, however, so that weightlessness would counteract this calculus forming effect of urinary stasis. The well known fact that static urine is more likely to become infected is another complicating factor. Although originally thought otherwise, operational experience in space is proving that another cause of urinary stasis - change in the sensation of urgency - is not a problem in the weightless environment [97]. It is probable that earlier reported difficulties in voiding in the weightless environment were psychogenic in origin, due primarily to the demand placed on subjects, relatively unfamiliar with the sensations of weightlessness, to initiate micturition within a short period of time in a small aircraft cabin.

Foreign bodies in the urinary tract, such as a urinary catheter, apparently stimulate urinary calculus formation not only by acting as a nidus for crystalloid deposition but also by promoting infection of the urinary tract [40].

Clinical Manifestations

The optimum use of measures directed at adequately controlling the various factors which could be responsible for urinary calculus formation in space would minimize not only the likelihood of urinary calculus in space, but also the rate at which a once initiated urinary calculus grows. As a result, the clinical manifestations of a urinary calculus might appear after an astronaut has been exposed to the weightless environment for many months

or even years.

Some indication of the time required for a urinary calculus to form and grow to a size which results in clinical manifestations can be derived from studies which have noted the date of immobilization and the date of appearance of signs and symptoms of urinary calculus in patients immobilized for prolonged periods of time due to orthopedic injuries. In one study, 15 out of 800 such patients developed urinary calculi [53]. The shortest duration for the appearance of symptoms was 74 days, the longest 1200 days, and the average 362 days. A similar study reported a shortest duration of 76 days, a longest of 622 days, and an average of 276 days [38]. In reviewing this data, it is important to note that the conditions under which calculi form in patients do not simulate conditions in space for, as pointed out above, urologists generally attribute calculus formation in recumbent patients to some renal complication attendant on recumbency, such as urinary infection, a congenital anomaly of the drainage system or perhaps drug-induced injury of the kidney. Furthermore, a calculus of a size which is sufficient to produce clinical manifestations may be present in the urinary tract for days to months, or even years before becoming clinically evident.

The major clinical manifestations produced by a urinary calculus are the pain which the calculus causes as it passes down a ureter, the secondary changes brought about by the irritation of the urinary tract by the calculus, and the manifestations associated with accompanying infection [40, 47, 82].

Pain is usually associated with the passage of the calculus down the ureter. It is classically described as intermittent or colicy (so-called ureteral colic), excruciating and agonizing, and is usually prostrating. Each attack of colic lasts a few minutes, and after a variable period of usually a few minutes, is repeated. Quite often, however, the pain produced by a urinary calculus is quite insidious, depending on the size, shape and position of the calculus. Occasionally, it might imitate other abdominal conditions, such as appendicitis. A calculus in the renal collecting system is frequently clinically silent for a prolonged period of time. Once in the

kidney pelvis, however, it usually produces almost immediate symptoms, particularly if it is of such a size to act as a proverbial ball in a funnel, blocking drainage from the kidney [99].

Ureteral colic is due either to distension and hyperactive peristaltic waves resulting from an obstructing calculus, or to vasospasm in the ureteral wall adjacent to the jagged surface of the calculus [57]. It is not really perceived as being along the course of the ureter, but in regions supplied by spinal segments T_{11}, T_{12}, L_1 and L_2 (ilioinguinal, iliohypogastric and genitofemoral nerves) [57]. Depending on the location of the calculus in the ureter, this "referred pain" may then arise in the costovertebral angle on the involved side and radiate around the loin anteriorly and caudally to the respective inguinal or medial thigh regions and testis, or even down into the penis. Ureteral colic often begins and is most severe in the costovertebral angle and flank and moves downwards as the calculus passes the ureter.

If muscular spasm accompanies ureteral colic, the muscles supplied by the spinal segments (T_{11} to L_2) will be involved [46]. These muscles include the lower portions of the external abdominal oblique, internal abdominal oblique, and transverse abdominal muscles and the cremaster muscles [57]. Nausea, vomiting, profuse perspiration and syncope may accompany severe ureteral colic [82]. Between attacks of colic, afflicted individuals often complain of soreness and tenderness, particularly in the renal and lower anterior abdominal areas [82].

The most frequently observed secondary changes brought about by the irritation of the urinary tract by a calculus are hematuria and dysuria. Hematuria is common, resulting from contact of a calculus with the lining of the ureter. Red blood cells can be found, intermittently or continuously, in the urine of persons with a urinary tract calculus.

Dysuria, or painful urination can be caused by reflex reaction in the bladder due to ureteral activity from a calculus in the terminal ureter by the calculus irritating the bladder wall, or by secondary infection [47].

Longstanding ureteral obstruction often leads to infection above the site of obstruction. The symptoms and signs are those of pyelonephritis, which

is characterized by chills and fever and other systemic toxic manifestations, loin and costovertebral angle aching and tenderness and renal enlargement on the affected side, and pyuria. A low grade infection often persists after an acute attack subsides, especially if a partially-obstructing calculus is present. Such an infection can be extremely debilitating [47].

Diagnosis

An afflicted astronaut's history and physical examination should yield the characteristic clinical findings outlined above. If his urine can be examined in space during a period of ureteral colic, blood will probably be found, if not masked by infection. It is important to note that red blood cells may be present in the urine in the absence of or for some time prior to the onset of symptoms of calculus. This gives good reason for serial urine analyses if a urinary calculus is suspected.

Almost all symptomatic urinary calculi should be visualized by simple x-ray techniques, if possible in space [47]. X-rays of the abdomen, including the urinary tract, prior to missions in space will assist in distinguishing a calculus from other abdominal calcium-containing structures, such as phleboliths and calcified mesenteric lymph nodes, as well as ruling out the existence of a urinary calculus. If ever possible in space, intravenous pyelography could be of great value in confirming the location of densities seen on the plain film, and in assessing the degree of urinary obstruction.

Prevention

The various factors which could influence the formation of a urinary calculus in space have been discussed previously. It is at these factors that optimum non-therapeutic and possibly various therapeutic measures must be directed. It is assumed that appropriate investigative procedures in astronaut candidates will rule out any tendency to urinary calculus formation. The fact that urinary calculus disease has a familial incidence should be kept in mind while taking a candidate's medical history. A normal urinary tract must be ensured by searching for congenital anomalies and infection of the urinary tract, and by assuring that there is no difficulty voiding or a

calculus already present in the urinary tract. Calcium metabolism must be studied intensively, especially with serum calcium and phosphorus determinations, and measurements of 24 hour urinary calcium output while the dietary calcium intake is controlled. As pointed out above, testing of the mineralizing propensity of the urine might be found feasible in all or certain cases in the future.

Hopefully, future studies will determine to what extent the intermittent use of selected exercises and other measures in space will simulate normal weightbearing stresses on the skeletal system. At the present time, it appears that the most appropriate exercises which an astronaut can undertake in space are of the isometric or dynamic tension type. It is assumed that an astronaut will be in optimal physical condition prior to a mission in space and that such exercises will maintain this level of physical condition, and hence prevent reabsorption of bone at least from reduced muscular activity in space. One question which requires answering by research is whether an individual with a higher than average urinary calcium output would have a greater than normal urine calcium excretion when immobilized or placed in a weightless environment [6].

To produce a significant lowering of a urinary calcium output by restricting an astronaut's dietary calcium intake, dietary measures would have to be so rigorous that they would be impractical. Since the dietary level of vitamin D directly influences the intestinal absorption of calcium, the daily intake of this vitamin in the diet should not exceed normal recommended values. It might also be necessary to restrict the amount of vitamin D production in an astronaut by controlling his exposure to ultraviolet light.

The urinary output should be maintained continuously at a reasonable level with an adequate oral fluid intake. A urinary output of at least 2000 ml per 24 hours has been recommended [87]. This would require a daily fluid intake of at least 3000 ml per 24 hours or more, depending on body fluid losses from other causes, such as perspiration [25, 87].

In order to maintain the urinary pH at as low a level as possible in space, the dietary intake of urine-alkalinizing foods should be kept to a minimum and urine-acidifying foods to a maximum, while still maintaining

adequate nutrition and food palatability. The rigorous treatment of urinary tract infections, which are usually caused by urine-alkalinizing organisms, is emphasized.

The role of citric acid in maintaining calculus salts in solution is controversial. It is again pointed out that even though certain alkaline foods increase urinary citric acid excretion, their tendency to alkalinize the urine would have a detrimental effect on the solubility of the calculus crystalloids, so contraindicating their use in an astronaut's diet.

At the present time, there appears to be no non-therapeutic measures which can be directed at inhibiting the excretion of calculus matrix-forming substances in the urine, other than the measures directed at preventing bone reabsorption in the weightless environment.

The maintenance of the urinary output at a reasonable level will help to maintain uromucoid in solution. It is pointed out that an adequate dietary intake of vitamin A must be assured to prevent the formation of the calculus nidus presumably made up of cells which are desquamated from the lining of the urinary tract secondary to a deficiency of this vitamin [87].

Further studies identifying constituents in the urine which might inhibit the deposition of crystalloids in the calculus matrix might give reason for increasing these constituents in the diet. As mentioned previously, an increased urinary concentration of trace metals, such as zinc and manganese, may not only decrease the mineralizing propensity of the urine but also inhibit calculus formation. Magnesium apparently enhances the inhibitory effect of the trace metals. These metals are non-toxic when ingested in the amounts considered as possibly being adequate for prevention of calculus formation [44].

Urinary voiding should be scheduled if there is any possibility of a diminution in the sensation of urgency in space, so minimizing the possibility of urinary stasis contributing to calculus formation. It is noted that if a urinal sealed to the skin is to be used in space, this apparatus should not produce an elevation of intravesical pressure above that required for normal micturition on earth in order to accomplish a complete voiding, which should leave a residual urine of less than 12 ml [31].

The use of an indwelling catheter should be avoided if possible in space.

If an indwelling or any other form of catheterization is required, however, an appropriate bacteriostatic agent, such as sulfadimethoxine, should be administered for a suitable duration to prevent secondary infection. If an indwelling catheter is used, the bladder should be irrigated with an appropriate solution, such as normal saline, and the catheter replaced periodically.

Since most therapeutic measures produce disagreeable side-effects, their use is indicated only if it appears that the non-therapeutic measures mentioned above could possibly fail to provide adequate protection of an astronaut from urinary calculus in space. One or more therapeutic measures might be attempted.

In the future, it might be possible to administer drugs which have an inhibiting effect on the bone reabsorption due to weightlessness. The drugs of current interest in this respect are derivatives of gonadal hormones [74, 100, 102]. It is noted that hormonal side-effects might be a problem with prolonged usage of such agents. Further research in this area is indicated, however.

Orally administered sodium phytate diminishes calcium absorption in the intestine by forming an insoluble complex with calcium in the intestinal lumen [40, 45, 87]. Cellulose phosphate has also been found to exert the same effect [29]. If the dosages of these compounds are adequate and the dietary calcium intake is minimized, it is conceivable that the hypercalciuria resulting from bone reabsorption in space could be effectively controlled. However, their use in space might be contraindicated because they have a tendency to produce a painless diarrhea [87]. Moreover, these compounds, especially phytate, increase the urinary phosphorus excretion, with the result that a favorable situation for calculus formation could possibly occur under certain conditions [29, 87].

Just as a decrease in the urinary excretion of calcium diminishes the formation of calcium-containing calculi, so also a decrease in the excretion of phosphate diminishes the formation of calcium phosphate calculi [87]. Shorr devised a low phosphate diet supplemented by aluminum-containing drugs in the form of either basic aluminum carbonate gel or aluminum

hydroxide gel. The aluminum impairs phosphate absorption in the intestine by forming the insoluble compound, aluminum phosphate, in the intestinal lumen. The Shorr regimen has been highly effective in the prophylactic treatment of chronic calculus formers [65, 66, 86, 87]. It might even be effective in maintaining a non-precipitating level of calcium phosphate in the urine in space, if excessive bone reabsorption should occur. However, the gel is constipating, and the diet tasteless and also constipating [65, 87]. Accordingly, the prolonged use of the Shorr regimen in space is not recommended.

Different orally administered substances have been used to increase the acidity of the urine, especially ammonium chloride, ammonium nitrate and sodium acid phosphate [23, 27, 87]. Menthenamine mandelate is currently being favored by most urologists and might be considered as being appropriate for use in space if acidification of the urine by drugs is indicated [73]. This drug also acts as a urinary antiseptic, and so could also reduce or eliminate the contribution of a urinary tract infection to stone formation [5]. It is almost without side-effects in contrast to the other drugs mentioned above [5].

Even if increased levels of urinary citric acid might have a solubilizing effect on urinary crystalloids, it must be remembered that ingested citric acid has little if any predictable effect on the level of citric acid in the urine. Moreover, even though ingested alkalis such as sodium bicarbonate increase urinary citric acid excretion, their tendency to alkalinize the urine would have a detrimental effect on the solubility of calculus crystalloids, so contraindicating their use.

The importance of adequately treating any infection in the urinary tract in space cannot be overemphasized. The marked influence which such an infection can have on stone formation, especially if the infection is caused by urea-splitting organisms, is well known.

The possibility of orally administered trace and other metals effectively preventing urinary calculus formation has been mentioned above. These metals would undoubtedly be administered in small quantities, and so could be added to the food. The toxicology of such metals should be thoroughly assessed before such a measure could be considered, however.

The encouraging results with orally administered orthophosphate in inhibiting calculus formation in chronic calculus-forming patients may prove this agent worthwhile for use in preventing urinary calculus in space. In "therapeutic" doses, the drug has apparently no side-effects other than occasionally producing diarrhea [6].

Treatment

In the foreseeable future, a urinary calculus which causes signs and symptoms in space will have to be managed conservatively either until it is passed spontaneously or until manipulative or surgical removal of it can be attempted back on Earth. Fortunately, upwards about 80 percent of all urinary calculi are passed spontaneously [80, 81, 98].

Ureteral colic, irrespective of type of stimulus causing it, can be alleviated to some degree by morphine, meperidine, or other central nervous system analgesic drugs [57]. If the colic is primarily due to vasospasm, its prompt relief might be achieved with the use of vasodilating drugs, which act either directly upon blood vessels (e.g., sodium nitrite and papaverine) or by blocking transmission of nerve impulses through sympathetic ganglia (e.g., a tetraethylammonium compound) [57].

An adequate urinary output in an astronaut suffering from urinary calculus should be maintained by forcing his oral intake of fluids or, if necessary, by giving him fluids intravenously. A urine output of at least 3000 ml per 24 hours should be assured.

A urinary bacteriostatic agent, such as sulfadimethoxine, should be administered to an astronaut from the time that clinical manifestations of a urinary calculus appear. An infection might still develop above a partially or completely obstructed site in a ureter, in which case the administration of a suitable antimicrobial, such as nitrofurantoin or chloramphenicol, is indicated.

A sedative, such as sodium phenobarbital might be required. Active movement of the astronaut should be encouraged, however.

There appear to be no orally or parenterally administered agents which are effective in dissolving a urinary calculus [87].

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CHAPTER 10

MEDICAL IMPLICATIONS OF CARDIOVASCULAR ADAPTATIONS TO WEIGHTLESSNESS

Even during prolonged space missions, optimum physical fitness, and hence the capacity of the cardiovascular system to respond adequately to a given work load in space, should be maintained by the combined effects of routine physical activity and an appropriate exercise regimen. It is generally thought, however, that certain cardiovascular adaptations to the weightless space environment will still occur. The question arises as to whether such adaptations could affect the likelihood of occurrence or severity of medical problems arising from certain hazards of space operations, especially if a medical problem should occur in the period immediately after an astronaut returns to a gravity environment.

In this chapter the literature is examined in an attempt to determine what cardiovascular adaptations to weightlessness do occur, the medical implications of these adaptations, and finally the appropriate measures which can be taken to prevent adverse effects of these adaptations on astronauts. This is not an exhaustive review of the physiology of weightlessness. Further information on more specific aspects of this area can be obtained from a number of recent reviews which will be cited.

Cardiovascular Adaptations

At the present time, cardiovascular adaptations to weightlessness can only be inferred from data obtained in a great number of ground-based experiments which were intended to simulate the effects of weightlessness on the cardiovascular system, and from in-flight and post-flight observations made on those astronauts who have been exposed to weightlessness for up to a few days in duration. By means of bed rest and water immersion, ground-based experiments have attempted to minimize the effect of intravascular hydrostatic pressures due to the force of gravity. Most of the work in this area has been conducted by Birkhead and co-workers (14, 16), Graveline and co-workers (46, 49, 50), Miller, Stevens and co-workers (75,

77, 78, 79, 94, 97), Vogt, Vallbona and co-workers (107, 111, 116, 117, 118, 119, 121) and others (69, 99). This area has been reviewed by Lamb (59, 60, 61), McCally and Graveline (71) and others (1, 43, 50, 70, 108, 128). The extrapolation to operational space conditions of cardiovascular findings in individuals exposed to prolonged bed rest or complete water immersion must be guarded, however, for these conditions do not completely eliminate the effects of gravity on the cardiovascular system. Moreover, even though physical and cardiovascular "fitness" has been maintained under such conditions with periodic exercises, the type and degree of routine physical activity, and in turn the cardiovascular dynamics of astronauts in the spacious cabins of spacecraft to be used for prolonged missions has not been, and probably can not be, simulated.

Most observations of cardiovascular responses of astronauts exposed to weightlessness have been made in the immediate post-flight period. Cardiovascular data for all American missions (up to 14 days) and Russian missions (up to 5 days) have been reported (8, 12, 39, 83, 87, 88, 91). Findings must again be viewed with caution. Restriction, limited physical activity during missions, and post-flight fatigue are factors which have effects on the cardiovascular system similar to those which have been predicted for weightlessness. Post-flight data might on occasion have also reflected the effects of dehydration, and physiologic events which might be associated with the vague feeling of "let-down" often experienced after a prolonged emotionally and physically stressful event.

During up to 42 days of bed rest, 7 days of complete water immersion and 14 days of weightlessness, recordings of systolic and diastolic pressures, pulse-rate, heart sounds, and electrical activity of the heart have remained within normal limits, even in the face of marked physical inactivity which led to diminished exercise tolerance (8, 12, 14, 28, 49, 50, 75, 77, 79, 83, 87, 88, 97, 107, 118). Therefore it appears likely that prolonged weightlessness should not alter cardiac function if cardiac work capacity is maintained. This is consistent with the conclusion drawn from application of sound biophysical principles to the circulation,

in that the hydrostatic factor (ρgh) does not affect the driving forces of the circulation directly and inertial factors in the circulation would not be affected at all by weightlessness [24, 71].

It is generally believed that a cardiovascular adaptation to prolonged weightlessness is lowering of blood volume, with decreases of both the plasma and red cell fractions of the blood. In conditions of bed rest and complete water immersion, healthy subjects have consistently demonstrated an acute fall in plasma volume, accompanied by a diuresis and a loss of weight [28, 49, 50, 61, 69, 75, 77, 79, 85, 94, 97, 119, 120, 121]. Most of this initial contraction of blood volume has occurred during the first 24 to 48 hours of exposure to these conditions [61]. The maximum decrease in plasma volume observed has usually been in the range of 500 ml, or about 10 percent of the body weight [49, 75, 77, 80, 94, 97]. Although decrease in blood plasma leads to hemoconcentration, prolonged bed rest studies have demonstrated that over a period of many days the hematocrit returns to normal values, presumably due primarily to suppression of red cell production [61, 75, 77]. Bed rest for 4 weeks has reportedly produced a decrease of over 700 ml in blood volume [61, 75, 77]. It should be pointed out, however, that in spite of the great amount of empirical evidence to the contrary, three well conducted bed rest studies of 14, 30 and 42 days in duration have yielded data indicating that after a typical initial decrease, blood volumes tended to return toward pre-exposure values [28, 67, 118].

Post-flight data on the command pilots and pilots of the 4 and 8 day Gemini missions indicated that the blood volume also decreases in the weightless environment [12]. A 7 to 15 percent decrease of blood volume occurred during these missions. The decrease in plasma volume was 4 to 13 percent. As compared to bed rest studies, the loss of red cell mass was accelerated, possibly due to one or more factors other than blood volume changes, including the atmosphere to which the astronauts were exposed [12]. It was also thought that a weight loss of usually 2 to 5 percent of body weight, recorded after these and all former space missions, might in part be due to this decrease of blood volume, especially since

weight loss did not correlate with mission duration, and pre-flight weights and plasma volumes were restored rapidly by fluid intake in the post-flight period [12, 124]. Immediately after the 14 day Gemini mission, however, the blood volumes of both astronauts were the same as those recorded pre-flight [12]. An increase of plasma volume had compensated for a decrease of red cell mass similar to that observed after the 4 and 8 day Gemini missions. It is clear that the results of the 14 day mission do not rule out the possibility that blood volume decreased during the early part of this mission. Interestingly, this data is supported by the few bed rest studies cited above.

A number of investigators have advanced reasonable explanations for the decrease of blood volume and the diuresis which occur during bed rest, complete water immersion and presumably on becoming weightless [5, 34, 35, 36, 51, 68, 70, 71, 110, 116, 124]. Negation of the gravitational component of intravascular hydrostatic pressures due to gravity leads to a redistribution of blood [90]. Sjöstrand [89] substantiated the earlier observations of Thompson [104], by finding that about 500 ml of the approximately 650 ml of blood pooled in the lower extremities of erect man shifted on tilt to the thorax. As well, total blood volume actually increases slightly for a short period of time when a normal ambulatory individual assumes the supine position [9, 17, 58, 64, 104, 105, 127]. This is presumably due to the reabsorption of fluid transudate, forced by gravity-activated intravascular hydrostatic pressures into the extravascular spaces of loosely bound tissues in the lower extremities and elsewhere. Gauer and co-workers [5, 6, 33, 34, 36, 37, 38, 53, 58] have shown that due to this redistribution of blood, central venous channels are distended. This leads to stimulation of central venous blood volume receptors, located mainly in the right atrium. Through reflex pathways, antidiuretic hormone production is inhibited. The resulting increase in plasma water excretion reestablishes normal central venous volume. Other responses to this shift in blood volume also occur, although to a much lesser degree. Due to one or more possible mechanisms involving venous and possibly arterial volume sensors, and probably osmoreceptors, aldosterone production is suppressed, leading to a natruresis [31, 32, 44, 45, 54, 70, 94, 102, 103].

Since this response is sluggish and highly variable, it appears that in this case the constancy of osmotic composition is sacrificed in favor of the constancy of blood volume (33, 54, 70, 80). Indirect evidence of a diuretic factor appearing in the blood plasma remains to be identified (3 Renal hemodynamics do not seem to be altered to a significant degree (20, 36, 70). Finally, experiments on normal individuals have shown that compensatory events opposite to those described above occur when central venous volume is lowered as a consequence of, for example, blood redistribution due to the force of gravity and measures which force or remove blood from the thorax, such as positive pressure breathing and the application of negative pressure to the lower half of the body (42, 44).

The question arises as to how much one or more factors other than simulated and actual weightlessness could have affected blood volume during bed rest and complete water immersion studies, and during the few space missions in which this parameter has been studied. For example, results from chair rest and confinement studies have shown that even though intravascular hydrostatic pressures due to gravity remained unaltered during these studies, subsequent physical inactivity is accompanied by a decrease in red cell mass and plasma volume (15, 62, 63, 65, 90). Since plasma volume decreases mostly during the first 48 hours of bed rest, and then changes little over a period of several weeks, it has been considered possible that physical inactivity might not enhance significantly the plasma volume contraction due to weightlessness per se (60). This possibility is supported by results of a few bed rest studies during which periodic exercise was performed (78, 112, 115, 117, 121). On the other hand, the decrease of red cell mass and further contraction of blood volume in most of the prolonged bed rest studies cited above might have been due in part to physical inactivity, for one might expect that blood volume would have been maintained by an increase in plasma volume, since homeostatic mechanisms restored the hematocrit to a normal level (124). This area does appear to require investigation.

A decrease in blood volume also accompanies body dehydration, which can be due either to inadequate fluid intake or to excessive loss of body water (60). The sensation of thirst can be markedly suppressed in

a stressful situation [52]. It is also well known that non-thermogenic sweating is increased in such a situation [124]. One wonders, therefore, if these factors existed to a significant degree during the critical terminal phases of space missions, and so accounted in part for the dehydration observed after all space flights to date and the decrease of blood volume recorded after the 4 and 8 day Gemini flights [12]. Sweating from heat loads experienced during re-entry and after landing might also have led to some dehydration [61]. Both physical and emotional stresses can suppress antidiuretic hormone production [61, 110]. Hence these too might have been factors producing dehydration, especially toward the end of space missions.

In conclusion, it is readily apparent that dynamic changes in the volume of blood, and in its plasma and red cell fractions while in the weightless environment, cannot be predicted with certainty at the present time. Definite answers in this area might only be obtained by further measurements on astronauts during space missions, with attempts to eliminate all factors other than weightlessness known to alter these parameters. Considerable evidence supports the view that blood redistribution in the weightless environment will lead to a decrease in blood volume, due initially to a decrease in plasma volume, and then to adjustments in both plasma volume and red cell mass as a normal hematocrit is gradually reestablished. On the other hand, there is evidence indicating that the blood volume could be diminished temporarily, possibly for only several days to a few weeks in duration. This rebound of blood volume, if it actually occurs, might be attributable to expansion of the venous circulation as peripheral venous tone, so important for preventing blood pooling in the gravity environment, relaxes as an adaptive response to weightlessness. On the other hand, the rebound of volume might be due to decreased sensitivity of blood volume receptors during chronic exposure to relatively high central venous pressure. This mechanism receives much off-on stimulation as a normal ambulatory individual moves about in the gravity environment, and like other reflex

mechanisms, may respond to chronic "on" stimulation by adaptation [86].

Other cardiovascular adaptations to weightlessness have been implied from observations made during passive upright tilt of bed rest and complete water immersion subjects, and post-flight astronauts. This is a provocative test of orthostatic tolerance. Since the individual is passively supported upright, it assesses the capacity of primarily cardiovascular mechanisms to compensate for intravascular hydrostatic pressure changes due to the force of gravity [113]. A minor reduction of orthostatic tolerance is accompanied by an excessive increase in heart rate, an excessive narrowing of pulse pressure and a fall in systemic arterial blood pressure while passively maintaining the erect posture [93]. Failure of cardiovascular compensation to gravity leads to the so-called vasodepressor reaction, the manifestations of which are presumably due to an overwhelming increase in parasympathetic nervous system activity [2, 59, 71, 92]. This reaction is characterized clinically by pallor, nausea, dimming of vision, sweating, "air-hunger" and eventually loss of consciousness, arising from an acute fall in systemic arterial blood pressure, occasioned by bradycardia and a decrease in peripheral vascular resistance [7, 30, 59].

Definite signs and symptoms of orthostatic intolerance have consistently appeared after as little as one week of bed rest and 6 to 12 hours of complete water immersion [14, 28, 46, 47, 48, 49, 51, 77, 101]. Orthostatic intolerance was observed after the 9 and 34 hour, one-man Mercury missions [12]. Abnormal tilt responses were also noted for periods of up to 50 hours after the 4, 8 and 14 day, two-man Gemini missions [12]. The 14 day Gemini pilot experienced a vasodepressor reaction during his first post-flight tilt; his responses to subsequent tilts were similar to those of the other Mercury and Gemini astronauts. Interestingly, the time for the return of the normal pre-flight response to tilt has not correlated with either the duration of space flights to date, or decreases in blood volume which occurred.

As discussed by Lamb [59, 60], McCally and Graveline [71], and Vogt [106] and summarized below, many complex physiologic events are thought to

maintain cardiovascular integrity in the upright position. Hence it has been difficult to determine with certainty what cardiovascular adaptations to simulated and actual weightlessness might have occurred to account for the decreased orthostatic tolerance that resulted from exposure to these conditions. According to the above named authors, cardiovascular reflex mechanisms increase heart rate on becoming upright, and augment adrenal epinephrine output to strengthen cardiac muscle contraction. Arteriolar tone is also increased in dependent parts of the body to maintain the required distribution of cardiac output to these parts. Venous pooling in the lower regions of the body is minimized to assure an adequate return of blood to the heart. This appears to be accomplished mainly by a reflex increase in venous tone, by the restricting effect of skeletal muscle tone on venous distension, by the pumping action of contracting leg muscles on the veins and by venous valve competence. Through mechanisms outlined above, blood volume must also be maintained in the face not only of gravitational pooling of blood, but also of transudation of protein-free fluid into the extravascular spaces of the lower extremities caused by excess intravascular over extravascular pressures, especially in loosely bound tissues [104, 116]. The tension created in tissues as fluid is forced into them would also serve to restrict venous distension.

There is no doubt that the decrease of blood volume and reabsorption of fluid transudate from tissues of the lower extremities during exposure to weightlessness would diminish orthostatic tolerance, since decrease of blood volume in a normal active individual from any cause, such as blood loss or dehydration, will result in a strain being placed on normal mechanisms required to maintain cardiovascular integrity in the upright position [3, 19, 52, 84, 99, 124]. The observations that there has been no correlation between the amount of blood volume decrease and the degree of orthostatic intolerance resulting from prolonged bed rest, and that post-flight Gemini astronauts demonstrated orthostatic intolerance for many hours after their blood volumes returned to pre-flight levels, suggest that cardiovascular adaptations to weightlessness other than decrease in blood volume contributed to this orthostatic intolerance [78, 94, 100, 126].

Since skeletal muscle loses tone, strength, work capacity, and mass when its activity is diminished for a period of time, the question arises as to whether smooth muscle in a blood vessel wall could undergo similar changes when it no longer plays a role in maintaining the wall tension required to compensate for the gravitational component of intravascular hydrostatic pressure. If so, this adaptive response would be expected to occur both in arterial vessels, especially arterioles, and in veins in dependent parts of the body, and thus predispose to orthostatic intolerance by failing to maintain normal distribution of cardiac output and by allowing excessive pooling of venous blood. This might well be a fruitful area for study.

It has been postulated that the mechanisms responsible for increasing arteriolar resistance and venous tone in the upright position become less responsive during prolonged exposure to weightlessness (42, 68, 71, 105, 109). Reflex vasoconstriction, as occurs on assuming an upright posture, is known to be mediated by the sympathetic nervous system, the vascular nerve endings of which release norepinephrine to cause vascular smooth muscle contraction (13, 28, 74, 122, 123). As shown by tilting normal active individuals to various angles, changes in the urinary excretion of norepinephrine correlate well with alterations in vasomotor activity (98). Hence various investigators have suggested that diminished responsiveness of vasoconstrictor mechanisms by weightlessness might be reflected by decrease of urinary norepinephrine excretion during upright tilt (43, 47, 105). Such was the case following complete immersion of subjects for 6 hours in one study, but not the case in the other similar study in this area (43, 105). Further investigation is therefore required to determine at what neuromuscular level vasoconstrictor mechanisms adapt to weightlessness.

A few other cardiovascular adaptations to weightlessness per se have been implicated as contributors to the decreased orthostatic tolerance after simulated and actual weightless exposures. Since the sympathetic nervous system is also presumed responsible for the cardioacceleration and the increase of adrenal epinephrine output associated with assuming upright posture, it has been suggested that these responses might be

diminished by weightlessness [106]. However, no evidence has been obtained in this area. Since tension exerted on veins by extravascular tissue is thought to play an important role in preventing venous pooling in the upright position, loss of fluid transudate from tissues of the lower extremities in the weightless environment might enhance venous pooling as well as loss of blood volume in the erect position, hence contributing, especially in the very immediate period after re-exposure to gravity, to orthostatic intolerance.

An enhanced tendency to venous pooling on assuming an upright posture does appear to be a major effect of simulated and actual weightlessness. Increases of venous engorgement and leg circumference, and dependent cyanosis have been observed during tilt of individuals subjected to prolonged periods of bed rest [28, 46, 78]. In fact, blood congestion has reportedly been great enough to produce purpuric hemorrhages about the feet and ankles, even though blood platelet and prothrombin levels were normal [28]. It has also been thought that strain gage data obtained on post-flight Gemini astronauts confirmed pooling of blood in their lower extremities for the period of time required for their tilt responses to return to normal [12]. The adaptive changes, and the relative contributions of such changes responsible for venous pooling remain to be determined.

With respect to the possible contribution of physical inactivity, the foregoing discussion indicated that failure to maintain skeletal muscle strength, tone, and mass would reduce the restrictive effect which extravascular tissue tension exerts on venous distension and possibly somewhat diminish the pumping effectiveness of muscle contraction, or even be severe enough that this effect, in combination with inadequate venous tone and diminished tissue turgor, could lead to venous valve incompetence. It is also wondered if physical inactivity could diminish the capacity of arterioles and veins to maintain adequate tone, or the responsiveness of vasoconstrictor and cardiac stimulating mechanisms required to maintain cardiovascular integrity on assuming an upright position. Miller [78] found that the dependent cyanosis associated with prolonged bed rest could be reduced with exercise. Hence it was suggested

that inactivity could have an effect on venous pooling, possibly through an associated loss of arteriolar or venous, or skeletal muscle tone. However, as will be discussed subsequently, attempts to reduce orthostatic intolerance from prolonged exposure to simulated and actual weightlessness by periodic exercise during exposure have on the whole proven unsuccessful. Moreover, one would not expect physical inactivity to contribute to orthostatic intolerance observed after 6 to 12 hours of complete water immersion, especially since the immersed subjects were usually unrestricted in movement. Thus it would appear that cardiovascular adaptations to weightlessness have overshadowed the role played by physical inactivity in producing the orthostatic intolerance observed after prolonged bed rest, complete water immersion and weightless exposures to date. More conclusive information in this area is still required.

A few other factors have been considered possible contributors to the post-flight orthostatic intolerance observed in astronauts. It must be kept in mind that their significance is difficult to judge, especially since they were not present in simulated weightlessness studies. It is a well established fact that post-flight fatigue, which has been observed to some degree in all post-flight astronauts to date, tends to increase the susceptibility to orthostatic intolerance [59]. The possible occurrence of mild dehydration which, through an associated decrease in blood volume, could be a factor in producing orthostatic intolerance in the immediate post-flight period has been discussed above. Finally, it has been considered possible that orthostatic intolerance might be contributed to by physiologic events which might be associated with the vague feeling of "let-down" often experienced after a prolonged emotionally and physically stressful event, such as a space mission [59].

In conclusion, studies of tilt responses of individuals who have been exposed for prolonged periods of time to simulated and actual weightlessness have indicated that the adaptive response of the cardiovascular system is not restricted just to blood volume changes. Although a decrease in blood volume no doubt contributes causally to orthostatic intolerance observed after such exposures, there is both direct and indirect evidence that the

ability of the cardiovascular system to maintain its integrity in the upright position decreases during exposure to the weightless environment. This is generally thought to result primarily from an enhanced tendency to venous pooling, the etiology of which remains to be determined. It has been postulated that arteriolar and cardiac responses to the upright position might also be involved.

Medical Implications

Other chapters in this report point out the fact that many of the medical problems which might arise from hazards of space operations can be influenced by, and have profound effects on the functional integrity of the cardiovascular system. In the light of the foregoing discussion in this chapter, one wonders what effects cardiovascular adaptations to weightlessness might have on medical problems. This very important area of clinical space medicine has received little attention to date. Hopefully, the following considerations will stimulate further thought and investigation in this area.

As the result of a decrease of blood volume associated with weightlessness, an astronaut who suffers "shock" in space will, in essence, not receive the benefit of the "transfusion" of pooled blood which a normal ambulatory individual on Earth receives on assuming the supine position. As well, it will not be possible in space to enhance brain blood flow of an astronaut in "shock" by tilting him to the head-down position. If blood volume actually returns to its pre-mission level as exposure to weightlessness continues, one would expect that an astronaut's susceptibility to "shock", especially from decrease of blood volume, would be somewhat reduced.

Otherwise, there is no reason to believe that the mechanisms which compensate for threats to the functional integrity of the cardiovascular system, such as blood loss or myocardial damage, should be any less efficient in the weightless environment than on Earth. This assumes of course that cardiovascular "fitness" is maintained at an optimum level in space. The absence of hydrostatic forces due to gravity should, in fact,

allow an astronaut to tolerate cardiovascular stresses better while moving about in space than while moving about on Earth. Since hydrostatic forces due to gravity play a great role in producing the vasodepressor reaction, be it on the basis of pain, heat load, postural blood shift or pathophysiologic reflex, this reaction might be much less likely to occur or to progress on to the syncopal stage in space than on Earth.

The cardiovascular adaptations to weightlessness are of great concern to an astronaut who is re-exposed to a gravity environment during exploration of a lunar or planetary surface, or is subjected to accelerative forces in the head-to-foot direction during take-off and landing operations. It is noted that data obtained during passive upright tilt of individuals who have been exposed for prolonged periods of time to simulated and actual weightlessness do not allow prediction of risks of the vasodepressor reaction facing astronauts while standing or moving about in gravity environments. This provocative test of cardiovascular function allows neither the pumping of venous blood by contraction of muscles of the lower extremities, nor the restriction of venous distension by the tone of these muscles associated with weightbearing. Accordingly, it is thought that if physical, and in turn cardiovascular "fitness" is maintained, the risks of an astronaut experiencing a vasodepressor reaction from orthostatic intolerance due to the effects of only the cardiovascular adaptations to weightlessness will probably be quite low, especially during operations in environments with gravitational forces less than that on Earth. This view is supported by the fact that astronauts have apparently not experienced manifestations of orthostatic tolerance while standing and walking about in the post-flight period. It should be noted, however, that the decrease of circulating blood volume associated with orthostatic intolerance will reduce physical work capacity, whether or not orthostatic intolerance is clinically manifest [124]. Thus there is obviously a great necessity for studies oriented toward determining not only the effects which cardiovascular adaptations to weightlessness can have on astronauts during operations in various gravity environments, but also the need for measures which confer protection from these effects.

As would be expected, prolonged exposure to simulated weightlessness has been found to markedly reduce tolerance to accelerative forces applied in the head-to-foot direction [10, 11, 99]. If cardiovascular fitness is maintained in space, there is no reason to believe that cardiovascular adaptations to weightlessness will alter an astronaut's tolerance to transversely applied accelerative forces associated with landing and take-off operations [75].

It is readily apparent from foregoing discussion that cardiovascular adaptations to weightlessness will render the cardiovascular system less able to maintain its functional integrity in the upright position when it is challenged by various stresses [3, 38, 43, 65, 66, 80]. One stress is a further reduction of blood volume by such factors as hemorrhage, plasma loss and dehydration. Another stress is an expansion of circulatory capacity, as occurs on exposure to heat, with exercise or during a vasodepressor reaction. Then too, inadequate cardiac output could result from an imposed stress of impeded return of blood to the heart by, for example, a constricting garment or pressure breathing.

Circulatory adjustments required to maintain orthostatic tolerance in the face of cardiovascular adaptations to prolonged weightlessness might conceivably increase the risk of an astronaut developing a medical problem during operations in a gravity environment. For example, the decrease in peripheral blood flow associated with orthostasis might be sufficient to render an astronaut more susceptible to cold injury or a heat disorder.

Finally, since any degree of orthostatic intolerance is associated with diminished cerebral perfusion and hence borderline cerebral hypoxia, it is thought that cardiovascular adaptations to weightlessness might reduce significantly an astronaut's "time of useful consciousness" on exposure to a low partial pressure of oxygen after return to a gravity environment (Chapter 1), even though lung-to-brain circulation time would be lowered. This hypothesis does require experimental verification.

Protective Measures

Foregoing discussion has pointed out the need to assure an astronaut that he will not suffer from the adverse effects of cardiovascular adaptations to weightlessness on being re-exposed to a gravity environment during exploration of a lunar or planetary surface, or on being subjected to head-to-foot accelerative forces during take-off and landing operations. There are two general preventive approaches, the investigative status of which has been periodically reviewed (60, 71, 75, 85, 117, 126). The one approach is to prevent the occurrence of cardiovascular adaptations to weightlessness. The other is to protect the astronaut from the adverse effects of these adaptations. Those methods which have received consideration and study to date in attempts to accomplish these approaches are outlined below. Particulars of their application can be obtained from cited references. Although some indication of their effectiveness can be given, it must be remembered that appropriate selection and optimum utilization of a particular method will be assured only by more intensive investigation in this area.

The greatest attention from the standpoint of preventing cardiovascular adaptations to weightlessness has been focused on periodic physical exercise as a way of maintaining an optimum level of physical "fitness" during space missions. Since exercising increases blood volume in a normal ambulatory individual on Earth, it was thought that an appropriate exercise regimen might minimize the decrease of blood volume associated with weightlessness (16, 21, 22, 27, 77, 90). As well, exercising the lower extremities in particular might reduce the tendency to venous pooling by maintaining muscle tone, strength and mass, and possibly to some extent the capacity of vasoconstrictor mechanisms to respond to intravascular hydrostatic forces due to gravity (60). However, a number of isotonic and isometric exercise regimens have reportedly had no really significant effect on either the blood volume or the degree of orthostatic intolerance associated with prolonged bed rest (16, 25, 27, 76, 109, 112, 117, 121, 125, 126). Bungee cord exercises during the 8 and 14 day, two-man Gemini missions were also not protective, even though the cardiovascular

response to a calibrated work load might for the most part have been maintained by these exercises [12, 91]. If exercise will ever be a method which could be used in space specifically for the prevention of cardiovascular adaptations to weightlessness is doubtful, but further study in this area still appears indicated.

Various combinations of periodically inflated cuffs placed proximally on the extremities have been used in attempts to prevent cardiovascular adaptations to weightlessness. It was thought that periodic increases of intravenous hydrostatic pressures, especially in the extremities, might maintain not only venomotor capacity but an optimum level of extravascular tissue tension during prolonged space missions [26, 29, 71]. Another effect postulated was reduction of the degree of central venous volume overload, and hence decrease of blood volume associated with weightlessness [26]. Indeed, Graveline [46] and then Vogt [111], found that periodic inflation of cuffs placed around all four extremities of subjects immersed up to the neck in water for 6 hours maintained orthostatic tolerance. When carried out during two weeks of bed rest, this technique conferred significant protection from orthostatic intolerance as tested by a 10 degree tilt, which presumably simulated the effect of the Moon's gravitational field on the cardiovascular system [76]. On the other hand, a variety of cuff configurations applied during a number of water immersion and prolonged bed rest studies have been unsuccessful in preventing either decrease of plasma volume or orthostatic intolerance [25, 73, 96, 112, 114, 117]. Periodic inflation of lower extremity cuffs on the pilots of the 8 and 14 day two-man Gemini missions was also ineffective in lessening post-flight orthostatic intolerance, even though there appeared to be some decrease in the degree of post-flight pooling of blood in the lower extremities as judged by the strain gage technique [29, 91]. Thus it has been concluded that in the light of failure to establish definite effectiveness of extremity cuffs in many simulated and actual weightless exposures to date, further consideration of the use of cuffs in the space flight situation is not warranted [114].

Exposure to lower-body negative pressure has been suggested as a method of preventing adverse effects of cardiovascular adaptations to

weightlessness, since its effect on the cardiovascular system is similar to that of increasing the gravitational component of hydrostatic pressure [60, 93]. It was thought that forced pooling of blood in the lower part of the body would serve to stimulate expansion of circulating blood volume by mechanisms outlined above [60]. Another effect anticipated was transudation of fluid, due to increased intravascular pressures, to rehydrate and restore tension to tissues of the lower extremities, possibly to pre-mission levels [60]. Although lower-body negative pressure has been found to produce less of an increase in peripheral venous tone than standing, this technique might conceivably restore to some degree the capability of veins and, if they are also affected by weightlessness, arterioles to respond to intravascular hydrostatic pressures due to gravity [4, 40]. A number of studies have shown that lower-body negative pressure can either prevent or restore the decreases of plasma volume and orthostatic tolerance which result from prolonged bed rest [16, 40, 64, 72, 78, 95, 97]. Of particular importance in terms of space missions of long duration is the fact that orthostatic tolerance was restored with this method over a period of only 2 days [60, 95, 97]. Hence for space missions of any length of time, orthostatic tolerance could be reestablished on a short-term basis just prior to entering a gravity environment [60]. Although exposure to lower-body negative pressure appears to be a very feasible measure for restoring an astronaut's orthostatic tolerance while in space, possible restrictions which this measure might place on an astronaut's activity during a critical phase of a mission must be taken into account. There is also an apparent need for studies aimed at determining time and pressure modes which would provide an optimum effect.

Again, in an attempt to readapt the cardiovascular system to gravity, periodic centrifugation has been assessed for its effectiveness in preventing orthostatic intolerance resulting from prolonged bed rest. White [125, 126] has reported that as little as four 7.5 min rides on a short-arm centrifuge largely prevents orthostatic intolerance as judged by syncope. However, heart rate and blood pressure responses to tilt, and decrease of plasma volume during bed rest, were essentially unaffected by this

measure. Interestingly, the steep heart-to-foot acceleration gradient of 256 percent created by this measure did not preclude movement of the head, arms and legs, and motion sickness was not a problem for the well trained individual when exposed to high angular rates and modest head or limb movements. Further testing of periodic centifugation appears indicated [126]. It is considered possible that the weight, power and volume penalties imposed by a short-radius centrifuge could be brought into perspective for spacecraft of the future, if the effectiveness of this measure is well established.

A few other protective measures which have been suggested for use in space have been studied, all being essentially ineffective in experiments to date. The administration of 9-alpha, fluorohydrocortisone for a short period of time towards the end of prolonged bed rest exposures did return blood volume to normal and in fact often above normal, but did not prevent the orthostatic intolerance resulting from these exposures [57, 94, 96]. It should also be noted that this drug produced occasional nausea, an effect which would be highly undesirable in the space situation [96].

Presumably to stimulate peripheral vasomotor reflexes otherwise dormant during exposure to weightlessness, variants of positive pressure breathing have been applied. However, they have had no significant effect on the orthostatic intolerance resulting from head-out water immersion and bed rest [55, 115].

The administration of pitressin, with and without concomitant water-loading to subjects immersed to the neck in water has prevented the diuresis, and associated decrease in plasma volume, but not the orthostatic intolerance which results from water immersion [55, 56, 73].

Based on the fact that many of the physiologic responses to hypoxia are the reverse of those to weightlessness, individuals have been exposed to 10,000 to 12,000 ft altitudes during bed rest [60, 61, 95, 97]. Although exposure to mild hypoxic conditions did prevent the decrease in red cell mass which occurred during bed rest exposures at ground level, it did not reduce the orthostatic intolerance produced by bed rest.

Periodic bouncing exercise on a railed cart between two trampolines has been carried out on prolonged bed rest subjects [27]. It was thought

that the vascular stimulation of exercise, as well as the repetitive "sloshing" of blood, would serve to maintain the capacity of both veins and arteries to compensate adequately for intravascular hydrostatic forces due to gravity. Although this measure was found ineffective, it might warrant further testing.

What appears to be the most effective measure assessed to date for the protection of bed rest and water immersion subjects from orthostatic intolerance has been the application of a pressure garment to the lower part of the body during tilt. The external pressure primarily acts to prevent excessive venous pooling and excessive loss of plasma volume through transudation of fluid into the tissues of the lower extremities in the upright position [60]. The partial pressure, or so-called "anti-G" suit has been used to prevent fainting of individuals suffering from postural hypotension [82]. Orthostatic tolerance after 6 hours of head-out water immersion was improved, beyond the pre-immersion tolerance with an elastic gradient leotard [73]. The partial pressure suit has been proven effective in preventing orthostatic intolerance after prolonged bed rest [76, 77]. It is therefore believed possible that any effective pressure garment that can be applied by an astronaut prior to re-exposure to a gravity environment will provide a large measure of protection against a possible significant decrease in orthostatic intolerance [60]. The most suitable garment would appear to be the Jobst stocking or elastic leotard. They can be adequately ventilated and permit normal body movement, and can be easily donned. In such a garment, one could perform normal activities.

Finally, protection from adverse effects from cardiovascular adaptations to weightlessness might be a factor coming into considerations of whether to provide astronauts artificial gravity in space. It is readily apparent from above discussion that the weight this factor should have in reaching this decision remains to be established. If artificial gravity is employed, the level required for preventing orthostatic intolerance in various gravity environments to be encountered during space missions will have to be determined.

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CHAPTER 11

ACUTE RADIATION EFFECTS

Assessments of the presently known and anticipated radiation hazards in space are indicating that serious acute radiation effects should not be suffered by astronauts if adequate precautions are taken. One must remember, however, that current information on ionizing radiations, particularly from solar flares in space, is based on relatively sparse data. Therefore, it is still considered necessary to assume that there could be a requirement for the treatment of acute radiation effects in space. This chapter briefly outlines the acute medical problems which result from unexpected exposure of astronauts to various radiations during space missions. Emphasis is placed on the characteristics and management of ionizing radiation effects which are presently thought most likely to occur following exposure to solar flare radiation.

Various radiation terms to be used in this chapter are defined in Figure 11.1. The relative biological effectiveness (RBE) of a particular type of radiation is a multiplier which equates the biologic response of this radiation to that of X or gamma radiation having a linear energy transfer (LET) equivalent to 3 Kv/μ of water and being delivered at the rate of 10 rads/min. When an RBE value is used for a specific biologic endpoint, it is commonly referred to as a quality factor (QF).

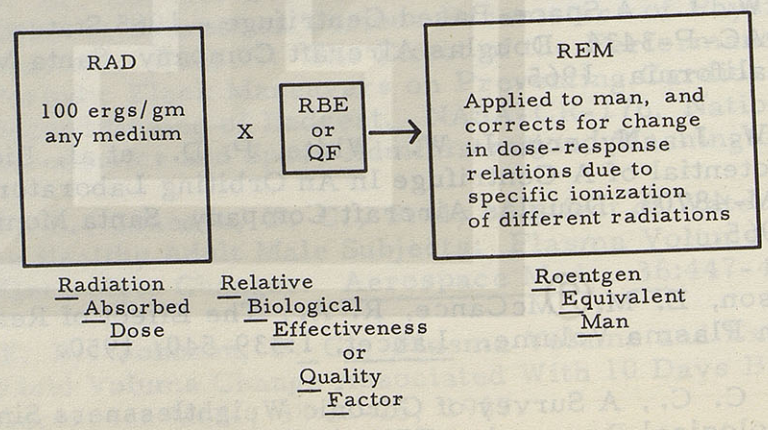

Figure 11.1 Radiation Terms

Space Radiation Hazards

The various radiations to be expected in the space environment have been discussed extensively in the literature. Therefore they are dealt with briefly below, with major references from which further detail can be obtained being cited.

Trapped (Van Allen) Radiation

Because flight plans usually call for orbits beneath or transient passage through the zones of geomagnetically trapped radiation surrounding the Earth, this source is considered a relatively minor hazard to astronauts. The location and characteristics of the zones are being so precisely defined that depending on the spacecraft shielding and trajectories selected, radiation exposure can be maintained at safe levels during both orbiting and non-orbiting missions. It is conceivable, however, that during an emergency extravehicular operation on the fringe of a zone, or intravehicular operations within the zones, there might be a danger of skin injury from high energy particles [117]. Radiation zones around planets being explored are yet to be identified and their characteristics thoroughly studied.

Artificial Radiation Belts

Artificial radiation zones of high energy electrons can be created by nuclear explosions in space. They could present a serious biologic hazard, especially to orbiting astronauts. The dose of radiation an astronaut could receive will depend on pre-flight planning and the amount of contingency exposure in flight. Dose rates measured four months after the Starfish nuclear explosion in space were dangerously high, at 30 rads/hr behind 4.5 gm/cm^2 brass shielding [18]. Due to flux decay, the dose rates were below 0.2 rad/day behind 5 gm/cm^2 aluminum two months later. Such a dosage would not produce acute radiation effects.

Galactic Cosmic Radiation

Galactic cosmic radiation is believed to originate outside of our solar system, but within our galaxy [28]. This radiation consists of extremely

high energy atomic nuclei, of which approximately 86 percent are protons, 13 percent are alpha particles and the remainder are elements of higher atomic number [120]. Since cosmic particles produce discreet dense ionization tracks in tissues, the possibility that they might seriously injure such vital organs as the lens of the eye, the retina, the hypothalamus, or the brain has been considered. Schaefer [97] has recently estimated that exposure to galactic cosmic radiation in free space would have a significant life-shortening effect, possibly as much as 20 percent. Inadequate simulation in ground-based experimentation and biologic exposures in space have precluded definitive evaluation of this hazard [25, 26, 94]. Otherwise, unless streams of cosmic radiation exist in space, these particles are so few in number that they do not now appear to be an acute hazard to astronauts [65, 94]. The average whole-body dose rate of this radiation in free space is generally thought to be about 5 rads/yr during the period of maximum solar activity and about 15 rads/yr during minimum solar activity [1, 41, 42, 47, 73, 80, 97]. It is noted that the latter dose is just about 100 times larger than the background dose at sea level on the Earth [97].

Radiation Sources On Spacecraft

Nuclear energy used for propulsion or as a source of power during space flight should not be a radiation hazard if adequate precautions are taken to ensure protection of astronauts both during normal operations and in an emergency. By the same token, it is assumed that astronauts will be adequately shielded from the strong magnetic fields which might be used in magnetohydrodynamic propulsion or for repelling high energy solar flare protons from the spacecraft hull, and from microwaves emanating from activated radar systems.

Solar Electromagnetic Radiation

Solar electromagnetic radiation should not be hazardous to an astronaut who is adequately shielded by the wall of his spacecraft or by his space suit. The radiant energy output of the sun in the ultraviolet, visible, and infrared spectrum is remarkably constant in spite of the

occurrence of sunspots and associated activity [94]. Even though adequate measures will presumedly be taken to maintain environmental temperatures in space at comfortable safe levels, it is still considered possible that breakdown of a temperature control system could cause an astronaut to suffer from a heat disorder (Chapter 6).

The visual spectrum can be dangerous in that the warning glow seen on Earth as the line of sight approaches the sun is not seen in space. Filtration of sunlight must be adequate to prevent temporary retinal effects such as glare or flash-blindness or permanent retinal burns, both of which could result from inadvertent glances by unprotected eyes at the sun. These disturbances are discussed in detail under meteoroid "flash" in Chapter 12.

The types of plastics used for visors or windows offer adequate protection from ultraviolet light. In selecting materials for the space suit visor, it must be kept in mind that repeated protracted exposures to ultraviolet light during extravehicular operations necessitate an optimum degree of protection [45]. If not, this radiation, especially at wave lengths shorter than 0.32μ, could damage the surface cells of the eye, leading to the condition variously known as "snow blindness", and sunlamp or welder's keratoconjunctivitis. Associated signs and symptoms, which characteristically appear after a latent period of up to several hours, are severe eye pain, photophobia, conjunctival congestion and swelling, marked lacrimation, disturbances of vision, a granular appearance within the corneal epithelium, and with relatively severe exposures, cloudiness of the corneal stroma. Although the pain can be controlled with a topical anesthetic and cold compresses to the eyelids (Chapter 8), this condition usually heals in one to several days. An astronaut could be seriously incapacitated by this condition, especially if he is extravehicular at the time of its onset or requires full visual function to perform a critical task.

Solar x-rays, even from the solar flares to be discussed below, appear to be of too low energy and flux rate to penetrate a spacecraft or space suit and administer a significant harmful dose of radiation to an astronaut.

Solar Particulate Radiation

Solar "Wind" - A large number of particles, mainly protons and electrons, are continuously given off by the sun [27, 47, 48]. Even during periods when the sun is more active, the kinetic energy of this plasma, or so-called solar "wind", does not reach levels which are high enough to cause concern as a radiation hazard to occupants inside of the spacecraft. On the other hand, this radiation must be carefully studied to determine whether or not it could be a potential hazard, especially to the skin, during extravehicular activity.

Solar Flares - Radiation emitted into space by the so-called solar flares or solar cosmic ray events presents the most uncertain and probably by far the greatest potential biologic radiation hazard in space. Therefore this hazard is discussed here in some detail, with emphasis being placed on anticipated flare characteristics which determine the risk of a serious exposure, the type and severity of acute radiation effects, and thus the possible requirements for the treatment in space of medical problems from radiation.

A solar flare is usually a short-lived increase in radiation intensity originating in the vicinity of a sunspot, persisting up to several days at any point in the solar system [94]. The higher energy components of the radiation flux from a flare is comprised mainly of protons with energies ranging from 10 Mev to a few Bev. Since these particles are the most biologically hazardous component, most shielding and biologic considerations have dealt only with them. Alpha particles can be nearly equal to or, on occasion, even greater in number than protons over a period of time during an event [47]. The contribution of alpha particles to the total biologic hazard is less well defined than is the case for proton radiation, although much is known of their biologic effects [52, 96]. Very little information is available on the distribution within flares and the biologic effects of heavier particles [87, 116]. The electromagnetic (e.g., ultraviolet, x-ray, gamma) components of a flare are not considered

a significant hazard to an astronaut behind typical space suit shielding [47, 53, 94].

The number of solar cosmic ray events follows the 11 year sunspot cycle in that these events tend to occur with greater frequency during the high incidence range of the cycle [80]. As shown in Table 11.1, the past cycle, which has allowed the first accurate studies of flare and sunspot occurrences, began in 1954, reached a maximum early in 1958, and reached a minimum in 1965. From this cycle it appears that even though the greatest number of events take place at sunspot maximum, most of the major events might occur from one to 2 years after this maximum [47, 53, 73]. Since over a period of many decades, the frequencies of sunspots and flares appear to correlate, long term (years) predictions of sunspot size, nature and frequencies might also be rough forecasts of future radiation hazards. On the other hand, there are at present apparently no substantial criteria for making short term (hours) predictions of solar flares [40, 94].

The arrival time and flux of solar flare protons at a point in space are related to the original velocities of the protons and the influence of magnetic fields in space. There is a delay from minutes to hours in the arrival of these particles, and their flux can be so dispersed that they can continue to arrive over a period of hours to days. Webber and Freier [122] have pointed out that for all flares, the protons with higher energies are detected sooner, and have a shorter rise time (time to reach maximum intensity) and a shorter decay time than protons with lower energies. Moreover, the flux decay of protons above a particular energy is exponential at most times for a wide range of proton energies [122]. With these characteristics of a solar flare applied to measured flux-time profiles of protons above certain energies, it may be possible to reasonably predict the magnitude of a flare from measurements made by instruments which not only integrate dose but also differentiate energies during the early part of an arriving flare. This knowledge could then indicate whether or not special shielding measures or, if such is available to astronauts, a radio-protective drug is required to prevent radiation injury.

Event Date	Exposure (Rads) Shielding gm/cm^2 1.0		2.0		5.0	
2-23-56	309.0		185.0		103.0	
8- 3-56	9.1		5.3		2.4	
1-20-57	112.0		45.8		7.1	
8-29-57	78.7		26.2		3.5	
10-20-57	19.3		10.0		4.7	
3-23-58	1.5		0.6		0.1	
7- 7-58	156.0		55.0		9.6	
8-16-58	24.0	151.2	9.3	48.0	1.7	6.9
8-22-58	46.0		15.3		2.0	
8-26-58	81.2		23.4		3.2	
9-22-58	4.4		1.3		0.2	
5-10-59	484.0		217.0		66.8	
7-10-59	440.0	1507.0	220.0	728.0	86.0	253.8
7-14-59	675.0		312.0		91.0	
7-16-59	392.0		196.0		76.8	
4- 1-60	2.0		1.0		0.5	
4-28-60	2.2	6.4	1.1	3.2	0.4	1.3
5- 4-60	2.3		1.2		0.6	
5-13-60	1.9		0.9		0.3	
9- 3-60	13.5		7.0		3.2	
9-26-60	1.2		0.5		0.1	
11-12-60	511.0	823.9	260.0	410.9	117.0	185.7
11-15-60	295.0		142.0		64.9	
11-20-60	17.9		8.9		3.8	
7-11-61	1.5		0.7		0.2	
7-12-61	26.3	161.8	8.8	72.5	1.2	27.0
7-18-61	132.0		63.0		25.2	
7-20-61	2.0		1.0		0.4	
9-28-61	2.4		1.1		0.5	
10-23-62	0.1		0.0		0.0	

Table 11.1 Integral Unit Sphere Free-Space Proton Exposures Under 1, 2, and 5 gm/cm^2 Aluminum Shielding for Major Cosmic Ray Events Occurring During Solar Cycle 19.

(After Langham, Brooks and Grahn [65]).

Because the proton flux from a solar flare event is widely distributed in energy and direction, and varies among different events and at different times during an event, no average biologic hazard can be described for solar flares. As shown in Table 11.1, the biologic hazard can be markedly modified due to a number of solar flares occurring over a period of several days. Finally, it should be kept in mind that until the next predicted period of maximum solar activity in 1969, few direct measurements of flares will have actually been made in free space.

Since shielding on most dosimeters has not allowed an adequate assess-

ment of the low energy radiation spectrum in space, the possible hazard of low energy protons and alpha particles to astronauts during extra-vehicular activity in free space remains to be defined. Solar flares which occur frequently and emit low energy protons are being identified [48]. These and the solar "wind" might be a skin hazard and require investigation for evaluation of shielding provided by space suit materials.

The air dose rate of radiation imposed on an astronaut in a spacecraft being bombarded by solar flare protons will be determined primarily by the energy-flux characteristics of the protons stream, the type (atomic weight), thickness and geometry of the spacecraft shielding and by the astronaut's spatial position in the spacecraft. Figure 11.2 illustrates the effect of shielding thickness on air dose rate from incident protons. It is noted that neutrons contribute negligibly to the total dosage at shielding thicknesses of less than 10 gm/cm^2 aluminum [72, 123]. Short electromagnetic waves produced by the interaction of protons with such a metal of low atomic weight can also be considered insignificant [65, 72, 94, 123].

Integral cabin air doses as a function of spherical shielding thickness have been estimated for a number of flares of the last solar cycle (Table 11.1). Since a better understanding of the contribution of high energy particles to the total flare dose was brought into these calculations, the data are considered the most accurate available up to the present time. Table 11.1 lists only solar flare events for which there was sufficient flux data to justify free-space dose estimates. The effect of shielding in attenuating solar flare radiation dosage is again well demonstrated. Assuming that such data are reasonably correct, it will become evident in subsequent discussions that only the cumulative doses from two solar flare series (1959 and 1960) would have been sufficient to have had a significant effect on an astronaut in a spacecraft providing him spherical shielding of from 2 to 5 gm/cm^2 aluminum.

Results of model calculations of proton depth-dose patterns using data of various flares are shown in Figures 11.3 and 11.4. Both serve to illustrate the marked decrease in tissue dose with increasing depth from

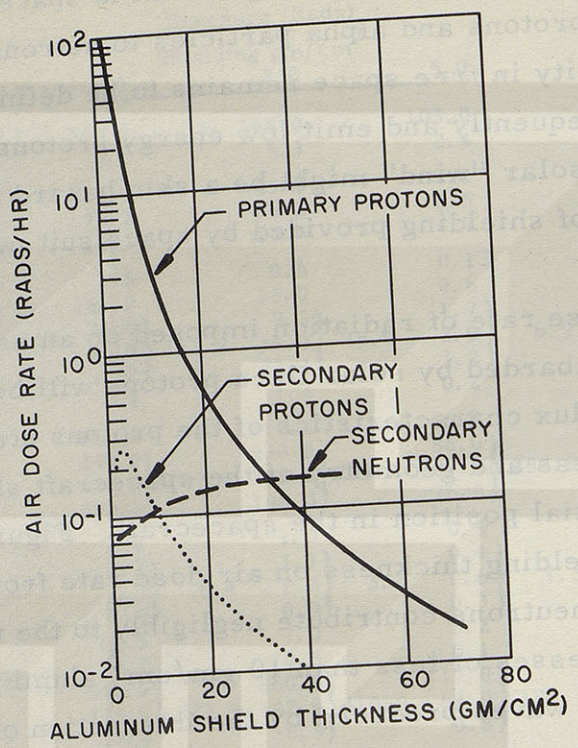

Figure 11.2 Calculated variations of primary and secondary point-target air dose rates as a function of the thickness of a spherical aluminum shield for the May 10, 1959 solar flare spectrum, measured 33 hours after onset. (After Langham et al,[65] redrawn from Wilson and Miller[123]).

the skin surface. Figure 11.3 represents calculated depth-dose patterns for three different solar flare rigidities considered representative of past flares. It is noted that even for the most energetic incident flare spectrum the tissue dose drops from about 30 percent of the skin surface dose at 5 cm depth. Figure 11.4 shows the depths of critical organs and tissues in relation to depth-dose distribution, in a spherical phantom, calculated for the May 10, 1959 solar flare event.

If past solar flare flux-energy-time, shielding, and tissue depth-dose data presented above are valid for predicting future radiation hazards in free space from flares, one can say with reasonable confidence that the occurrence of serious injury to deep tissues, such as the hematopoietic system and gastrointestinal tract, from a flare or series of flares with the order of magnitude and separation of those recorded in the last solar

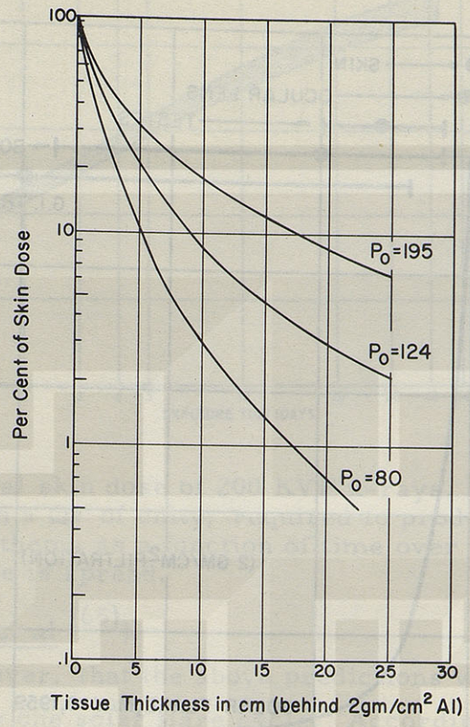

Figure 11.3 Tissue dose variation with increasing depth from skin for various incident flare spectra (P_o represents the rigidity, or spectrum of particle momenta at the time of maximum flare intensity).

(After Jones et al [61]).

cycle, will be highly unlikely. The skin may, however, be damaged under these conditions.

The acute skin dose of 200 KVP x-rays required to produce erythema is about 650 to 700 rads [65]. As shown in Figure 11.5, protraction of exposure allows some repair of skin damage to take place during exposure, so that the dose required to produce erythema is increased. By the same token, Figure 11.6 demonstrates that previous skin exposure reduces the allowable next dose because of residual unrepaired damage. If it is assumed that solar flare protons and 200 KVP x-rays have the same QF for skin injury, and solar flare data in Table 11.1 are reasonably accurate, then Figures 11.5 and 11.6 indicate that past flares and series

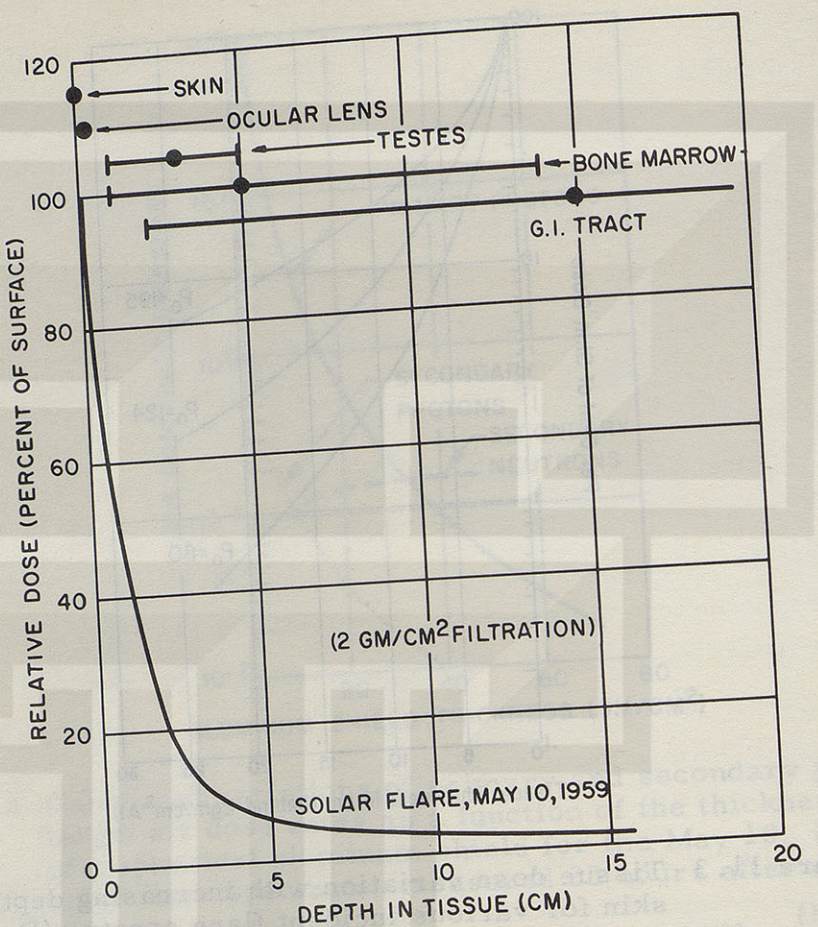

Figure 11.4 Depth range and mean depths of critical organs and tissues in relation to proton depth-dose distribution inside a spherical phantom placed behind 2 gm/cm^2 shielding, calculated for the May 12, 1959 solar event. (After Langham et al, [65] drawn from Grahn [49] and Schaefer [95]).

of flares would probably not have been sufficient magnitudes to produce erythema of skin protected by spherical shielding equivalent to 2 to 5 gm/cm^2 aluminum shielding. Such shielding is thought to be representative of present day manned spacecraft hulls [1]. On the other hand, at 1 gm/cm^2 aluminum, protraction and fractionation would probably not have been sufficient to prevent the occurrence of erythema [65].

In conclusion, an optomistic picture of the potential solar flare hazard to astronauts on prolonged space missions has been presented. It should

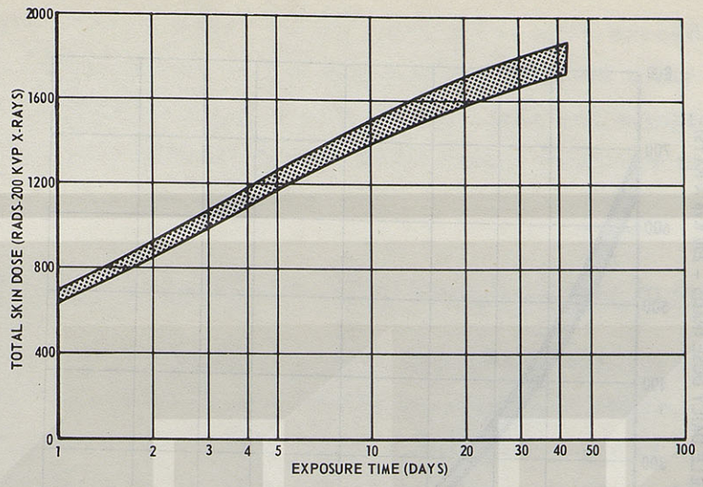

Figure 11.5 Total skin dose of 200 KVP x-rays, or a radiation with a QF of unity, required to produce a slight erythema as a function of time over which exposure is spread.

(After Langham et al [65]).

be remembered, however, that the above predictions were based on limited data from only one solar flare cycle. Accordingly, the treatment in space of various acute radiation effects, particularly skin injury, should be considered in emergency planning.

Acute Ionizing Radiation Effects

Studies of humans suffering from acute ionizing radiation effects following radiotherapeutic, nuclear reactor and nuclear bomb exposures have indicated that a stereotyped clinical picture of such effects, based on dosage alone, cannot be described [16, 24, 54, 65, 66, 79, 88, 101, 121]. This applies even more so to radiation exposures in space. The different component particles and the energy-flux-time spectra of space radiations, with resulting variations in RBE and tissue depth-dose distributions of these radiations, are critical. These are only the major determinants of doses received by individual organs and tissues which, when damaged, are directly or indirectly responsible for producing the medical problems from radiation exposure.

The wide differences in species sensitivity to radiation is well known,

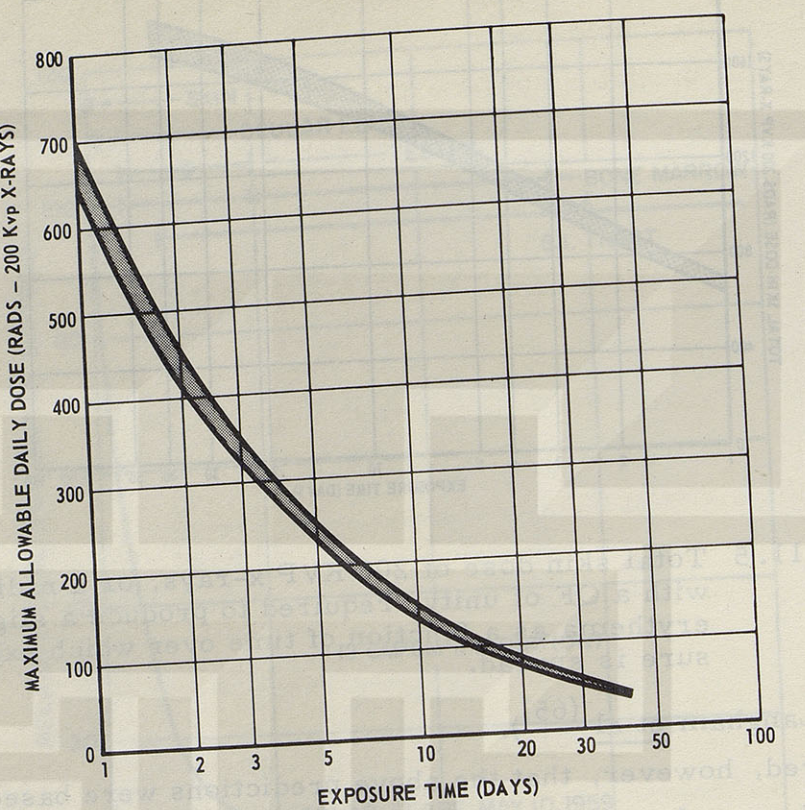

Figure 11.6 Maximum daily dose of 200 KVP x-rays, or a radiation with a QF of unity that can be given and not exceed the slight erythema threshold as a function of the period over which the exposure is protracted.

(After Langham et al [65]).

so that extrapolation of even subhuman primate radiation exposure data to man must be made with caution [13, 23, 32]. The effects of protons on animals have been studied and compared to the effects of other radiations [4, 15, 30, 31, 32, 33, 34, 61, 67, 103, 104, 105, 114]. In contrast to gamma or x-irradiation, studies of several species have indicated that for a total body dose, protons are more prone to damage the gastrointestinal tract than the bone marrow [30, 31, 32, 33, 34, 61, 67, 103, 114]. Early findings that hemorrhagic phenomena occur earlier and are more severe in large animals irradiated with protons than those irradiated with x-rays have not always been substantiated [31, 33, 83, 114].

The clinical manifestations of early, or acute effects of a radiation exposure, tend to appear when the total dose of radiation absorbed by a

critical volume of tissue within a certain period of time exceeds some critical level, or threshold. For a single uncomplicated solar flare, this threshold will probably not be exceeded if signs and symptoms of radiation effects do not appear within 60 days after exposure to the flare [65].

Clinical Picture Following a Highly Penetrating Exposure in the LD_{50} Range

For the purpose of determining what therapeutic measures might be required for the treatment of acute radiation effects in space, a rather idealized clinical picture resulting from a total body dose of highly penetrating radiation given at a mid-lethal dose (LD_{50}), such as 450 to 500 rads of 250 KVP x-rays, is described here [3, 14, 21, 24, 51, 65, 76]. What usually occurs at this dose level is the so-called hematopoietic form of the acute radiation syndrome. The clinical course of this form of reaction passes through four phases - the initial or prodromal phase, the latent phase, the bone marrow depression phase, and the recovery phase [3]. At lower dose levels, the bone marrow depression phase is less likely to become clinically apparent; symptoms characteristic of only the prodromal phase occur in about 5 to 10 percent of individuals receiving 50 to 100 rads, and in about 25 to 50 percent of those receiving 100 to 200 rads [61]. At levels above the LD_{50}, evidence of gastrointestinal damage will appear. This so-called gastrointestinal form of the acute radiation syndrome, characterized by a severe prodromal phase, a short latent phase and a phase of usually fatal gastrointestinal disturbances, overshadows clinical manifestations from bone marrow depression at a total body dose in the range of 750 to 800 rads. As mentioned above, for a given total body dose, the human gastrointestinal tract might be more susceptible to proton injury than to injury from x-rays or gamma irradiation. The predominance of gastrointestinal injury might therefore occur at a somewhat lower dose after proton irradiation from a highly penetrating solar flare. At still higher total body radiation doses, the so-called cerebral form of the acute radiation syndrome appears, being characterized by an explosive initial phase followed by irrational behavior,

neuromuscular incoordination, convulsions and death within a few hours. Finally, it should be remembered that since depth-dose patterns are considerably different from those of the LD_{50} x-ray model, the clinical manifestations resulting from doses between 450 and 500 rads from solar flares may also be quite different than those discussed below.

Initial, or Prodromal Phase - Anorexia, nausea, retching, vomiting, listlessness, apathy, increased fatigability and occasionally diarrhea usually begin within 2 hours after an acute radiation exposure in the LD_{50} range (20, 43, 65, 79, 86, 88, 119). Weakness, fatigue, lethargy, and irritability, which have been attributed to the direct cerebral effects of radiation, may also become evident (98). Clinical experience indicates that the higher the integral dose, the shorter the latency of whatever prodromal symptoms occur. Signs and symptoms in the prodromal phase usually reach a peak within 4 to 6 hours after exposure, then improve rapidly, seldom lasting beyond 48 hours in duration.

The severity of clinical manifestations occurring in the prodromal phase correlates poorly with the integral dose of radiation received, being markedly influenced by individual susceptibility, which cannot be pre-determined, and by psychologic factors such as motivation (16, 65, 98). Some authors are of the opinion that the severity of nausea and vomiting might be proportional to the amount of food in the stomach at the time of injury, and may be prolonged by attempting to feed the irradiated individual (3). Symptoms might also be aggravated by fluid and electrolyte losses in vomiting.

It is readily apparent that the prodromal phase could be a threat to continued astronaut performance, especially if severe signs and symptoms occur during a crucial spacecraft maneuver. Vomiting into the weightless environment will also create a potentially disasterous droplet hazard (Chapter 8).

Latent Phase - The prodromal phase is usually followed by an asymptomatic period, or latent phase of up to several days in duration. Weakness

and fatigue can continue into this phase due to fluid and electrolyte losses from vomiting in the prodromal phase. Epilation usually occurs within two weeks, and involves mainly head and body hair, the eyelashes and eyebrows being less sensitive to radiation [3]. The duration of the latent phase is governed by the severity of the radiation exposure, and hence the damage incurred by the exposure.

Bone Marrow Depression Phase - Marked depression of circulating white blood cells, with associated failure of the body's immune mechanisms, leads to enhanced susceptibility to infection. Inflammation, with chills, fever and general malaise, is usually suffered first in the oropharyngeal region. Gingival and pharyngeal tissues, and tonsils can become severely swollen and ulcerated. Step-like fever suggests septicemia. A bacteremia can lead to abcess formation in any tissue of the body. Bacterial pneumonia and gastroenteritis can also be the cause of fatality.

Due to marked depression of circulating platelets, disturbance of blood clotting also becomes clinically evident. The gingival tissues bruise and bleed easily. Petechiae and ecchymoses may involve broad areas of skin. Gastrointestinal and urinary tract bleeding may also occur. Gross hemorrhage from body orfices and into hollow organs is, however, usually not massive and continuous, but is self limiting [3].

In the average individual, clinical manifestations from an LD_{50} dose of total body radiation usually reaches a peak about the fourth to fifth week after exposure. Death may occur primarily from infection or bleeding, or both.

Recovery Phase - The recovery phase is usually quite prolonged, lasting from 2 to several months in duration. Repeated infections, involving especially the respiratory system and skin, may occur. Bacterial resistance to available antibiotics can become a serious problem during this period.

Skin Manifestations

If the skin receives a radiation dose which is less than that required to

produce wet desquamation or ulceration, it will show a variable amount of flushing, or erythema [3]. This primary effect appears within hours, increases to a maximum intensity within 24 hours and disappears completely by the third day after exposure. There might be an accompanying sensation of warmth or itching resembling a mild sunburn. About 10 to 15 days after exposure, the skin again becomes erythematous, this time more intensely than the more fleeting early erythema. The involved skin in this so-called main erythema phase, which usually lasts about 2 weeks in duration, gives symptoms of a severe sunburn. Depending on the body sites and surface areas involved, it is readily apparent that an astronaut could be markedly impaired during this phase, especially if affected sites must be in contact with tight-fitting or potentially chafing parts of a space suit.

With larger doses of radiation, the skin may develop a bluish-red color with superficial scaling (dry desquamation) or a more severe reaction with blisters (moist desquamation). These extremely irritating, painful conditions usually develop by the ninth day after exposure. Severe toxicity and the serious sequelae of plasma protein, fluid and electrolyte losses can become part of the clinical picture if a large area of the body surface is involved with blistering. After still larger doses of radiation, blisters may ulcerate to form so-called roentgen ulcers over a period of several weeks [3]. These extremely painful, slow healing ulcers are characterized by marked pain, a punched out appearance, undermining growth and a tendency to recur [3]. Any areas of skin breakdown are markedly prone to become infected. It is noted that the clinical course of primates dying from proton radiation injury to skin is in many ways similar to that following third degree thermal burns (Chapter 13) [27, 29]. A severe, persistent edema, which often progresses to fibrosis or necrosis, can develop under severely irradiated skin from many weeks to many months after exposure [50]. This delayed phenomenon has been well demonstrated in primates whose skin was irradiated with high doses of 32 Mev protons, and is thought to be due to increased capillary permeability in conjunction with a moderate hypoalbuminemia [27, 29]. Severe subcutaneous fibrosis with contracture

and decreased mobility often leads to slow starvation death in these primates.

The effect of radiation on the skin varies, depending on the RBE of the radiation, on the degree of protraction or fractionation of the dose, on the site exposed, and probably on the surface area exposed. Reference is again made to data depicting the effect of dose protraction and fractionation on the production of skin erythema, presented in Figures 11.5 and 11.6. In general, the threshold dose at a depth of 1 mm for a slight erythema is about 650 to 700 rads of rapidly administered 200 KVP x-rays [59, 65]. After an acute exposure with 200 KVP x-rays, a sharp erythema is seen about 1050 rads and a blistering reaction about 2000 rads.

Diagnosis

For the most part, the diagnosis of acute radiation effects, especially skin injury, should be easily made in space. Measurement of the energy-flux-time characteristics of a radiation exposure and subsequent estimation, especially of tissue dose received by an astronaut over a period of time should, based on prior human and animal studies, allow reasonably accurate prediction of clinical outcome. Hopefully the time sequence and characteristics of acute radiation effects will not have to be relied upon as the first warning of radiation exposure. Whenever possible on board future spacecraft, hematologic studies, such as total and differential white cell count, and hemoglobin and hematocrit determination, to assess the degree of hematopoietic depression or secondary blood loss, could be a valuable aid for therapeutic decisions and prognosis. As well, fluid and electrolyte studies might be indicated for assessing the degree of fluid and electrolyte imbalance resulting from a radiation exposure, and for accurately determining the required replacement therapy.

Prevention

The importance of minimizing the amount of radiation which an astronaut receives by the use of adequate shielding and, whenever possible, by controlling the duration of his exposure, has been emphasized. For

necessary exposures, daily fractionation in equal exposure increments would be simpler and preferred, so that the limits within which an exposed astronaut can operate without decrement in health or performance can be predicted [68]. Radiation dose limits currently recommended by the National Aeronautics and Space Administration are listed in Table 11.2. The models of man on which these standards were based are presented elsewhere [44]. It has been stated that these maximum permissible doses are probably on the conservative side when one takes into consideration the effect such doses would have on astronaut performance and consequently on the safety of a mission [9]. For example, fatal mistakes might be made if a radiation prodromal reaction peak should occur in one or more crew members when some critical maneuver such as rendezvous and docking, or a mid-course trajectory correction would be required. On the other hand, this peak might occur over a period when only a minimum amount of crew activity would be required. The mission plan could then be altered so that this period could be pro-

Critical organ	Maximum permissible integrated dose (rem)	RBE (rem/rad)	Average yearly dose (rad)	Maximum permissible single acute emergency exposure, protons only (rad)	Maximum permissible single acute emergency exposure, alpha particles and protons (rem)
Skin of whole body	1600	1.4 (approx)	250	500*	700*
Blood-forming tissues	270	1.0	55	200	200
Feet, ankles, and hands	4000	1.4	550	700**	980**
Eyes	270	2***	27	100	200

*Based on skin erythema level.
**Based on skin erythema level; however, these appendages are believed to be less radiosensitive.
***Slightly higher RBE assumed since eyes are believed more radiosensitive.

Table 11.2 Radiation exposure dose limits currently recommended by the National Aeronautics and Space Administration.

(After Gill [35], National Academy of Sciences Space Science Board [59], and Billingham [8]).

longed enough to allow recovery. Finally, it should be pointed out that one important change was made in the original radiation exposure limits table established by the National Academy of Sciences Space Science Board [84]. Pointing out that alpha particles may be present in greater numbers in large solar flares than originally predicted, Billingham [9] suggested that it was more logical to specify biologic limits in terms of rem since the alpha particles encountered during space missions would probably have an RBE greater than 1. Although penetration of the space suit by solar "wind" alpha particles will be so small that these particles will have essentially no biologic effectiveness, alpha particles from high energy solar flares could, on the other hand, present a significant hazard to occupants of spacecraft, especially if shielding is minimal [22, 96].

If there is a significant risk of an astronaut being exposed to levels of radiation dosage above those in Table 11.2 or its future modifications, it will be necessary to have him take special protective measures. This is based on the fact that increasing the shielding incorporated in a spacecraft hull or providing a highly shielded compartment in a spacecraft might not be possible in the light of the great weight penalties these measures impose. Optimum cabin shielding should be provided by distributing on-board systems and stores to keep the doses to critical organs to a minimum. Since estimated doses received from solar flares tend to vary considerably in different parts of space cabins, an astronaut may be able to take up a "safer" position in the cabin during a solar flare. The early high-energy component of a flare is essentially unidirectional in space [73]. Orienting the spacecraft in the direction of the arriving flux could therefore be an effective protective measure. Appropriate distribution of moveable on-board equipment and stores might add to the directional shielding effect. In an emergency situation it might be found necessary to provide an astronaut with local shielding which could be placed over critical areas of his body, such as eyes, thorax or abdomen. Lastly, the space suit should be designed to provide adequate shielding during extravehicular operations, or the durations of such

operations carefully controlled to protect an astronaut, especially from skin injury.

Several recent reviews have indicated that there is no radio-protective drug with a therapeutic index suitable for human use at the present time [6, 7, 58, 65, 89, 93, 99, 100, 112, 115]. Although hundreds of chemical compounds have been shown to have some radio-protective effect in mammals, marked species variability, especially with respect to toxicity, has prevented extrapolation of results with such compounds to man [35, 37, 38, 58, 65, 69, 85, 93, 100, 112, 115, 119]. Furthermore, no data are available on the single or combined use of such drugs on humans.

A rather "shotgun" approach to drug studies has evolved from a failure to define the exact mechanism of radiation injury. Current thought supports simultaneous action of radiation on critical biologic molecules through direct hit phenomena and harmful secondary reactions of chemically reactive ions and radicals with critical sites on molecules. Free radicals are created mainly by the action of radiation on the abundant intra- and extracellular water. Apparently by scavenging free radicals, compounds consisting of a free sulfhydryl group separated by not more than 3 carbon atoms (e.g., cysteine, glutathione, cysteamine, AET or aminoethylisothiourea, MEA or mercaptoethylguanidine) have, especially in the light of their relatively low toxicity, been the more effective radiotherapeutic agents in animal studies [35, 37, 58, 65, 69, 77, 93, 100, 112]. Other antioxidants (e.g., ascorbic acid, BHT or butylated hydroxytoluene) have been particularly effective in the rat [38]. Possibly on the same basis, various natural food substances (e.g., alfalfa, broccoli, vitamin mixtures) have been mildly effective in the guinea pig [85]. The radioprotective effect of drugs such as 5-hydroxytryptamine, histamine, and epinephrine has been attributed to the lowering of tissue oxygen, an increased amount of which appears to enhance the production of these harmful radicals [65, 112]. Several investigators have recently found that for some unknown reason, dimethylsulfoxide (DMSO), which has remarkably low systemic toxicity in both animals and humans, exerts a radioprotective effect in animals [5, 39, 63, 81, 91]. Since this agent

has a high penetrating power through intact skin and promotes the cutaneous penetration of certain drugs, the question is raised as to whether or not it alone or in combination with another radioprotective agent might give not only systemic, but also selective dermatologic protection from radiation when applied topically (63, 108, 109).

The toxicity and rapid detoxification or metabolic breakdown of almost all radioprotective drugs and the extreme rapidity of ion and free radical formation in the tissues have dictated that virtually all of these drugs be administered just prior to exposure (35, 58, 65, 112). Analysis of the energy-flux relationships in early stages of a flare may allow prediction of organ-specific doses during the remainder of the flare and the subsequent potential value of radioprotective drugs.

An adequate tissue level of the prophylactic agent must be maintained during the anticipated exposure. At the present time, the low therapeutic index of radioprotective drugs renders their use in space impractical. Toxicity might be adequately reduced, however, by using combinations of these drugs, each in a lower dosage. It cannot be overstressed that the potential hazard presented by a radiation exposure must always be weighed against the potential toxicity of the radioprotective drug in the light of maintaining optimum astronaut efficiency and assuring mission success.

Finally, since skin injury appears to be the most likely radiation effect beyond prodromal reactions to occur in space, one might suggest the development of a radioprotective agent which would selectively fix in the skin. Such drugs would require freedom from local and systemic toxicity to make their use in space practicable. It is also hoped that skin fixation may reduce the systemic component which is currently the limiting factor in the use of radioprotective agents.

Treatment

From past experience with acute effects of radiation on humans, it would, in general, seem best to treat in space clinical manifestations from radiation exposure as they arise, providing symptomatic therapy as dictated by sound clinical judgment (17, 21, 57, 65, 74, 76, 106).

This is due to the fact that many acute radiation effects are non-specific, so that therapeutic measures are directed mainly at signs and symptoms, such as nausea and vomiting, and infection.

Many drugs, given both orally and systemically, have been used to treat especially nausea and vomiting in the prodromal phase of the acute radiation sickness syndrome (19, 55, 60, 64, 70, 102, 110, 111, 118). Assessment of their effectiveness is difficult, however, due to the lack of well controlled clinical studies, ignorance of the precise etiologic mechanisms involved in the prodromal phase, and the fact that psychogenic overlay in tense, nervous individuals, especially those already suffering from unrelated illness, undoubtedly influences response to such drugs (16, 64, 111). Vitamins of the B complex, particularly pyridoxine, were the first agents with reported effectiveness, and are still widely used (102, 111, 118). Although antihistamines, such as cyclizine hydrochloride and diphenhydramine, have proven useful for motion sickness, they have not successfully controlled clinical manifestations in the prodromal phase (110, 111). In the past few years, phenothiazine derivatives, such as chlorpromazine, prochlorperazine thiopropazate, fluopromazine, pecazine, trifluoperazine and triethylperazine have been tried extensively and found to be more effective than all other drugs (19, 55, 60, 70, 110, 111). Of these tranquilizing agents, triethylperazine has shown the greatest promise for the control of nausea and vomiting in the prodromal phase (19, 55, 60). This drug, which appears to sedate both the chemoreceptor trigger zone and the vomiting center, is relatively free of side effects (19, 55, 60, 64). Further substantiation of the drug's effectiveness is still required. Finally, in the light of the lack of overwhelming success of any drug in controlling clinical manifestations in the prodromal phase, this area demands intensive investigation.

If a drug is available in space for the prodromal phase it might be given prophylactically to an astronaut who has received a high dose of radiation. In this respect, one must keep in mind the dangerous situation

which will result if an astronaut vomits into the weightless environment (Chapter 8).

Diarrhea following radiation exposure might be controlled with an antidiarrheal drug, such as methscopolamine bromide or diphenoxylate hydrochloride. The administration of an intravenous electrolyte solution, such as Ringer's lactate solution, might be indicated for the restoration or maintenance of fluid and electrolyte balance. Any infection must be treated with an appropriate broad spectrum antibiotic.

No specific treatment of radiation injury of the skin has evolved from past experience in this area. Artz [3] recommends application of a bland ointment, protection of lesions from further trauma and air with large bulky dressings, and relief of associated discomfort with an analgesic. Topical anesthetics are apparently ineffective in controlling pain. Radiation lesions would then be managed in space in a manner similar to that described for thermal burns in Chapter 13.

Recently, attempts have been made to modify the skin reaction to radiation with topical and oral cortisone preparations [11, 56, 62, 71, 82, 113]. Results, however, have been equivocal. There may be some suppression of the early erythema and some delay in the onset and initial severity of the main erythema phase, but the degree of skin damage eventually incurred by radiation has not been significantly altered by these preparations. Pertinent to an astronaut's performance following a severe skin dose of radiation is the fact that it has not been noted whether or not cortisone agents can reduce discomfort associated with the early and main erythema phases.

As previously mentioned, a significant risk of damage to an astronaut's bone marrow by solar flares in space cannot be definitely established from data to date. Accordingly, a requirement for transfusions of blood elements (e.g., red blood cell, white blood cell or platelet concentrates) or bone marrow transplants in space, cannot be predicted. If the need for such measures is indicated by future assessments of space radiation hazards, the cryogenic storage of blood cell concentrates and homologous

or autogenous bone marrow should be considered [2, 8, 12, 75, 76, 78, 107]. It is hoped that rapid advances in this technology could make such an approach feasible for space operations.

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