Immune System Effects Associated With Travel in Space

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Weightlessness and other stresses associated with space flight are known to produce a large variety of physiological changes, including cardiovascular adjustments, shifts in body fluid distribution, and alterations in body composition. Included among these changes, but less well studied, are subtle deviations in immune system parameters. A variety of abnormal immune system measurements have been observed repeatedly in both American astronauts and Soviet cosmonauts (1, 7), although all of the immunological abnormalities acquired during space flight appear to be reversible. Immune system changes have also been detected in experimental animals during space flight.

In space flights conducted to date, no important clinical derangements have been ascribed to immune system alterations. Nevertheless, the observed immunological changes are of potential concern for a number of reasons. Space travelers have experienced a variety of mild infectious illnesses or inflammatory processes. These have chiefly involved the skin and mucous membranes of the eyes, mouth, and respiratory tract. Despite careful attention to oral hygiene, postflight scores for gingival inflammation, and dental calculus were double those noted in astronauts prior to flight (3).

Further, the body flora of American and Soviet space crews have shown relatively consistent alterations (1, 2), including changes in the colonization of various body sites and well-documented spread of potentially pathogenic microorganisms among all crew members of a given flight.

In future flights to distant targets, derangements of the immune system may become more prominent over the course of time, and their clinical importance may grow. The immunological changes detected in cosmonauts who remained in space for more than 100 days included some subtle changes that were not noted in American or Soviet flights of shorter duration (7).

Further, in future flights, the potential dangers to the immune system arising from the high energy and high charge components of cosmic radiation will probably be magnified (1).

Immunological Aspects of Space Flight

Changes in Human White Blood Cell Counts. Human beings who venture into space have consistently shown neutrophilia in postflight blood samples as well as variable alterations in lymphocyte counts (1, 5, 7). In recent U.S. Space Shuttle flights, neutrophil numbers were doubled, although no increase in immature forms was noted. Total white blood cell counts were generally increased because of neutrophilia. These changes were transient and generally reverted to normal within several days to a week after returning to Earth. Total lymphocyte counts have not shown consistent changes, but after some flights, T-lymphocyte numbers were depressed. Blood samples collected after some flights have also shown depressed monocyte and eosinophil counts (1).

The postflight neutrophilia has been ascribed to increased blood epinephrine and steroid levels associated with the stresses of space flight (1, 2). However, white blood cell counts have not been performed in flight to determine the time of onset and magnitude of neutrophilia during flight. The doubling of leukocyte numbers in postflight blood samples is consistent with an epinephrine effect, but the gradual, week-long return to normal is not (1). The lack of band cells argues against a causal role for steroids. As an alternative possibility, the neutrophilia may result from a weightlessness-induced recirculation of neutrophils that, with the Earth's normal gravity, usually comprise the pool of margined white blood cells along the intima of blood vessels. The magnitude of the transient post-flight neutrophilia is in keeping with such a possibility (1).

Functional Changes in Human Blood Lymphocytes. In vitro studies conducted on postflight samples of purified human blood lymphocytes indicated a transient depression of T-lymphocyte function when compared with preflight values. T cells, when challenged with phytohemagglutinin, have shown impaired blast transformation in both United States and Soviet studies (5, 7). When measured, DNA production was also depressed. In some instances, T cells have also responded poorly in mixed lymphocyte cultures. A transient depression of nonspecific lymphocyte rosette formation with sheep red blood cells has also been observed in blood samples taken from astronauts as well as cosmonauts (5, 7). Lymphocytes obtained post-flight from astronauts after only 7 days in space showed an impaired production of alpha-interferon.

After two prolonged Soviet flights, the 140-day Salyut 6 and the 175-day Soyuz missions, minimal evidence of in-flight development of delayed hypersensitivity to "microallergens" of the normal body flora (Staphylococcus and Streptococcus sp.) and to formaldehyde led to a conclusion that, "The regularity of the changes in immunological reactivity found after long space flights confirms the need to search for means and methods of returning immunological reactivity to normal" (7). Studies in cosmonauts following a 185-day mission showed reductions in T-helper and natural killer cells, with unchanged suppressor activity. These indices gradually returned to normal during readaptation on Earth (7).

In a study conducted in the Spacelab (4), cultured human lymphocytes were treated with mitogenic concentrations of Con A. The cells studied under conditions of weightlessness demonstrated...
less than a 3% response when compared with control samples studied on Earth. Interpretation of these data is obscured because the experiments lacked an adequate positive control (1).

A full immune response requires physical cell-to-cell interaction among lymphocytes and macrophage/monocytes. Whether the weightlessness of space flight adversely affects these cell-to-cell interactions (in vivo or in vitro) is unknown.

**Measurement of Humoral Factors.** In most space flights conducted to date, no significant changes have been noted in serum immunoglobulins (5, 7, 8), but after certain Soviet missions including a 49-day Salyut flight, increases in total serum IgA, IgG, and IgM were reported (7). Because such changes were not observed after more prolonged flights, their cause and importance remain in doubt. To date, no attempts have been made to administer vaccines or standardized test antigens during space flights to determine the adequacy of primary or secondary humoral immune responses in human subjects.

Complement factors have generally remained normal, although postflight values of C3 were elevated after several of the mid-duration Salyut flights, and C4 increases were present after the same 49-day mission in which immunoglobulin increases were noted (7). During the American Skylab program, significant changes were rarely found in related plasma proteins such as transport proteins, protease inhibitors, or other plasma proteins. The few scattered exceptions included elevated concentrations of α-2-macroglobulin, and in two crewmen, slight increases in lysozyme values which persisted for several days (1).

**Microbiological Data from Manned Space Flights.** Numerous microbiological studies have been done in both United States and Soviet space programs (1, 2, 7). Data on several virus groups were obtained in the Apollo program. Among causes for future concern were a consistent interpersonal transfer of potentially pathogenic bacteria and fungi among crew members of each flight studied, and repeatedly, an increased microbial concentration and contamination of cabin air, potable water, and internal cabin surfaces (2, 6, 9).

The microflora of space crew members have shown a tendency for intercrew transfer; increases in the microbial colonization of new body sites and of new foci of pathogenic microflora on the skin and in the upper respiratory tract; a tendency toward increased virulence of pathogenic autoflora; increases in the numbers and types of aerobic bacteria and of carrier states for Mycoplasma; but decreases in the number and variety of fungi and anaerobic bacteria (1, 6, 7, 9).

**Animal Studies.** Much valuable immunological information could be gained by conducting studies in animals taken aboard space flights, but very little has been done in this regard. No studies have been reported of sensitization to test agents or of primary or secondary responses to well-studied immunogenic antigens, or to resistance against a variety of standardized microbial challenges.

In one study, 14 rats flown in a 22-day mission showed thymic and splenic hypoplasia, with a reduction of lymphocyte numbers in these organs. In an unexpected finding, splenic lymphocytes obtained postflight from another group of rats carried on a 20-day space flight showed an increased in vitro responsiveness to the mitogens PHA and Con A as well as to both specific and nonspecific antigens (1). However, very few rats were studied, and standard deviations in the data were large.

**Missing Essential Information.** Although 200 individuals have traveled in space for periods up to 8 months without demonstrating more than incidental problems from infection or inflammatory processes, available data indicate that some aspect of space flight clearly alters the cells that are primarily responsible for providing normal host immunity and microbial defenses. Other data reveal that the environmental conditions within currently available space vehicles will lead to an increased exposure to crew members to potentially dangerous microorganisms.

The report of the ad hoc Working Group on Research Opportunities on Immunocompetence in Space (1) listed 15 general areas in which essential immunologic information is missing. These included questions about the reliability and importance of the available data, the need for longitudinal, serially collected data to define immune system changes during space flights, and the need for information on the numbers and functional capacities of key cells of the immune system. Information is needed about the secretory products of these cells, including the ability to produce, release, and respond to these important bioactive factors.

No studies have been reported on aspects of mucosal immunity or on the organ-related lymphoid tissues of the gut and skin. The ability of the immune system to respond to new antigens and immunogens while in space is unknown. Information is also lacking about the identity and mechanisms of the space-related factors that can cause the observed immunological changes. The importance of microgravity, per se, in affecting the immune system is also unknown (1). Finally, more information is needed, from studies inflight, about the shedding and interpersonal exchange of potentially dangerous viruses such as those that cause hepatitis and respiratory infections.

It is possible to design a number of research studies in an effort to gain much of this basic information (1). However, if cell-mediated and humoral immune responses could both be shown to function within normal limits in human beings during lengthy space flights, many concerns would be alleviated about the available data that show slightly abnormal parameters of immunocompetence. The uncertainty about overall functional effects of the immunological abnormalities detected to date remains the crux of the problem.

**References**

The National Institute of Allergy and Infectious Diseases (NIAID) has awarded a 5-year contract to ERCI Facilities Service Corporation based in Fairfax, Virginia, to establish and operate a reference and research reagent repository to facilitate AIDS research. The total projected funding for the repository is approximately $7.7 million for 1988 through 1992. Advanced Biotechnologies Inc., a subcontractor to ERCI, will be responsible for reagent assay and evaluation. The repository, which is also designated as one of several World Health Organization (WHO) AIDS repositories, is expected to be operational by April 1988. Materials from the repository will be available to any qualified investigator whose research relates to AIDS, whether they are NIAID supported or not.

When fully operational, the repository will be a clearinghouse for biological and chemical substances required for AIDS research. These will include available clones of the human immunodeficiency virus (HIV), HIV-2 (the AIDS virus found primarily in West Africa), the closely related simian immunodeficiency virus (SIV), other related retroviral and cellular proteins, and plasmids that express viral enzymes. The repository will also contain standardized reference antisera (antibodies), and monoclonal antibodies to primate retroviruses. Biological response modifiers such as lymphokines, cytokines, and monokines (cellular hormones that influence cell function), and chemicals or drugs used to modulate the immune system will be standardized and distributed to the scientific community. At present, only the interferons have an international reference standard; these other biological response modifiers have no reference units.

A survey is being sent to approximately 1400 researchers worldwide, chosen from scientific literature, to obtain a consensus about what reagents should be included in the repository. All reagents will be available as standards in quantities sufficient to compare the activity or purity of proteins being obtained by research laboratories. Comparison of various reagent samples by the repository scientists will also allow standardization of reagents within the repository, and determination of the most active products.

Materials from the repository will be given out for research purposes only, and with assurance that the recipient will not give the material to a third party. (Reagents will not be given out for therapeutic use, or for purification purposes for commercialization.) Each organization donating a reagent will receive information about requests for the reagent, such as who has requested it. Any organization that donates a reagent to the repository will be listed in the repository's biannual catalog of reagents and will be cited in informational material about the reagent. The repository will be represented at all appropriate scientific meetings. NIAID is collaborating with WHO to make the repository available to AIDS researchers worldwide.

AIDS, first recognized in 1981, is now a global epidemic. The Centers for Disease Control (CDC) estimate that between 1.5 and 2 million Americans are currently infected with HIV. More than 52,000 cases of AIDS have been reported to the CDC since 1981 and about 60 percent of these people have died.

Research on AIDS at institutions around the world is progressing at an unparalleled rate. Nonetheless, much remains to be learned about HIV, and how it interferes with normal function of human cells. HIV preferentially infects a crucial part of the immune system, the T4 cells, that coordinate and direct the many immune response components. When T4 cells are unable to perform their normal role, the immune system collapses and is unable to defend the body from microorganisms and certain types of cancer.

Basic research, for example, to determine precisely how HIV interacts with a CD4 receptor on a T4 cell to gain entry to the cell, or what causes latent (inactive) HIV to become active and cause disease, often requires difficult-to-obtain experimental materials. Because this research is necessary to provide information to design prevention strategies and effective therapies,