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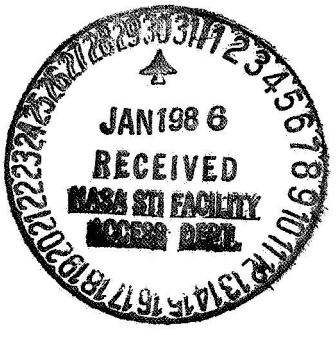
RESEARCH OPPORTUNITIES ON IMMUNOCOMPETENCE IN SPACE

December 1985

Prepared for

THE LIFE SCIENCES DIVISION
OFFICE OF SPACE SCIENCE AND APPLICATIONS
NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
WASHINGTON, D.C. 20546



under

Contract Number NASW 3924

FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY

LIFE SCIENCES RESEARCH OFFICE
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FOREWORD

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments of topics in the biomedical sciences. Reports are based upon comprehensive literature reviews and the scientific opinions of knowledgeable investigators engaged in work in specific areas of biology and medicine.

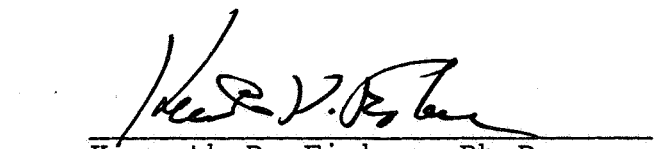
This technical report was developed for the National Aeronautics and Space Administration (NASA) in accordance with the provisions of Contract Number NASW 3924. It was prepared and edited by William R. Beisel, M.D., of The John Hopkins School of Hygiene and Public Health, and John M. Talbot, M.D., Senior Medical Consultant, LSRO.

The LSRO acknowledges the contributions of the investigators and consultants who assisted with this study. The report reflects the opinions expressed by an ad hoc Working Group that met at the Federation on July 25-26, 1985 and other consultants who contributed to the study. The study participants reviewed a draft of the report and their various viewpoints were incorporated into the final report. The study participants and LSRO accept responsibility for the accuracy of the report; however, the listing of these individuals in Section VI does not imply that they specifically endorse each study conclusion.

The report was reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent Society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures, the report was approved and transmitted to NASA by the Executive Director, FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of each individual member of the FASEB constituent Societies.

December 31, 1985
(Date)



Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office

SUMMARY

Neutrophilia, relative lymphopenia, and impaired blastogenic responsiveness of T-lymphocytes have been demonstrated repeatedly in postflight blood samples from space crews. These abnormalities of the cellular immune system apparently revert to preflight values within approximately one week postflight. Other space-related alterations of human immune function have been described such as postflight eosinopenia, monocytopenia, reduced percentage of B-lymphocytes, and decreased natural killer cell activity and production of α-interferon by lymphocytes. No consistent alterations of humoral immune function have been reported. The causes and mechanisms involved in these responses are unknown, nor is it known at which stages of flight the reported responses occur.

Microbiologic assays of space crews and spacecraft suggest that interpersonal transfer of pathogenic bacteria and fungi occurs inflight along with increased growth of opportunistic microorganisms, spread of the normal skin flora to more body sites, and simplification of the anaerobic bacteria in the spacecraft. Bacterial contamination of air and onboard potable water supplies is a recognized potential source of illness.

Whether the aforementioned changes in elements of the immune system and the microflora of space crews and spacecraft represent a significant, potential health problem for space crews needs to be determined. To date, resistance to infection during and following missions of up to seven months' duration has apparently been adequate. Episodes of inflight illness have generally been mild, brief, and readily controlled. Postflight illness attributed to impaired immunocompetence has not been reported.

Currently, a paucity of reliable data on the effects of space flight on immunocompetence prevents a firm scientific conclusion about the potential operational and clinical significance of reported changes. The ad hoc Working Group participants regarded the following as the most significant of the available data: (1) reduced postflight blastogenic response of peripheral lymphocytes from space crew members; (2) postflight neutrophilia, persisting up to seven days; (3) gingival inflammation of the Skylab astronauts; (4) postflight lymphocytopenia, eosinopenia, and monocytopenia; (5) modifications and shifts in the microflora of space crews and spacecraft; and (6) microbial contamination of cabin air and drinking water. Discussion of these responses and other available data disclosed numerous gaps in knowledge that is essential for an adequate understanding of space-related changes in immunocompetence. These missing data are listed as questions in Section III.

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The ad hoc Working Group discussed the significance of the available data. For example, if the data on the altered blastogenic responsiveness of lymphocytes from postflight blood specimens are valid, this is an important change that needs precise explanation. Such an explanation might be an inability of T-lymphocytes to generate growth factors and growth factor receptors, suggesting marked dysfunction with implications for serious impairment of immunocompetence. Another example is the question of the functional condition of the circulating neutrophils. The gingivitis experienced in the Skylab Program could reflect neutrophil dysfunction such as impairment of cell surface adhesion reactions. Whether neutrophil function remains normal inflight and during the first few days postflight is unknown.

In the opinion of the ad hoc Working Group, if NASA contemplates future studies of the immunologic aspects of space flight, first priority should be given to tests and experiments that could indicate whether space flight impairs cellular and humoral immunity. Pre-, in-, and postflight tests of space crew personnel would be mandatory parts of such a program. Despite the sophisticated studies that could be attempted, a clear-cut demonstration of normal cell-mediated immunity as measured by delayed dermal hypersensitivity reactions during and/or postflight along with normal inflight humoral responses to a defined antigen would alleviate many of the concerns that have been expressed on the basis of our current lack of knowledge.

Finally, if further experience demonstrates that space flight does compromise immunocompetence, NASA should plan a series of investigations to determine the causes and mechanisms and develop methods of intervention. Specific approaches, tests, and methodologies that would aid in accomplishing these objectives are presented in Section IV.

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I. INTRODUCTION

A. BACKGROUND

The National Aeronautics and Space Administration (NASA), through its various life sciences programs, conducts and supports scientific investigations of the biological changes that are associated with space flight. Among the effects whose causes and potential significance are not well understood are those involving the immune system. Few, if any, instances of inflight or postflight illnesses or other untoward effects have been ascribed to impairment of cellular immune function; yet neutrophilia, relative lymphopenia, and a diminished blastogenic responsiveness of T-lymphocytes present in postflight samples of blood obtained from the astronauts and cosmonauts have been observed repeatedly (Barone and Caren, 1984; Cogoli and Tschopp, 1985; Kimzey, 1975a,b; 1977; Konstantinova et al., 1973; Pestov and Geratewohl, 1975; Taylor and Dardano, 1983).

The humoral immune system has shown no detectable abnormalities in space flight on the basis of relatively limited studies, except for inconsistent variations in Complement Factor 3 (C3) and immunoglobulin levels observed postflight. The microflora associated with space crew members as well as that of the interiors of spacecraft undergoes changes during flight; however, no adverse effects of these changes on crew health have been reported to date. Changes observed in the immune system and microflora of astronauts, in combination, raise the very real possibility that dangerous consequences could ensue in the future, especially when missions last for extended periods.

NASA-supported research on the immunologic aspects of space flight has been modest in comparison with programs on other adverse biomedical phenomena such as space sickness, cardiovascular deconditioning, bone loss, and muscle atrophy. Reports of advisory groups such as the NASA Life Sciences Advisory Committee (Whedon, 1978) and the Space Science Board of the National Research Council (Bricker, 1979) have not emphasized space-related immunologic changes among topics identified for further research. Currently, NASA has no formal plan for generating extramural immunologic studies except for some limited experiments in the future Spacelab mission dedicated to the life sciences. However, it should be recognized that the science of immunology has progressed tremendously in the past decade. Immunologic advances and current testing methods render some previously acquired data on the immunologic aspects of space flight obsolescent and in need of reevaluation. A thorough evaluation of available data and expert judgment on the health and safety implications of space-related alterations in immune functions are necessary to determine the possible need for additional state-of-the-art investigation in immunology. Therefore, NASA requested that the Life Sciences Research Office of the

Federation of American Societies for Experimental Biology undertake a review of its research program and research needs in relation to immunologic effects and microbial flora changes during space flight. This report is based upon the opinions and suggestions of an ad hoc Working Group of knowledgeable scientists (see Section VI) whose members met at the Federation on July 25-26, 1985, and other experts who contributed data and refinements.

B. OBJECTIVES AND SCOPE

The objectives of the LSRO study are:

(1) to review extant knowledge of the subject;

(2) to examine NASA's current and projected research program;

(3) to identify significant gaps in essential knowledge;

(4) to formulate additional suggestions for future research consideration by NASA; and,

(5) to produce a documented report of the foregoing items that can be used for NASA research program planning.

The scope of the study includes a review of available data on immunologic and microbiologic responses observed from inflight as well as ground-based investigations, changes in humoral and cell-mediated limbs of the immune system, stress and neuroendocrinologic immune modulation, nutritional influences, neutrophils, monocytes and macrophages, activators and modulators, possible therapeutic intervention, and investigational techniques, methods and facilities. This report incorporates the opinions of the members of the ad hoc Working Group on the practical significance of space-related immunologic changes in future long-term space missions including the Space Station and the additional studies needed to establish whether the observed changes imply potentially serious consequences for space crews.

II. AVAILABLE INFORMATION ON IMMUNOLOGIC ASPECTS OF SPACE FLIGHT

A. DATA FROM SPACE FLIGHT

1. Human Data

Prior to the time when published data became available from the Skylab series of manned space missions (December 1972 to February 1974), alterations of some indices of immunologic function in space-flown animals, astronauts, and cosmonauts had been reported (Berry, 1974; Konstantinova et al., 1973; Vorobyev et al., 1983). Data suggested that both animal and human subjects demonstrated postflight neutrophilia and either lymphopenia or lymphocytosis. Transient neutrophilia, reversible by the second postflight day, was observed in the Apollo astronauts. NASA space medical specialists considered that the neutrophilia probably resulted from increased blood epinephrine and steroid levels associated with mission stress (Berry, 1974), but other causes must be considered. Postflight lymphocyte counts tended toward a delayed but fluctuating increase. The immunocompetence of the Apollo astronauts' lymphocytes, estimated by in vitro response to mitogenic stimulation, was considered unimpaired (Berry, 1974).

In the Skylab Program, indices of humoral immunity measured in pre-, in-, and postflight blood specimens of the astronauts (i.e., plasma immunoglobulins and complement factors) were within normal limits except for a slight decrease in C3 levels in postflight samples. No significant changes were found in related plasma proteins such as transport proteins, protease inhibitors, and other plasma proteins except for elevated levels of α_2-macroglobulin and, in two of the three crewmen of Skylab 2 (28-d mission), a slight increase in lysozyme levels that persisted for several days (Kimzey, 1977; Kimzey et al., 1975b). No studies have been performed to determine how humoral immunity would respond to standardized antigenic stimuli. At recovery, the Skylab astronauts demonstrated an increase in the absolute white cell count, reflected by increased numbers of neutrophils. There were no significant changes in the absolute numbers of lymphocytes, but T-lymphocytes were depressed (Kimzey, 1977). Several measures of the functional capacity of the T-cell component of the cellular immune system were done in the Skylab Program: (1) blast transformation of purified lymphocytes by in vitro mitogenic challenge with phytohemagglutinin (PHA); (2) mixed lymphocyte cultures; and (3) rosette formation by lymphocytes with sheep erythrocytes. Results from Skylab missions 2 and 3 (28- and 59-d respectively) showed a depression of RNA synthetic response to PHA on the day of recovery (R+0) with return to preflight values within 3-7 d. The decrease in RNA responsiveness was less pronounced in lymphocytes from the crew of Skylab 4 (84-d). DNA production in response to PHA appeared to be depressed in seven of the nine crew members (Kimzey, 1977); however, Taylor and Dardano (1983) indicated that the depression

of DNA synthesis rates was not significant. The mixed lymphocyte culture responses were within normal limits, and the E-rosette test indicated a reduced number of circulating T-lymphocytes on R+0, with return to normal levels by R+3 d (Kimzey, 1977).

Comparison of pre-, in-, and postflight classes of immunoglobulins (IgG, IgM, IgA, IgE, and IgD) of four crew members who participated in the 10-d Spacelab 1 mission (November 28 to December 8, 1983) revealed only minor fluctuations that were considered insignificant (Voss, 1984). The experimental protocol included control studies for circadian rhythm effects and a sampling of 20 Caucasian males for normative data. The results substantiate the findings in the Skylab program of essentially no influence of space flight on immunoglobulin concentrations (Kimzey, 1977).

The reactivity of lymphocytes from two cosmonauts to T-cell mitogenic stimulation was reported as depressed to approximately 42% of preflight values following a 63-d Salyut-4 space mission (Konstantinova et al., 1978). Similar results were reported from Soviet missions of 5, 30, and 140, but not of 96 days' duration (Cogoli and Tschopp, 1985; Konstantinova et al., 1973). On day R+2, one of the crew of the 63-d mission showed a 4-fold reduction in numbers of T-lymphocytes as estimated by nonspecific rosette formation with sheep erythrocytes. By R+7, T-lymphocyte levels were normal. IgA content of blood taken on R+2 was decreased 3.8-fold in one and 6- to 7-fold in the other crew member, with a tendency toward normalization by R+7. This had not been observed in previous Soviet and United States space missions (Konstantinova et al., 1978). The authors also reported sensitization of lymphocytes to staphylococcal and streptococcal "allergens" of the "main representatives of human automicroflora" by three methods: (1) lymphocyte specific blast transformation; (2) inhibition of macrophage migration; and (3) intracutaneous injection of 0.1 ml of four "allergens" on R+15, with examination of the local skin reaction after 24 and 48 h.

Pre- and postflight measurements of blood from cosmonauts in a series of space missions showed in a majority of instances a postflight leukocytosis and lymphocytopenia (Konstantinova et al., 1978; Legen'kov et al., 1977). Noting that previously used methods had made detailed reappraisal and comparison of results of earlier studies impossible, Taylor and Dardano (1983) reported the results of tests of lymphocyte transformability in which a modification of Apollo and Skylab methodology was used. The method permitted direct correlation of ^{3}H thymidine uptake with incubation time as well as mitogen concentrations. Lymphocytes from astronauts who flew in the first four Shuttle flights (durations varied from 2-8 d) demonstrated a significant reduction in blastogenic responsiveness ranging from approximately 39 to 82% of mean preflight values. In addition, immediate postflight neutrophilia and a decreased number of eosinophils were observed (Taylor and Dardano, 1983). In six of the eight subjects tested, the lymphocyte blastogenic

reactivity remained depressed at R+3 to R+5 relative to preflight values; however, the trend was toward normalization. The ad hoc Working Group regarded this as the best of the studies reported to date on the effects of space flight on human lymphocyte blastogenic responsiveness.

Finally, human lymphocytes exposed inflight in culture to mitogenic concentrations of Concanavalin A (ConA) during the Spacelab 1 mission demonstrated less than 3% of the levels of activation of ground control samples (Cogoli and Tschopp, 1985; Cogoli et al., 1984).

The Soviet flights in the period 1977-1981 in the Salyut 6-Soyuz program involved 30 cosmonauts and included five 2-man missions of 96, 140, 175, 185, and 75 days' duration (Vorobyev et al., 1984). The authors reported consistent postflight immunologic changes including a decrease in blood T-lymphocytes and diminished reactivity and capacity for proliferation of these cells. Blood studies of the cosmonauts following the 185-d flight showed reductions in T-helper and natural killer cells, with unchanged suppressor activity. These indices gradually returned to normal during readaptation on Earth. No serious inflight illnesses were reported.

Postflight values of serum C3 were elevated following 16-, 18-, and 49-d Salyut missions; C4 levels were unchanged except for a significant increase in the 49-d mission (Guseva and Tashpulatov, 1979, 1980). Pronounced postflight increases in serum concentrations of IgA, IgG, and IgM were reported from the 49-d flight (Cogoli, 1981).

During the first few postflight days of the 140-d Salyut 6-Soyuz mission (MC-2), blood from the two cosmonauts showed a marked decrease in T-lymphocytes, which normalized by postflight day 7 (Yegorov, 1979); however, after the 175-d mission (MC-3), this index was depressed in only one of the two crewmen (Yegorov, 1980). After both missions, the responsiveness of the T-lymphocytes to blastogenic transformation by PHA was depressed. This index had normalized by postflight day 24 of MC-2 (time of second blood sampling) and by postflight day 8 in the commander of MC-3. Early postflight depression of serum IgG values was reported in one of the two crew members in the MC-2 mission (Yegorov, 1979) and apparently in one member of the MC-3 crew (Yegorov, 1980). Minimal evidence of inflight development of delayed hypersensitivity to "microallergens" of the normal flora of the body (staphylococcus and streptococcus) and to chemicals (formaldehyde) was presented based on inconsistent, slight increases in production of leukocyte migration inhibiting factor and on delayed dermal hypersensitivity responses (Yegorov, 1979, 1980). The author concluded: "The regularity of the changes in immunological reactivity found after long space flights confirms the need to search for means and methods of returning it to normal."

In general, the inflight clinical condition of the astronauts and cosmonauts has remained good (Berry, 1974; Nicogossian and Parker, 1982; Vorobyev et al., 1983, 1984). Inflight infections and inflammations of the skin, conjunctiva, mouth, nose, throat, and larynx of the 27 Apollo astronauts are listed in Table 1 (Berry, 1974). These medical problems were mostly mild, self-limited, or responded promptly to treatment.

Among the total nine astronauts in Skylab, three instances of mild dermatitis, one sty, one incipient axillary furuncle, and a brief episode of unilateral serous otitis were reported (Hordinsky, 1977). Mean scores for gingival inflammation and dental calculus approximately doubled over preflight values; but the degrees of change were less in Skylab 3 (59-d), and, in no case was there dental or oral disability (Brown et al., 1977). However, it is noteworthy that careful oral hygiene was maintained by all the Skylab astronauts before the missions, including removal of all dental plaque and calculus on preflight day 4.

In summary, the results of a series of investigations of the effects of space flight on various aspects of human immunocompetence commencing with blood counts in the earliest missions and progressing to measurements of several indices of cellular and humoral immunity suggest that space flight induces some changes in immunocompetence, the best documented being suppression of T-lymphocyte numbers and blastogenic transformation.

2. Animal Studies

Hypoplasia of spleens and thymus glands with reduced numbers of cells in the splenic red and white pulp as well as decreased numbers of lymphocytes in the cortex of thymus glands of 14 rats flown in space for 22-d were reported by Durnova et al. (1976). Structural recovery of the lymphoid organs approached normal by postflight day 27 except for delayed recovery of the splenic mantle zones composed of small lymphocytes. Ground-based experimental controls subjected to simulated space flight conditions (except for weightlessness and acceleration) showed qualitatively similar, but quantitatively lesser, histologic changes in the lymphoid organs; splenograms from simulated flight rats did not show the changes induced by space flight.

Splenic lymphocytes from rats flown in space for 20-d did not show a decreased blastogenic activity when compared with ground controls; instead, they demonstrated an increased responsiveness to the nonspecific mitogens PHA and ConA as well as certain specific and nonspecific antigens (Mandel and Balish, 1977). The findings did not support a hypothesis that a 20-d space flight may cause degradation of cell-mediated immunity.

Table 1. Apollo Inflight Medical Problems

Symptoms/Findings	Etiology	Number of Occurrences
Inguinal rash	Collection device	1
Inguinal rash	*Tricophyton rubrum*	1
Urinary tract infection associated with prostatic congestion	*Pseudomonas aeruginosa*	1
Conjunctival injection	Spacecraft atmosphere	4
Eye irritation	Fiber glass	1
Skin irritation	Fiber glass	2
Skin irritation	Biosensor sites	9
Respiratory irritation	Fiber glass	1
Recurrence of facial rash	Contact dermatitis	1
Stomatitis	Aphthous ulcers	1
Stomatitis	Undetermined	1
Rhinitis	Oxygen and low humidity	2
Laryngitis	Undetermined	1
Barotitis	Barotrauma	1
Coryza	Undetermined	3
Seborrhea	Activated by spacecraft environment	2
Dermatitis, pustular	Biosensor sites	2

Adapted from Berry, 1974

However, the authors noted that the small number of animals in each experimental group and the large standard deviations in the data indicated a need for replication of the experiments and caution in interpretation of the results.

B. DATA FROM GROUND-BASED STUDIES

Six healthy male subjects were kept at strict horizontal bed rest for 62 d during which three of the subjects performed daily physical exercises. On test days 1 and 18 all subjects, and on day 50 three subjects, were exposed to transverse acceleration on a centrifuge (Mikhaylovskiy et al., 1967). After day 46, blood properdin was detectable in only one subject. A 17-26% decline in neutrophil phagocytosis occurred in the three nonexercising men. Toward the end of the test period, saliva lysozyme activity decreased 5 to 8-fold compared with initial levels, and, between days 13 and 33, the bactericidal activity of the skin decreased, again predominantly in the nonexercising group. The authors noted a parallelism between hypokinesia and susceptibility to "inflammatory ailments" (for example, rhinopharyngitis, follicular angina, acute periodontitis).

In a 56-d ground simulation of a Skylab mission in which the environmental factors essentially duplicated those of the Skylab orbiting station except for weightlessness, radiation, and accelerations of launch-orbit and deorbit-reentry, no change in the reactivity of small lymphocytes of the three-man crew was demonstrable (Ritzmann and Levin, 1973).

Human lymphocytes exposed to 1.8% of 1 G by rapid rotation in a clinostat were 50% less active in response to ConA mitogenic stimulation than 1 G controls (Cogoli et al., 1980). Based on their own investigations and analyses of other reports on gravitational biology, the authors suggested that hypogravity depresses, whereas hypergravity enhances lymphocyte activation by mitogens.

Several investigators have reported the effects on susceptibility of experimental animals to certain infectious organisms resulting from exposure to environmental variables in simulated closed environments (Angrick et al., 1974; Giron et al., 1967; Gillmore and Gordon, 1974; Gordon and Gillmore, 1974a,b). For example, in a study of the effects of a simulated space cabin environment on host resistance to infection, mice were subjected to a chamber barometric pressure of 380 mm Hg (18,000 ft equivalent) at 43% oxygen partial pressure (ground equivalent) before, during, or after challenge by intraperitoneal injection of a mengovirus suspension (Giron et al., 1967). Four groups of 100 mice were exposed to the test environment in the space cabin; the other two groups remained at ground level: (1) experimental group A remained at ground level before, during, and after an intraperitoneal injection of a mengovirus suspension; (2) group B was injected at ground level, then taken to the test

environment of 18,000 ft equivalent; (3) group C remained in the test environment for 2 wk, then was injected and kept at ground level; (4) group D was kept in the test environment before, during, and after injection; (5) group E was kept in the test environment, then brought to ground level for 1 h for injection and returned to altitude; and (6) group F animals were kept at altitude, brought to ground level for injection, kept there for 24 h, then returned to altitude. Groups B, C, and E, but not group D, demonstrated increased susceptibility to the viral infection compared with controls. Group F animals, which were exposed to increased barometric pressure at ground level for 24 h following injection, did not show a significant change in susceptibility. Thus, increased susceptibility in these experiments was associated with either an increase or a decrease of ambient barometric pressure by 380 mm Hg. The authors noted that even temporary and apparently minor changes in environmental conditions may alter host resistance (Giron et al., 1967).

Rats were suspended in harnesses in a head-down position with forepaws touching the bottom of the enclosure to simulate some of the aspects of weightlessness (Caren et al., 1980; Morey, 1979). They were immunized with sheep erythrocytes and kept in the antiorthostatic, hypokinesic, hypodynamic mode for selected periods of up to 23 d for studies of antibody response, serum immunoglobulins, spleen and thymus weights, hematocrit, and white cell differential counts. In comparison with untreated cage controls, thymus glands were smaller in the experimental group (N=21) and a group of harnessed, weight-bearing controls (N=20). Otherwise, no significant differences were observed among the experimental and control groups (Caren et al., 1980).

When compared with conventionally housed controls, rats subjected to simulated weightlessness for 2 wk by means of the same model (Morey, 1979) showed an 80% decline in interferon production when challenged with polyriboinosinic-polyribocytidylic acid (Sonnenfeld et al., 1982). Ivanov et al. (1983) exposed 3-year-old Macaca mulatta monkeys to 7- to 12-d periods of hypokinesia in a head-down position; before entering the antiorthostatic position, two animals spent 2 d in a primate chair, and three were subjected to clinostatic hypokinesis for 7 d. After sacrifice, both experimental groups demonstrated a significant rise in serum complement activity and a decline in heterophil antibodies to ram erythrocytes. The authors inferred that an increase in complement content reflects adaptation to head-down tilt and a decrease in heterophil antibodies, an inhibition of B-lymphocytes.

C. MICROBIOLOGIC DATA

Numerous microbiologic studies have been done during United States and Soviet space programs. These have varied in scope and comprehensiveness, tending to emphasize the bacteria and fungi and to omit the viruses. In different missions,

microbial data were obtained from cultures of specimens including interior cabin surface swabs, samples of air and water, and swabs from skin and mucus membranes of the crews. These data are organized chronologically in the following paragraphs. The potential importance of the observed microbiologic changes must be evaluated with due consideration given to the immunologic effects of space flight.

Studies of the microflora of the Apollo astronauts before and after the space flights showed that interpersonal transfer of pathogenic bacteria and fungi occurred regularly, that growth of opportunistic organisms seemed to be favored, and certain organisms showed decreased antibiotic resistance postflight (Berry, 1973, 1974). Berry (1973) listed the following changes from pre- to postflight:

- Decrease in anaerobic bacteria
- Increase in numbers and types of aerobic bacteria
- Increase in body sites with microorganisms
- Tendency for intercrew microbial transfer (e.g., Staphylococcus aureus)
- Decrease in fungal isolates
- Increased carrier states for Mycoplasma

Potential pathogens in the throat, especially Candida albicans, were present before, during, and after Apollo missions. Species of Proteus, Pseudomonas, and other pathogens increased markedly on the urine collectors. Trichophyton rubrum was linked with chronic dermatitis of one Apollo astronaut, and species of Haemophilus and Pseudomonas with urinary tract infections in two others (Berry, 1973, 1974). Microbiologic assessment in the Apollo Program included characterization of the viral and mycoplasma flora of the crew members and serologic assays for antibodies to approximately 13 specific viral antigens and two viral groups (ECHO and adenovirus). In addition, viral identification was done pre- or postflight when crew members had signs or symptoms of illness (Ferguson et al., 1975). Unusual episodes of viral illnesses were not experienced in the Apollo missions. Viral assays have apparently not been done in subsequent United States space programs.

During the Apollo 16 mission, spores of Bacillus thuringiensis were exposed to space flight conditions to determine the effects on viability and ability to produce toxins. Exposure to full sunlight resulted in decreased viability whereas the spacecraft environment without light or with solar irradiation at peak wavelengths of 254 and 280 nm did not change viability. Postflight toxin production did not differ statistically from that of ground-based controls (Simmonds et al., 1974).

Sampling and analysis of the spacecraft atmosphere during a 56-d simulated Skylab mission revealed no consistent changes in concentrations or types of airborne microorganisms (Brockett and Ferguson, 1975). Microbiologic studies of the Skylab astronauts and their orbital workshop and command modules done before, during, and after the flights generally corroborated the findings in earlier manned space flights: gross contamination of the Skylab environment, microbial simplification of anaerobic bacteria, intercrew transfer of pathogens, and no evidence of postflight "microbial shock" (defined on p.15) (Taylor et al., 1977). Swab and gargle samples from 10 body sites, urine and fecal specimens, cabin air, and surface samples were collected before, during, and after each mission. Inflight concentrations of bacteria in the air of Skylab 2 and 3 were low, but a relatively high concentration occurred in Skylab 4, attributable to contamination by Serratia marcescens. This organism was subsequently recovered as a new colonizer from all three Skylab 4 astronauts and was shown to have colonized the nasal mucosa of one crew member.

Compared with preflight levels, inflight surface contamination by aerobic bacteria was low in the first manned mission (Skylab 2) and nearly doubled in Skylabs 3 and 4. Inflight anaerobic surface contamination more than doubled preflight levels in Skylab 2, increased 5-fold by mission day 54 in Skylab 3, and approximated preflight values in Skylab 4, the latter condition having been caused by the loss from the bacteriologic milieu of Proprionibacterium acnes, reflecting a diminution of the occurrence of this species in the skin of the astronauts (Taylor et al., 1977). Inflight fungal isolations from surfaces in Skylab 2 were unremarkable, more than double preflight levels at day 57 in Skylab 3, and increased about 10-fold in Skylab 4, which was subsequently traced to "mildewed" liquid-cooled garments stowed aboard Skylab. The investigators concluded that mission duration up to 84 d (Skylab 4) does not correlate with gross numerical changes in the autoflora, viable aerobic bacteria tend to increase in total numbers, anaerobes to decrease, and, while the numbers of aerobic genera and species change little, the numbers of anaerobic types decrease. Inflight cross-contamination, colonization, and infection with S. aureus were demonstrated in the Skylab series, corroborating previous reports of intercrew transfer of pathogenic organisms in missions lasting up to 18 d (Ferguson et al., 1975; Taylor, 1974).

Yegorov (1979) listed general conclusions from microbiologic studies in some earlier flights of the Soyuz series and the Salyut orbiting station:

- Changes in total numbers of representatives of normal microflora of the skin
- Appearance on upper respiratory tract mucus membranes of organisms not normally present

- Increased number of foci of pathogenic microflora on the skin of carriers
- Temporary colonization by pathogenic staphylococci on mucous membranes of previous noncarriers by intercrew microbial exchange
- Tendency toward increased virulence of pathogenic autoflora
- Increased concentration of microorganisms including certain pathogens in cabin air and on internal surfaces
- Apparent development of microbiologic and immunologic conditions favoring increased susceptibility to postflight infections.

Marked inflight changes in the species composition of the microflora of the upper respiratory tract were found in the MC-1 cosmonauts (96-d mission), but not in the MC-2 crew who showed, in addition, no significant changes in their dermal autoflora (Yegorov, 1979). In MC-3, there was a moderate increase in numbers of staphylococci in the nasal passages of one crew member. On the day of landing and 4 d later, the numbers of pathogenic staphylococci and β-hemolytic streptococci in the mouths and throats of the MC-2 crew were very high, but had normalized by postflight day 7. Phage typing of oral specimens of staphylococci provided some evidence of probable intercrew exchange; however, there was no evidence of exchange in the MC-3 cosmonauts (Yegorov, 1980). As in the MC-1 and MC-2 expeditions, microflora appeared in the mouths and throats of the MC-3 cosmonauts that were not normally indigenous: Streptococcus faecalis, Klebsiella pneumoniae, and Enterobacter hafnia. These findings were ascribed to weakening of local mucosal immunity. No remarkable postflight changes were observed in the microflora of the gastrointestinal tract. For example, at 3 d postflight, the intestinal flora of the MC-3 cosmonauts showed no shifts "... against a background of Bifidobacterum stability ..." which had been achieved by preflight use of the drug, "Biphydumbacterin," and by inflight use of an amino acid/vitamin supplement (Yegorov, 1980). Technical details of the drug and the nutritional supplement were not reported.

Medical microbiology of the crews of the first four orbital test flights of the Shuttle was done as a part of the medical program to maintain the health and safety of the crew members (Pierson, 1983). Samples were collected at about 30, 10, and 2 d preflight and on the day of recovery and postflight day 5 from ears, nose, throat, and rectum (or a fecal specimen) and a morning urine specimen. Interior surfaces of the spacecraft, cabin air, and waste management systems were sampled 30 and 2 d prelaunch and on recovery day, and the potable water

system was sampled following servicing for flight and 3 d post-flight. In addition, random samples of food stores onboard the orbiter were analyzed. The four flights, each with a crew of two, were all in the spacecraft Columbia, and their durations were from 2+ to 8 d. Tables 2 and 3 list microflora isolated from the samples.

Although a variety of potential pathogens is evident from the list in Table 2, no overt clinical manifestations of infections were observed in the crews nor was there evidence of cross-contamination between members of the 2-man crews (Pierson, 1983). However, after landing in the third mission, bacteria present in the cabin air were also isolated from the upper respiratory mucosae of the crew, who had not shown the presence of these forms in preflight samples (species were not identified in Pierson, 1983). This finding emphasized the need for careful monitoring of the cabin air. During the sampling periods of the potable water supply, the numbers of colony-forming units ranged from 5 to 9100 per 100 ml water.

The effects of living and working in isolated environments on the microbiologic and immunologic defenses of the inhabitants are of interest as partial analogues of spacecraft environments. Moreover, there is some evidence that certain viral pathogens may persist undetected in carriers for many weeks until conditions favor their activation. For example, two outbreaks of respiratory tract illness occurred in a group of 18 personnel at 8 and 20 wk following total isolation at South Pole Station, Antarctica (Parkinson et al., 1980). In a similar environment, outbreaks of common colds occurred 17 wk after complete isolation of an Antarctic station party, long after the accepted incubation periods of human respiratory viruses and at a time when the introduction of new viruses was apparently impossible (Allen et al., 1973). In both of these studies, the investigators were unable to recover the causative viruses from specimens collected during the outbreaks. Another partial analogue of the environment of a spacecraft is the submarine. In typical 60-d patrols in Polaris nuclear submarines, the reported pattern of acute respiratory illness, based upon 10 years' experience, indicated a maximum prevalence during the 3-wk refit period when crews mingled with shore personnel. This was followed in one reported instance by a short secondary peak during the second week of patrol (Tansey et al., 1979; Watkins, 1970). In most crews, the prevalence of acute respiratory illness remained low throughout the patrol. However, there are two reports of mid-patrol outbreaks of respiratory infections in nuclear submarine crews, one attributed to long incubation of the offending agent, the other to activation of an unidentified virus (Sawyer and Sommerville, 1966; Watkins, 1970). These data from Antarctica and the two mid-patrol outbreaks of acute respiratory illness in nuclear submarine crews raise important questions about the possible persistence and reactivation of respiratory (and other) viruses in space flights of long duration, especially if immunosuppression reduces the resistance of crew members.

Table 2. Potential Pathogens from Shuttle Crew Members

Potential Pathogens	Isolation Site
Staphylococcus aureus	Nose, throat, ear
Pseudomonas aeruginosa	Nose, throat
Enterobacter aerogenes	Nose, throat
Enterobacter hafnia	Throat
Á-hemolytic *Streptococcus*	Throat
Candida albicans	Throat, feces
Candida parapsilosis	Nose, ear
Aspergillus (six species)	Nose, throat, ear, feces
Klebsiella pneumonia	Throat
Proteus morganii	Nose
Penicillium citrinum	Urine, feces
Rhodotorula rubra	Ear

Source: Pierson, 1983

Table 3. Potential Pathogens from Shuttle Spacecraft and Potable Water System after Four OFT* Missions

Interior Surfaces	Potable Water Supply
Staphylococcus aureus	*Pseudomonas denitrificans*
Drechslera hawaiiensis	*Pseudomonas fluorescens*
Rhodotorula rubra	*Pseudomonas* sp.
Paecilomyces variotti	*Flavobacterium* sp.
Trichosporon cutaneum	*Enterobacter* sp.
Geotrichum candidum	*Rhodotorula minuto*
Enterobacter agglomerans	
Aspergillus (six species)	
Acinetobacter calcoaceticus	

Source: Pierson, 1983

* orbital flight test

The term, locked flora, relates to a type of isolation in which a host organism, such as a mammal, remains in a locked environment in which sterile food, water, and air are provided and there is no exogenous microbial contamination (Balish et al., 1977). As reviewed by Luckey (1966), a series of studies of animals with locked flora which were reported during the period 1895-1965, generally showed a marked decrease in the numbers of intestinal species, with disappearance of many organisms. In some studies, only one or two bacterial species and perhaps one yeast could be isolated from intestinal sites. Luckey (1966) reviewed the anticipated anatomic, physiologic, and biochemical changes associated with simplification of the microflora. These included the possibility of microbial shock, which was defined by the author as "the precipitous and harmful action of micro-organisms and/or their products upon the host." Maintenance of a normal, diversified intestinal microflora was considered essential as a host defense mechanism; apparently this requires periodic reinoculation of microorganisms. The author suggested ways of maintaining a balanced intestinal microflora during space flight in order to prevent possible microbial shock after return to Earth (Luckey, 1966).

In a study to test the hypothesis that the microbial flora of mammals might change markedly toward simplification in an isolated environment, Balish et al. (1977) investigated the microbiology of beagles maintained in a locked environment (sterile food, water, and air, and no exogenous microbial contamination) for 30 mo. The results indicated that long-term confinement of beagles in such an environment was associated with increased diversity of the microflora. In comparison with non-isolated controls, larger populations of anaerobes, staphylococci (mainly S. epidermidis) and Candida albicans were observed in the isolated beagles. Conversely, the control dogs showed larger populations of aerobic and facultative bacteria (Balish et al., 1977). The data suggested to the investigators a decreased capacity of the intestinal microbial flora of the isolated dogs to inhibit the growth of potential pathogens. According to the authors, such a response in long-term space flight could represent a serious infectious threat for the crew.

Conclusion

Although microbiologic assays of spacecrews, spacecraft, and associated systems and equipment continue to be done as a part of medical surveillance, space medical authorities in the United States and the Soviet Union have, in recent years, apparently regarded the possible need for additional basic investigations of the microbiologic aspects of space flight as low in priority.

III. OPINIONS OF THE AD HOC WORKING GROUP

A. APPRAISAL OF AVAILABLE DATA

NASA scientists provided the LSRO ad hoc Working Group on Immunocompetence in Space with information and data from the United States and Soviet Union on the immunologic and microbiologic aspects of space flight. The participants examined pertinent data, and assessed the available information in terms of its scientific validity and adequacy for use in manned space programs.

1. Potentially Serious Immunologic and Microbiologic Changes

The cumulative experience with the health of space crews in terms of resistance to infections during and following missions of up to 7 mo duration has apparently been favorable to date. Episodes of inflight illness have been mild, brief, and readily controlled. Postflight illness that might involve impaired immunocompetence has not been documented (Berry, 1974; Dietlein, 1977; Nicogossian and Parker, 1982; Vorobyev et al., 1983, 1984). However, longitudinal studies of possible changes in immunocompetence have been neither extensive nor complete.

The Working Group emphasized the paucity of data on immunologic functions in space. However, if the data on altered blastogenic responsiveness of lymphocytes (PHA response) are valid, this is an important change. The data are consistent in showing abnormal effects, some of which persist for at least 7 d postflight. The most recent data represent an excellent, careful study of the PHA response featuring such refinements as different doses of PHA and different time points to check proliferation (Taylor and Dardano, 1983). Despite the results obtained in this study, the PHA response is a crude test. The results could mean nothing more than a slight, clinically insignificant decline in the numbers of T-cells in the peripheral blood. Conversely, for example, if the impaired PHA response represents a pronounced inability of the cells to generate lymphokines or lymphokine receptors, it is potentially important, especially for long-term flights. In view of the variations in this response in past studies of cosmonauts and astronauts, and the relatively small number of subjects involved to date, additional validation of the PHA data is needed.

Postflight neutrophilia has been observed consistently. Of itself, the postflight neutrophilia is not necessarily important; that is, it could well be a physiologic response to elevated circulating stress hormones associated with the critical processes of reentry and landing on Earth (Berry, 1974). However, the question whether neutrophils are abnormal in the neutrophilia is very important as is the companion question pertaining to the lymphocytes.

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Some of the in vitro data are also potentially important such as the impaired production of α-interferon by lymphocytes taken from cosmonauts after 7 d in space (Talas et al., 1983) and the marked depression of blastogenic responses of human lymphocytes flown in Spacelab 1 (Cogoli and Tschopp, 1985). However, the participants noted that Cogoli and Tschopp (1985) carried out a very limited study, and no positive controls were used. The question of in vitro changes in lymphocyte blastogenesis, conducted in space, should be considered unresolved at this time.

The importance of space-related effects on the immune system could exceed that of other biomedical effects of space flight because, in some circumstances, the microbiologic environment in spacecraft and crew could become hazardous in the presence of impaired immunocompetence. There is some evidence of a relative increase in potential pathogens during flight and of intercrew microbial transfer. For example, malfunction of the food or human waste management systems could allow growth of microorganisms that could overcome the immunological competence of space crew personnel.

Other relevant facets of microbiologic-immunologic relationships in space flight involve the incomplete knowledge of the characteristics of changes in the microflora of crew and surroundings in space flight. More data are needed on such questions as simplification of the flora in restricted, isolated circumstances; persistence of potential pathogens, intercrew microbial exchange; and the influence of inflight microfloral changes on host resistance.

2. Possible Etiology and Mechanisms

Environmental factors and certain biologic responses to space flight that possibly influence immunologic functions are listed below; the related opinions and concepts of the Working Group are noted. The participants emphasized that the cause(s) of the observed changes in lymphocytic responsiveness and in numbers of circulating lymphocytes and neutrophils postflight is unknown. Whether such changes are of practical importance must await further elaboration of what happens to the immune system during space flight.

- Environmental physical factors such as microgravity, accelerations, and space radiation

- Physiologic and psychologic factors and "stress"

  - adaptive responses to 0-G: loss of approximately 2.0 l body fluid, decreased plasma volume, altered hemodynamics and lymph flow, bone loss, muscle atrophy, cardiovascular deconditioning, etc.
  - nutritional and metabolic disturbances
  - altered fluid/electrolyte/hormonal balances

  - confinement, hypodynamia, hypokinesia, reduced oxygen demand
  - lack of privacy, social isolation, boredom
  - perceived danger, anxiety
  - problems of crew leadership, cohesion, and compatibility

- Increased osteoclastic activity at the expense of other cell types including lymphocytes and monocytes

- Sequestration of T-lymphocytes that are capable of blastogenic transformation

- Abnormal splenic hemodynamics and function

- Inhibition of helper factors

- Enhancement of suppressor factors

- Changes in bone marrow metabolism related to altered bone marrow hemodynamics

Discussion and Opinion

The aggregate of the psychophysiologic stress effects must be somewhat unique when one considers the limited human experience with microgravity and the environment of space flight and the unusual accelerations of launch-orbit and deorbit-reentry. Although the stresses associated with space flight are not well defined in terms of their biologic effects, they have been proved operationally acceptable in view of the successful accomplishment of manned space missions lasting up to 7 mo. A majority of space medical experts apparently regard the net effect of such stresses as physiologically acceptable in the absence of overt functional impairment. During uncomplicated space flights, the combined stresses are probably of moderate degree, but with considerable individual variability in responses. For example, during the immediate prelaunch period, some spacecrew members experience heart rates of 120-160; others remain around 60. The reported changes in levels of stress hormones during space flight appear unremarkable in terms of possible effects on the immune system. However, available inflight data do not exclude the possibility of a surge in secretion of stress hormones and other neurohormones sufficient to cause substantial immunologic changes that are probably undetectable in spot blood samples or 24-h urine collections. Psychologic factors are believed by some investigators to influence immune regulation (Anonymous, 1985; Bartrop et al., 1977; Chang, 1984; Park et al., 1971; Poteliakhoff, 1985). The subject of psychoneuroendocrinologic modulation of immunity, while a relatively new field of special investigation, is attracting numerous adherents (Blalock and Smith, 1985; Plotnikoff and Murgo, 1985; Riley, 1981; Rose, 1980; Spector, 1983).

The members of the Working Group noted the vagaries associated with use of the term, stress, and emphasized the need for improved definition and characterization of stress responses during space flight. While such assessments are hampered by lack of precise methodology, the traditional physiologic and biochemical indices and the flight surgeon's appraisal of stress effects should be retained in NASA's study protocols in order to expand the data bases. Additional measurements should be considered so that a practical stress assessment protocol may be developed and put into practice. Voice analysis, expert behavioral observation by video or photography, intention tremor, and performance tests are candidate methods (Christensen and Talbot, 1985).

Further to the subject of psychoneuroendocrinologic influences, the in vitro production of an ACTH-like peptide by mouse lymphocytes infected with Newcastle disease virus, and other experimental evidence have suggested the existence of a lymphoid-adrenal axis (Blalock and Smith, 1985). The molecule appears to be identical with ACTH, and the ACTH receptor from the lymphocytes appears to be identical to ACTH receptors on cells of the adrenal gland. If interactions of the neuroendocrine and immune systems prove to be additive or involved in cybernetic regulatory loops, it may become feasible to measure these interactive endocrine and nervous system functions (possibly including some stress effects) via fluorescence microscopic analysis of receptors on lymphocytes. Other methods to assess these molecules and interactions include: radioimmunoassays, Western blotting, and messenger RNA analysis such as cytoplasmic RNA dot blotting. These methods of measuring such molecules could be used in future studies of possible direct correlations between stress effects and altered immune function in space crews.

Nutritional imbalances, particularly those involving deficient protein, energy, vitamin, zinc, and iron status, are known to affect immunocompetency (Beisel et al., 1981; Gershwin et al., 1985). Transient deficiencies of these and other nutrients as a result of loss from the body, sequestration, or diminished intake occur during generalized febrile illnesses, and may even accompany common infections, such as colds. Moreover, the losses of red blood cell mass, bone mineral, and lean body mass that occur in space flight, while not clinically debilitating in missions lasting up to 7 mo, could conceivably alter essential aspects of nutrition in flight members. These changes in turn, could lead to immunoincompetence of varying degrees and forms. The Working Group members noted that spacecrew meals contain quantities of micronutrients based on the U.S. Recommended Dietary Allowances (National Research Council, 1980). Under normal flight conditions, these should provide adequate dietary intakes. However, adequate in vivo data on indicators of nutritional status such as serum zinc and iron concentrations and those of other essential trace nutrients during space flight are not available.

Whether microgravity exerts a direct effect on the immune system is essentially unknown. Results of some experiments suggest that it does, but it is not feasible, based on available data, to exclude other variables that may contribute to such effects as the depressed blastogenic responsiveness of human lymphocytes flown in Spacelab 1 (Cogoli and Tschopp, 1985) or the enhanced inflight production of interferon by human lymphocytes and the reduced natural killer cell activity and interferon production of lymphocytes from cosmonauts following a 7-d flight (Talas et al., 1983). As mentioned in Section II-A, the impairment of blastogenic responsiveness of lymphocytes from postflight samples of space crew members' blood appears to be well documented by both U.S. and Soviet observers (Taylor and Dardano, 1983; Yegorov, 1979, 1980). Such space-associated changes in lymphocyte responsiveness are potentially important if they reflect something more than a slight decrease in the number of T-cells in the peripheral blood, such as an inability to produce interleukin-2 receptors. From a practical point of view, establishing that space flight induces important functional changes in the cellular elements of the immune system is probably a more pressing matter than determining the exact cause although both types of information are needed.

Radiation

The records of exposures to ionizing radiation to date indicate that inflight dose rates and total doses have been well within the operational safety limits employed by NASA (National Research Council, 1970). The crude mean total dose in the ten Apollo translunar missions, each lasting an average of 9.3+ d, was approximately 0.43 rad (Bailey, 1975). In the 84-d Skylab 4 mission, the mean dose was 7.8 rad, and in eight Space Shuttle missions, the overall mean total dose was 0.42 rad (Benton et al., 1984). Estimated crew exposures for the 90-d Space Station mission range from 15-20 rad, and for a 1-y mission to Mars, approximately 200 rad. Based on the 20 rad estimate, an average daily dose of approximately 220 mrad in the Space Station nearly matches the recommended limit for bone marrow, falls within the limit for eye lens and skin, but exceeds the limit for testis (National Research Council, 1970).

For obvious reasons, no experimental data are available on the hematologic effects of prolonged, continuous, low-dose, whole body exposures of human subjects to low-LET (linear energy transfer) radiation such as gamma radiation. Consequently, animal data must be used for estimating probable biologic effects of low-dose irradiation during space flight. For example, as reviewed by Casarett (1969), dogs, mice, rats, and rabbits chronically exposed (e.g., >100 wk in rabbits, 79 wk in mice, 24 wk in guinea pigs) to whole body gamma or x-irradiation showed persistent depression of blood lymphocyte counts at 0.5, 2.2, >1.0, and 2.2 R/d; and of neutrophil counts at 3.0, 4.4, 10, and

›10 R/d respectively. In guinea pigs, lymphocyte counts declined at 0.11 R/d and neutrophil counts at 2.2 R/d (Casarett, 1969). Dogs exposed to brief daily doses of x-irradiation 6 d/wk at rates extending from 0.1 to 10.0 R/d demonstrated no significant change in blood lymphocyte counts during 2 y of exposure at 0.1 R/d, but a substantial decrease at 0.5 R/d. Blood neutrophil count was mildly depressed after 1 y at 1.0 and 3 R/d but not at 0.1 or 0.5 R/d (Casarett, 1969).

More recently, Seed et al. (1984) reported some of the hematologic effects of continuous, lifetime exposures of beagles to ^{60}Co gamma irradiation. At 4 R/d absorbed dose, two of 25 animals developed aplasia, 11 showed myeloproliferative disorders, and one, a lymphoproliferative disorder. In animals with these disorders, median times to death, respectively, were: 1462 d, 1435 d, and 2076 d. The authors noted that transitions in lethality rates during continuous, very low dose-rate radiation exposure (defined as 5 R/d) probably result from the sparing of lymphohematopoietic function which appeared to prevent aplastic anemia and septicemias and to enable a time-dependent development of late-arising, nonhematopoietic syndromes such as solid tumors and degenerative disorders in long-term survivors. At 5 R/d such late-arising syndromes were similar in type and frequency to those in the nonirradiated controls. At the 5 R/d rate of exposure, the hematopoietic progenitor cells appeared to acquire radioresistance (Seed et al., 1984).

The members of the Working Group were of the opinion that radiation exposures of the magnitudes and durations experienced thus far in manned space missions would probably not account for the reported space-related changes in the immune system. Nevertheless, they recognized that little is known about several aspects of this subject, such as the possible influence on immune competence of the high energy (HZE) and high charge (Z›2) particle components of cosmic radiation, the combination of environmental factors in space flight with low-dose, continuous radiation, or the reliability of extrapolating animal data to human beings.

In 1984, NASA commissioned an extensive review of the biomedical problems of space radiation by the National Council on Radiation Protection and Measurements. It is understood that the results of the review will be used for revising recommended permissible limits for use in the Space Station and other manned space programs.

Interactions of Cells of the Immune System. Postflight flow cytometry of crew members' blood after Shuttle missions STS 41-B and 41-D (N=11) showed a reduction in percentage of B-lymphocytes and monocytes. Monocytes and macrophages interact importantly with lymphocytes via lymphokines and monokines as well as by direct contact. Whether these factors have anything to do with immunologic changes in space flight is unknown. With respect to stress effects, under in vitro conditions, corticosteroids

in reasonably physiologic concentrations can inhibit both synthesis and secretion by macrophages and other cells of the immune system of a variety of materials such as interferons, that are involved in immunologic functions. Decreased monocyte counts may reflect a reduction in production rate in the bone marrow or possibly a change in numbers of monocytes in marginating pools in the blood vessels. Gamma-interferon produced by helper T-cells is an important modulator of macrophage activity, in part because it stimulates a complex system which leads to toxic oxygen intermediates that are involved in both intra- and extracellular killing mechanisms.

T-lymphocytes interact with other cell types in generating the immune response, including macrophages, B-cells, and other non-T-lymphocyte accessory cells. In tissue culture and probably in vivo, cluster formation involving T-cells, B-cells, and macrophages is required for initial T-cell activation and subsequent development of the full immune response. Certain steps in the activation of T-lymphocytes apparently require direct cell-cell physical contact while other steps require humoral factors acting at short or long distances. Moreover, activation of T-cells apparently requires physical interaction with a non-T accessory cell, usually a macrophage or monocyte (Unanue, 1981). Whether the weightlessness of space flight adversely influences cell-cell physical interactions is unknown. The recent in vitro demonstration that human T-lymphocytes were evidently not activated inflight by ConA as they were in paired ground level controls suggests possible impairment of cell-cell physical interaction (Cogoli and Tschopp, 1985); however, the ad hoc Working Group considered it unlikely that microgravity would interfere with the agglutination process initiated by ConA in a lymphocyte culture. Interpretation of these data is obscured because the experiments lacked an adequate positive control. These controls could be generated, for example, by means of a macrophage-depleted culture of lymphocytes with added ConA and phorbol esters.

Neutrophils. A consistent finding appears to be a postflight neutrophilia. It has traditionally been attributed to an elevation of stress hormones especially during the critical phases of atmospheric reentry and landing (Berry, 1973, 1974). In recent Shuttle flights, the numbers of neutrophils were doubled; this size of an increase is characteristic of the release of the marginated pool. Such neutrophilia can be induced experimentally by exercise or adminstration of epinephrine. Thus, the reported elevation of blood epinephrine may be a correct explanation for the release of the marginated pool of mature neutrophils. Increases in band forms were not reported, which suggests that elevated concentrations of corticosteroids were probably not involved in causing the neutrophilia. The cause of the neutrophilia is somewhat clouded by its reported persistence postflight for approximately 7 d, which suggests that epinephrine is not a fully suitable explanation because the normal turnover of neutrophils is rapid, ~ 7 h.

Whether the neutrophils retain normal function during space flight is an important and unresolved question. Presumably, they do remain normal in view of the generally favorable record of good health of space crews. However, the good health of space crews may be deceptive because patients with severe neutrophil dysfunction can go months or even years without a major infection, only to die of an overwhelming microbial infection at a later date. The gingivitis reported in the Skylab series (Brown et al., 1977) could reflect neutrophil dysfunction such as an impairment of cell surface adhesion reactions or chemotactic and phagocytic responsiveness (Cogen et al., 1983). For example, even though white blood cell counts may be two to three times normal (magnitude similar to space-associated neutrophilia), patients with recurrent, severe, bacterial infections associated with functional deficiencies of their neutrophils, such as a deficiency of the C3bi receptor in which the cells lose their ability to stick and agglutinate, have severe gingivitis. The blood neutrophil count in these patients is twice normal, similar to those of space crews. For details of this type of deficiency, the reader is referred to Anderson et al. (1985), Arnaout et al. (1985), and Springer (1985).

Severe neutrophil problems are associated with severe gingivitis whereas patients with life-threatening disorders who have normal neutrophils do not have gingivitis. The gingivitis reported in the Skylab astronauts was described as nondebilitating but as "... prominently elevated increments of ... gingival inflammation postflight as compared with preflight values" (Brown et al., 1977). There is no evidence that the Skylab astronauts experienced severe functional disorder of their neutrophils; nevertheless, the occurrence of gingival inflammation suggests that transient impairment of neutrophil function may have occurred. It is important to determine whether abnormal neutrophil function occurs in space flight, for, in long-term missions, impaired neutrophil function could be disastrous. Accordingly, the cause of the gingivitis in the Skylab astronauts deserves an adequate explanation. Suggestions for evaluating the functional status of neutrophils are presented in Section IV.

Factors that Influence Microbiologic Changes. Well-known features of the space flight environment that contribute to microbiologic changes include the confined living space and crowding, closed recirculating cabin atmosphere, suboptimal human waste disposal, and lack of opportunity for customary quality and amounts of personal hygiene such as frequent bathing and changes of clothing. The enforced crowding presumably favors exchange of microflora among crew members. Inadequate microbial containment in the spacecraft is another deficiency as exemplified by reports of the escape of human and animal excreta into the living and working environment. Some of these factors may be amenable to improved engineering of environmental control and waste disposal systems.

The effects of such "locked" environments on human autoflora are not clear. In animal studies, the phenomenon of locked microbial flora reportedly results in simplification of the intestinal flora (Luckey, 1966). However, Balish et al. (1977) observed increased diversity of the intestinal microflora of beagles that were kept in an isolated environment for 30 mo. Theoretically, marked simplification of, for example, the gastrointestinal microflora would deprive the host of part of the antigenic challenge that is considered necessary for maintaining immune competence.

There is some evidence of simplification of the anaerobic bacteria in the microflora of the air in spacecraft (see p.10-11), which apparently results from continuous recirculation through the filters and carbon dioxide adsorber beds of the environmental control systems.

B. SIGNIFICANCE OF AVAILABLE DATA

It is apparent that a decision by NASA management to establish a comprehensive research and analysis program in immunocompetence would require convincing evidence of a definite probability that space crews in future missions would experience clinically significant immune dysfunction. To determine whether such a probability exists, gaps in essential information must be filled. These are outlined in Section III-C.

The participants regarded the following as the most significant of the available data:

- Reduced postflight blastogenic response of peripheral lymphocytes from space crew members
- Postflight neutrophilia persisting for up to 7 d
- Gingival inflammation in the Skylab astronauts
- Postflight lymphocytopenia, eosinopenia, and monocytopenia
- Modifications in microflora of crews and spacecraft
- Bacterial contamination of air and drinking water

As previously noted, the impaired postflight response of lymphocytes to blastogenic activation by PHA is of major concern if it reflects lymphocyte dysfunction such as the inability to generate essential growth factors and growth factor receptors. A dysfunction of this sort persisting during the course of many months could compromise immunocompetence. The persistent postflight neutrophilia does not appear to result simply from increases in stress hormones. If it represents a functional

abnormality of the neutrophils, this could lead to the breakdown of host defenses against microbial infections. The gingivitis that occurred in the Skylab series is consistent with impaired neutrophilic cell-surface reactions.

Although supporting data are scanty, the apparent disappearance of monocytes from the peripheral blood is extremely important if it reflects a true depletion of this essential cell type. Unpublished data from recent Shuttle flights appear inconsistent in that monocytes were observed in standard differential preparations but not by flow cytometry. Finally, the bacterial contamination of Shuttle drinking water (Pierson, 1983) which was observed during the first three orbital flight tests of the Columbia spacecraft is of obvious concern. It is understood that NASA is attempting to correct this deficiency in order to meet its set standard of a microbe-free drinking water supply. Similar attention should be paid to contamination of the air.

C. MISSING ESSENTIAL INFORMATION

For a variety of reasons, the program of investigation of the immunologic aspects of manned space flight has been inadequate. However, as reviewed in Section II, a number of studies of the subject, some of which were of high quality, have provided useful data and some concepts for future research planning. Nevertheless, competent judgment of whether space-related immunologic and microbiologic changes have finite clinical and operational implications is hampered by lack of knowledge, the most significant elements of which may be identified by the following questions:

- Because there are very few reliable basic data, the question remains: Does space flight cause untoward effects on the immune system?

- During a space mission, when does the blastogenic responsiveness of the crew members' lymphocytes change?

- What happens to the white blood cell (WBC) count during space flight? When does the neutrophilia commence? What changes occur in the WBC differential picture? Do immature forms of neutrophils appear in peripheral blood? What happens to the lymphocyte differential distribution?

- What factors influence the depressed incorporation of thymidine by lymphocytes in response to mitogenic stimulation? Are humoral factors or changes in cell composition involved? Is autologous serum needed in vitro to reproduce the blunted PHA response?

- What happens to the functional capacities of neutrophils, monocytes, and macrophages? Do they retain normal chemotactic, phagocytic, bactericidal, and receptor-generating abilities and the ability to produce and release their important bioactive factors?

- Do monocytes and eosinophils really disappear from the peripheral blood? If so, why?

- How long do the following persist postflight: neutrophilia, lymphocytopenia, monocytopenia, eosinopenia, and the depressed blastogenic responsiveness of the lymphocytes?

- Are delayed-type hypersensitivity reactions normal during space flight?

- What is the prevalence of infectious diseases in space crew members during the first 2 mo postflight?

- What happens to viral parameters during space flight such as intracrew exchanges, changes in virulence, numbers, and possible contamination of air, water, and food?

- What happens to body stores of essential trace nutrients and minerals, such as zinc and iron that can influence the immune system?

- What happens to mucosal immunity in the conjunctivae, nose, oropharynx, larynx, trachea, bronchi, and the gastrointestinal and genitourinary tracts? Do organ-related lymphoid tissues such as those in the gut (GALT) and skin (SALT) undergo alterations?

- Does microgravity itself affect the immune system?

- Does gingivitis continue to occur during space flights? What are its incidence and duration? Is it attributable to trauma from preflight dental hygiene procedures, neutrophil dysfunction, or other identifiable factors?

- Are there laboratory signs of previously unrecognized subclinical infections among crew members immediately after landing and after several days to weeks post-flight? Laboratory tests for probing these questions might include red cell sedimentation rate, C-reactive protein, haptoglobin, orosomucoid, ceruloplasmin, and alpha-1-antitrypsin.

IV. RESEARCH SUGGESTIONS

In the opinion of the ad hoc Working Group on Immunocompetence in Space, NASA should plan and conduct a series of investigations aimed at settling the question of whether space flight induces changes in immune competence. The goal should be to characterize the changes in terms of their potential clinical and operational significance. Inflight investigations should predominate, with primary emphasis on human studies; however, inflight animal studies are also justified as a part of such a program. Postflight studies are important also, and all studies must be compared with ample preflight data. If the suggested research demonstrates potentially serious changes in immunocompetence, further attention could then focus upon causes, mechanisms, and means of intervention. The suggestions of the ad hoc Working Group are divided into four sections: immediate research needs, potential research needs, tests and methodology, and facilities and equipment. These research needs are derived, in part, from the questions raised in the preceding section.

A. IMMEDIATE RESEARCH NEEDS

Data from the following types of studies should lead to a firm conclusion on whether space flight causes changes in immunocompetence that imply potentially serious adverse health effects for space crews. The suggestions are presented in descending order of approximate priority.

- Determine inflight immune responses of space crew members including antibody production and delayed type hypersensitivity reactions to common antigens. (See Section IV-C for suggested methods.)

- Study the capacity of activated T-lymphocytes obtained postflight from space crews to make lymphokines such as interleukin-2, interleukin-3, and gamma-interferon and to generate lymphokine receptor such as that for interleukin-2. RNA extraction and Northern blots for five or six monokines and lymphokines can be done on a single frozen cell pellet (Wiskocil et al., 1985). For T-lymphocyte transformations, PHA and ConA are appropriate nonspecific mitogens; PPD, mumps, streptokinase-streptodornase, tetanus toxoid, and Candida albicans are useful specific antigens (Lane et al., 1986).

- Examine recruitment of human neutrophils and mononuclear cells and the release of their lysosomal contents inflight as well as postflight by means of in vivo induction of localized skin inflammation via the Rebuck skin window or blister machine techniques (Dale and Wolff, 1971; Hellum and Solberg, 1977; Rebuck and Crowley,

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1955; Scheja and Forsgren, 1985). The methods are essentially innocuous and frequently used in children. The resulting minor skin lesions offer a means of observing wound healing as well. Examining mouth washings for neutrophils is another means of acquiring some data on the inflammatory response as it relates to gingivitis or other oral lesions (Wright et al., 1986).

- Determine the temporal pattern of changes in key human immunologic parameters such as white blood cell count, differential count, and blastogenic responsiveness of T-lymphocytes. To be adequate, sampling times must include preflight baseline values, inflight at 24-48 h, mid-mission, and shortly before reentry; postflight at 24-48 h, as well as 7, 14, 21, and 30 d. Possibly related variables should also be measured in the blood specimens for this study including epinephrine, cortisol, acute phase reactants (C-reactive protein, haptoglobin, ceruloplasmin, orosomucoid, alpha-1-antitrypsin) as well as plasma zinc, iron, and copper.

- Determine the following functional capacities of peripheral blood neutrophils and monocytes obtained from specimens from space crew personnel at selected times postflight including within 24 h of landing, as well as 7 and 14 d: chemotactic response, adherence, locomotion, phagocytosis, degranulation, bactericidal activity, oxidative metabolism, and respiratory burst.

- Pre- and postflight studies of the uptake of complement-altered red blood cells by the reticuloendothelial system should be considered. Macrophage phagocytosis can be measured in vivo by the uptake of chromium-tagged, antibody-coated red blood cells by the splenic macrophages and the hepatic Kupfer cells. The procedure requires a series of blood samplings to estimate clearance of the tagged red cells (Frank et al., 1979, 1983). (See also Section IV-C, Methods.)

B. RESEARCH NEEDS SHOULD SPACE-RELATED IMMUNOLOGIC CHANGES DEMONSTRATE POTENTIALLY UNACCEPTABLE HEALTH RISKS

Laboratory evidence of impaired immunocompetence is not always associated with disease. However, if the results of the investigations suggested in Section IV-A should provide convincing evidence that long space missions (arbitrarily defined as >30 d) induce potentially unacceptable changes in immunocompetence, studies such as those described below will be advisable to determine the causes, mechanisms, and detailed characteristics of the changes and to develop means of intervention. The suggestions are listed roughly in descending order of priority.

- Determine functional responses of human T-lymphocytes activated during space flight by specific and non-specific antigens in terms of blastogenic transformation and ability to produce monokines and lymphokines.

- Examine the following functional and histologic parameters of neutrophils and monocytes from human blood obtained within 24-48 h after landing: morphology, motility, spreading ability, cell aggregation, adherence, degranulation, and oxidative metabolism. Measure the markers for the C3bi receptors such as the OKM-1 and LFA-1 antigens in neutrophils from crew members who demonstrate postflight neutrophilia.

- In vitro studies of the generation of human and animal cytotoxic T-cell populations against an appropriate battery of allogeneic stimulator cells should be conducted in space. The cytotoxic activity of these cultures could easily be measured on the appropriate radiolabeled cultured target cells such as K562 cells. Such studies need appropriate positive and negative controls in space and a full replicate of ground-based studies (Grabstein, 1980).

- Other in vitro flight experiments that would aid in characterizing cellular responses to the space flight environment should be considered. Examples would include changes in in vitro morphogenesis of monocytes over a period of 7 d in space and in endothelial cells in culture for contact inhibition and the laying down of basement membrane. In addition, it would be useful to determine the effects of space flight on activated cultures of HL60 cells in terms of their ability to differentiate into mononuclear and polymorphonuclear types of cells. Cells could be fixed and stained appropriately and culture fluid saved at various times of differentiation inflight for subsequent evaluation postflight.

- Other postflight assays of lymphocytic responses that should be considered include: (1) spontaneous lymphocyte proliferation in fresh specimens observed during the first few hours following venipuncture; (2) the response to a soluble antigen such as tetanus toxoid; (3) the response to alloantigen; (4) changes in patterns of subsets of lymphocytes; (5) numbers and functional capacity of natural killer cells; and (6) the cytotoxic lymphocyte response, that is, the interaction of the cytotoxic T-cell with an appropriate target cell (Lane et al., 1986).

- Flight experiments with mice or rats should be devised to examine the effects of space flight on several immunologic parameters including antibody responses to a variety of antigens administered immediately before or during flight (see Section IV-C for suggested antigens), possible changes in the morphology and immunologic characteristics of crucial organs and tissues of the immune system such as bone marrow, spleen, liver, lymph nodes, and organ-related lymphoid tissues of the upper and lower respiratory systems, gastrointestinal and genitourinary tracts and the skin, and measurement of prostaglandins in representative tissues of the immune system as well as pituitary gland neuropeptides. Acute phase reactants in serum should be measured as well (see p.30 for examples). All such parameters can be done with blood and tissues obtained postflight; animals preserved postflight would permit an assessment of temporal patterns of recovery. Procedural permutations could be added such as administering immunogens during flight instead of preflight, and taking specimens of body fluids, tissues, and microflora inflight.

- A set of measurements should be selected and added to NASA's routine pre- and postflight laboratory and clinical assessment batteries to develop a data base that would aid in evaluating changes in immunocompetence. Candidate measures should include the stress hormones, the several immunoglobulins, acute phase reactants, serum iron, total iron binding capacity, serum zinc, and serum copper, white cell count, differential white cell count, and platelets. Clinical procedures should include a careful examination by a trained expert for gingival inflammation and plaque formation (Charon et al., 1985) and a check of the nasal and conjunctival mucosae. Any parameter not within normal limits should be followed until return to the normal range. An expert psychologic or neuropsychiatric appraisal of each crew member should be a routine postflight procedure as an approach to evaluating stress responses. Wherever possible, individual crew members should serve as their own controls. (See also Section IV-C.)

- Ground-based studies of the effects of various stresses on populations of human lymphocytes and circulating hormones should be considered. If the stresses produce changes in lymphocytes, follow-up studies could be done to determine whether individual stress hormones given in doses to reproduce blood concentrations measured during stress exposures cause similar responses. Frequency of blood sampling should allow for detection of momentary

peak hormone values. Such studies need very careful planning because of the diversity of stresses that could be used, steroid and neural hormones that might be released, and attendant difficulties in hormone analysis.

Details of methodology for the following suggestions should be the subject of a separate workshop on the microbiologic aspects of space flight:

- Crew members who are scheduled for a space mission and who have evidence of latent viral infection, such as herpes simplex or cytomegalovirus, would be prime candidates for some relatively simple virology studies. Culturing such individuals for viral shedding before and after space flights could provide data on the effects of transient decreases in immunocompetence.

- Experiments should be designed to acquire data on possible changes in the types and virulence of human gingival and dental plaque flora during flight as one approach toward an explanation of the gingivitis of the Skylab astronauts.

- The question whether weightlessness induces changes in interfaces and interactions among liquids, solids, gases, and mucosal surfaces of the small and large bowel, urinary, and respiratory tracts and possible associated effects such as changes in the microflora including overgrowth of certain species or colonization of normally sterile sites should be considered. For example, quantitation of the numbers and types of bacteria present in freshly voided urine; this should include cultures of fresh urine samples which could be assayed for bacteria and the presence of mucus (glucose aminoglycans) that lines the urinary tract. The loss of mucus would predispose to bacterial colonization of the urinary tract. Studies of this sort could be a part of other inflight and postflight human observations and animal experiments.

- Factors that favor the multiplication and conversion of a normally nonpathogenic microbe of the normal human microflora to a pathogen during space flight are of special interest, especially in the presence of partially altered immunocompetence. Data are needed for predicting such opportunistic infections inflight and postflight in healthy as well as immunocompromised crew members.

- There is some evidence of changes in microfloral ecology in spacecraft during flight that result in alterations of the total array of antigens to which crew members are exposed. Data are needed on whether changes such as simplification of the flora affect human immunocompetence and, if so, to what degree and by which specific microorganisms.

C. TESTS AND METHODOLOGIES

- The effects of space flight on cell-mediated immunity could be tested by administering a battery of ubiquitous antigens intradermally several weeks before flight and again during or immediately postflight.

- A booster shot of tetanus toxoid can be given pre- or during flight to test the secondary humoral immune responsiveness in space to a well-defined recall antigen.

- A sensitive method of assessing the ability of a host to elicit an antigen-specific primary humoral and cellular immune response would be to immunize during flight with a primary antigen such as keyhole limpet hemocyanin (KLH), followed in 2 wk by a booster to test for a secondary humoral response. In addition, a skin test for delayed-type hypersensitivity may be done to test for cell-mediated immunity. This series of procedures would require a space flight lasting at least 3 wk. Serial blood samples during and after flight would permit monitoring of the serologic response to KLH and possible changes in immunoglobulin levels. Postflight blast transformation of the subjects' T-lymphocytes would complete the test package.

- In vivo phagocytic function of macrophages in the spleen and liver can be estimated by a tracer technique. Erythrocytes obtained postflight from individual spacecrew members can be coated with IgG, radiolabeled with ^{51}Cr, and then reinfused into the donor. The removal of the tagged cells from the circulation can be measured conveniently. The rate of clearance is a good indicator of macrophage function in vivo in terms of phagocytosis or dissociation by the reticuloendothelial system. Baseline values should be established by preflight estimates in the same individuals (Frank et al., 1983).

- A convenient technique for estimating the possible influence of monocytopenia on the blastogenic transformability of T-lymphocytes taken postflight from spacecrew members is to add autologous monocytes to the test culture and observe whether the decreased PHA response becomes normal (Lewis and Robbins, 1970).

- Relatively simple observations of living neutrophils are possible during spaceflight such as (1) morphology, (2) motility, (3) content of lysosomal granules, (4) phagocytosis, and (5) the nitroblue tetrazolium (NBT) test and cytochrome C reduction assay for oxidative metabolism. Necessary equipment would include microscope, glass slides, simple reagents, and blood samples. Some tests performed inflight could be quantitated postflight.

- Immediately postflight, neutrophils can be tested for (1) degranulation (release of lactoferrin and enzymes), (2) C3bi receptors using such antigens as OKM-1 and LFA-1, (3) phagocytosis, (4) chemotaxis, and (5) bactericidal activity.

- For ease of handling and analysis, certain well-defined tumor cell lines that have some of the properties of normal lymphocytes, such as Jurkat cells, are available and could be used in in vitro flight tests of lymphocyte activation in experiments similar to those of Cogoli and Tschopp (1985). This human T-cell tumor line can make interleukin-2 in the absence of accessory cells by adding phorbol esters and PHA (Weiss and Stobo, 1984). Similar studies can also be performed on purified mouse T-cells (Malek et al., 1985). Thus, one can distinguish the effect of space flight on activation responses of cells that do not require cell interaction from those that do, such as normal T-lymphocytes.

- If NASA concurs in the suggestions for future studies of the immunologic aspects of space flight presented in this report, it may be useful to devise and adopt a protocol for assessing the immunocompetence of spacecrews. From a practical point of view, comprehensive plans for immunologic assessment should be based on well standardized protocols which should be formulated by a committee of experts and should include or exceed state-of-the-art classical testing of patients with clinical immunodeficiency disorders.

D. FACILITIES AND EQUIPMENT

Scientists who may be interested in participating in NASA-sponsored studies in immunology and microbiology should be aware of the availability of certain items of Life Sciences Laboratory Equipment (LSLE) that have been designed and tested for inflight experiments. Some LSLE can be carried in the Shuttle spacecraft without need for the Spacelab configuration. Examples include a carry-on incubator, which is described in Cogoli and Tschopp (1985), and an Animal Exposure Module (AEM) for small animals. The AEM is a self-contained unit requiring no handling by the crew. More elaborate inflight facilities include the Research Animal Holding Facility (RAHF), which is currently in development, and the European Space Agency (ESA) Biorack. Both units have been designed for use in the Spacelab and offer considerable flexibility in experimental procedures. Other equipment has been developed and flight tested for small animals as well as in vitro experiments in space biology. A primary source of information on NASA's facilities and equipment for inflight investigations is the Director, Life Sciences Division, Headquarters, National Aeronautics and Space Administration, Code EB, Washington, DC 20546.

E. CONCLUDING REMARKS

In conclusion, the ad hoc Working Group noted that data on the immunologic effects of space flight are conflicting. On one hand, approximately 200 spacecrew members have participated in missions lasting from a few days up to 7 mo without demonstrating overt adverse effects on immunity and host resistance. On the other hand, changes in neutrophil populations and inflight and postflight changes in T-lymphocyte responsivity to activation show that some aspect of space flight clearly alters cells that are primarily responsible for providing normal host immunity and microbial defenses.

The ad hoc Working Group reviewed the evidence carefully and suggested numerous studies to overcome current gaps in knowledge about immunity in space. Despite the sophisticated studies that could be attempted, a clear-cut demonstration of normal cell-mediated immunity as measured by delayed dermal hypersensitivity reactions during and/or postflight along with normal inflight humoral responses to a defined antigen would alleviate many of the concerns that have been expressed on the basis of the current lack of knowledge.

V. LITERATURE CITED

Allen, T.R.; Bradburne, A.F.; Stott, E.J.; Goodwin, C.S.; Tyrrell, D.A.J. 1973. An outbreak of common colds at an Antarctic base after seventeen weeks of complete isolation. J. Hyg. (Cambridge) 71:657-667.

Anderson, D.C.; Schmalstieg, F.C.; Shearer, W.; Becker-Freeman, K.; Kohl, S.; Smith, C.W.; Tosi, M.F.; Springer, T. 1985. Leukocyte LFA-1, OKM1, p150,95 deficiency syndrome: functional and biosynthetic studies of three kindreds. Fed. Proc. Fed. Am. Soc. Exp. Biol. 44:2671-2677.

Angrick, E.J.; Somerson, N.L.; Weiss, H.S. 1974. Oxygen effects on mortality of mice infected with Diplococcus pneumoniae. Aerospace Med. 45:730-734.

Anonymous. 1985. Emotion and immunity. Lancet 2:133-134.

Arnaout, M.A.; Dana, N.; Pitt, J.; Todd, R.F., III. 1985. Deficiency of two human leukocyte surface membrane glycoproteins (Mol and LFA-1). Fed. Proc. Fed. Am. Soc. Exp. Biol. 44:2664-2670.

Bailey, J.V. 1975. Radiation protection and instrumentation. In: Johnston, R.S.; Dietlein, L.F.; Berry, C.A., eds. Biomedical results of Apollo. NASA SP-368. Washington, DC: National Aeronautics and Space Administration.

Balish, E.; Shih, C.-N.; Yale, C.E.; Mandel, A.D. 1977. Effect of 30 months in a locked environment on the microbial flora of dogs. Aviat. Space Environ. Med. 48:424-431.

Barone, R.P.; Caren, L.D. 1984. The immune system: effects of hypergravity and hypogravity. Aviat. Space Environ. Med. 55:1063-1068.

Bartrop, R.W.; Luckhurst, E.; Lazarus, L.; Kiloh, L.G.; Penny, R. 1977. Depressed lymphocyte function after bereavement. Lancet 1:834-836.

Beisel, W.R.; Edelman, R.; Nauss, K.; Suskind, R.M. 1981. Single-nutrient effects on immunologic functions. J. Am. Med. Assoc. 245:53-58.

Benton, E.V.; Almasi, J.; Cassow, R.; Frank, A.; Henke, R.P.; Rowe, V.; Parnell, T.A.; Schopper, E. 1984. Radiation measurements aboard Spacelab 1. Science 225:224-226.

Berry, C.A. 1973. The medical legacy of Apollo. Paper presented at 21st International Congress of Aviation and Space Medicine, Munich, September 17.

Berry, C.A. 1974. The medical legacy of Apollo. Aerospace Med. 45:1046-1057.

Blalock, J.E.; Smith, E.M. 1985. A complete regulatory loop between the immune and neuroendocrine systems. Fed. Proc. Fed. Am. Soc. Exp. Biol. 44:108-111.

Bricker, N.S., chairman. 1979. Life beyond the Earth's environment: the biology of living organisms in space. Report of the Committee on Space Biology and Medicine, Space Science Board. Washington, DC: National Academy of Sciences.

Brockett, R.M.; Ferguson, J.K. 1975. Microbiological sampling of the spacecraft atmosphere during a simulated Skylab mission. Aviat. Space Environ. Med. 46:30-32.

Brown, L.R.; Frome, W.J.; Handler, S.; Wheatcroft, M.G.; Rider, L.J. 1977. Skylab oral health studies. In: Johnston, R.S.; Dietlein, L.F., eds. Biomedical results from Skylab. NASA SP-377. Washington, DC: National Aeronautics and Space Administration. p.35-44.

Caren, L.D.; Mandel, A.D.; Nunes, J.A. 1980. Effect of simulated weightlessness on the immune system in rats. Aviat. Space Environ. Med. 51:251-255.

Casarett, G.W. 1969. Pathological changes after protracted exposures to low-dose radiation. In: Fry, R.J.M.; Grahn, D.; Griem, M.L.; Rust, J.H., eds. Late effects of radiation. New York: Van Nostrand Reinhold. p.85-100.

Chang, K.-J. 1984. Opioid peptides have actions on the immune system. Trends Neurosci. 7:234-235.

Charon, J.A.; Mergenhagen, S.E.; Gallin, J.I. 1985. Gingivitis and oral ulceration in patients with neutrophil dysfunction. J. Oral Pathol. 14:150-155.

Christensen, J.M.; Talbot, J.M., editors. 1985. Research opportunities in human behavior and performance. Report prepared for the National Aeronautics and Space Administration, Washington, DC, under Contract No. NASW 3924 by the Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, MD. 73p. Available from: FASEB Special Publications, Bethesda, MD.

Cogen, R.B.; Stevens, A.W., Jr.; Cohen-Cole, S.; Kirk, K.; Freeman, A. 1983. Leukocyte function in the etiology of acute necrotizing ulcerative gingivitis. J. Periodontol. 54:402-407.

Cogoli, A. 1981. Hematological and immunological changes during space flight. Acta Astronautica 8:995-1002.

Cogoli, A.; Tschopp, A. 1985. Lymphocyte reactivity during spaceflight. Immunol. Today 6:1-4.

Cogoli, A.; Tschopp, A.; Fuchs-Bislin, P. 1984. Cell sensitivity to gravity. Science 225:228-230.

Cogoli, A.; Valluchi-Morf, M.; Mueller, M.; Briegleb, W. 1980. Effect of hypogravity on human lymphocyte activation. Aviat. Space Environ. Med. 51:29-34.

Dale, D.C.; Wolff, S.M. 1971. Skin window studies of the acute inflammatory responses of neutropenic patients. Blood 38:138-142.

Dietlein, L.F. 1977. Skylab: a beginning. In: Johnston, R.S.; Dietlein, L.F., eds. Biomedical results from Skylab. NASA SP-377. Washington, DC: National Aeronautics and Space Administration. p.408-414.

Durnova, G.N.; Kaplansky, A.S.; Portugalov, V.V. 1976. Effect of a 22-day space flight on the lymphoid organs of rats. Aviat. Space Environ. Med. 47:588-591.

Ferguson, J.K.; Taylor, G.R.; Mieszkuc, B.J. 1975. Microbiological investigations. In: Johnston, R.S.; Dietlein, L.F.; Berry, C.A., eds. Biomedical results of Apollo. NASA SP-368. Washington, DC: National Aeronautics and Space Administration. p.83-104.

Frank, M.M.; Hamburger, M.I.; Lawley T.J.; Kimberly, R.P.; Plotz, P.H. 1979. Defective reticuloendothelial system Fc receptor function in systemic lupus erythematosus. New Engl. J. Med. 300:518-523.

Frank, M.M.; Lawley, T.J.; Hamburger, M.I.; Brown, E.J. 1983. Immunoglobulin G Fc receptor-mediated clearance in autoimmune disease. Ann. Intern. Med. 98:206-218.

Gershwin, M.E.; Beach, R.S.; Hurley, L.S. 1985. Nutrition and immunity. New York: Academic Press. p.1-417.

Gillmore, J.D.; Gordon, F.B. 1974. Parabarosis and experimental infection. 5. Effect of altered oxygen tension on Coxsackie B-1 infection in adult mice. Aerospace Med. 45:840-842.

Giron, D.J.; Pindak, F.F.; Schmidt, J.P. 1967. Effects of a space cabin environment on viral infection. Aerospace Med. 38:832-834.

Gordon, F.B.; Gillmore, J.D. 1974a. Parabarosis and experimental infections. 1. Effect of varying O_2 tensions on influenza virus infection in mice. Aerospace Med. 45:241-248.

Gordon, F.B.; Gillmore, J.D. 1974b. Parabarosis and experimental infections. 4. Effect of varying O_2 tensions on Chlamydial infection in mice and cell cultures. Aerospace Med. 45:257-262.

Grabstein, K. 1980. Cell-mediated cytolytic responses. In: Mishell, B.B.; Shiigi, S.M., eds. Selected methods in cellular immunology. San Francisco: W.H. Freeman and Company. p.124-137.

Guseva, Ye. V.; Tashpulatov, R. Yu. 1979. Effects of 49-day space flight on parameters of immunological reactivity and protein composition of blood in the crew of Salyut-5. Space Biol. Aerospace Med. 13(1):1-7. [Translation of Kosmicheskaya Biologiya i Aviakosmicheskaya Meditsina 13(1):3-8].

Guseva, Ye. V.; Tashpulatov, R. Yu. 1980. Effect of flights differing in duration on protein composition of cosmonauts' blood. Space Biol. Aerospace Med. 14(1):15-20. [Translation of Kosmicheskaya Biologiya i Aviakosmicheskaya Meditsina 14(1):13-17].

Hellum, K.B.; Solberg, C.O. 1977. Human leucocyte migration: studies with an improved skin chamber technique. Acta Pathol. Microbiol. Scand. Section C. 85:413-423.

Hordinsky, J.R. 1977. Skylab crew health--crew surgeons' reports. In: Johnston, R.S.; Dietlein, L.F., eds. Biomedical results from Skylab. NASA SP-377. Washington, DC: National Aeronautics and Space Administration. p.30-34.

Ivanov, A.A.; Shvets, V.N.; Boyko, M.I. 1983. Complement and heterophil antibody levels in monkeys during antiorthostatic hypokinesia. Space Biol. Med. 17(1):93-95. [Translation of Kosmicheskaya Biologiya i Aviakosmicheskaya Meditsina 17(1):66-67].

Kimzey, S.L. 1977. Hematology and immunology studies. In: Johnston, R.S.; Dietlein, L.F., eds. Biomedical results from Skylab. NASA SP-377. Washington, DC: National Aeronautics and Space Administration. p.249-283.

Kimzey, S.L.; Fischer, C.L.; Johnson, P.C.; Ritzmann, S.E.; Mengel, C.E. 1975a. Hematology and immunology studies. In: Johnston, R.S.; Dietlein, L.F.; Berry, C.A., eds. Biomedical results of Apollo. NASA SP-368. Washington, DC: National Aeronautics and Space Administration. p.197-226.

Kimzey, S.L.; Ritzmann, S.E.; Mengel, C.E.; Fischer, C.L. 1975b. Skylab experiment results: hematology studies. Acta Astronautica 2:141-154.

Konstantinova, I.V.; Antropova, Ye. N.; Legen'kov, V.I.; Zazhirey, V.D. 1973. Study of reactivity of blood lymphoid cells in crew members of the Soyuz-6, Soyuz-7 and Soyuz-8 spaceships before and after flight. Space Biol. Med. 7(6):48-55. [Translation of Kosmicheskaya Biologiya i Aviakosmicheskaya Meditsina 7(6):35-40].

Konstantinova, I.V.; Nefedov, Yu. G.; Yeremin, A.V.; Drozdova, V.I.; Skryabin, A.S.; Guseva, D.A.; Mukhina, N.N. 1978. Immunological reactivity and prediction of allergic complications in the crew of the second expedition of Salyut-4. Space Biol. Med. 12(2):16-21. [Translation of Kosmicheskaya Biologiya i Aviakosmicheskaya Meditsina 12(2):15-19].

Lane, H.C.; Whalen, G.; Fauci, A.S. [1986]. In vitro evaluation of human lymphocyte function. In: Weir, D.M.; Herzenberg, L.A.; Blackwell, C.C.; Herzenberg, L.A., eds. Handbook of experimental immunology. 4th ed. Edinburgh: Blackwell Scientific Publishers. In press.

Legen'kov, V.I.; Kiselev, R.K.; Gudim, V.I.; Moskaleva, G.P. 1977. Changes in peripheral blood of crew members of the Salyut-4 orbital station. Space Biol. Med. 11(6):1-12. [Translation of Kosmicheskaya Biologiya i Aviakosmicheskaya Meditsina 11(6):3-12].

Lewis, W.R.; Robbins, J.H. 1970. Effect of glass-adherent cells on the blastogenic response of purified lymphocytes to phytohemagglutinin. Exp. Cell Res. 61:153-158.

Luckey, T.D. 1966. Potential microbic shock in manned aerospace systems. Aerospace Med. 37:1223-1228.

Malek, T.R.; Schmidt, J.A.; Shevach, E.M. 1985. The murine IL 2 receptor. III. Cellular requirements for the induction of IL 2 receptor expression on T cell subpopulations. J. Immunol. 134:2405-2413.

Mandel, A.D.; Balish, E. 1977. Effect of space flight on cell-mediated immunity. Aviat. Space Environ. Med. 48:1051-1057.

Mikhaylovskiy, G.P.; Dobronravova, N.N.; Kozar, M.I.; Korotayev, M.M.; Tsiganova, N.I.; Shilov, V.M.; Yakovleva, I. Ya. 1967. Variation in overall body tolerance during a 62-day exposure to hypokinesia and acceleration. Space Biol. Med. 1(6):101-108. [Translation of Kosmicheskaya Biologiya i Aviakosmicheskaya Meditsina 1(6):66-70].

Morey, E.R. 1979. Spaceflight and bone turnover: correlation with a new rat model of weightlessness. Bioscience 29:168-172.

National Research Council, Committee on Space Medicine. 1970. Radiation protection guides and constraints for space mission and vehicle design studies involving nuclear systems. Washington, DC: National Academy of Sciences.

National Research Council, Food and Nutrition Board. 1980. Recommended dietary allowances. 9th rev. ed. Washington, DC: National Academy of Sciences. 185p.

Nicogossian, A.E.; Parker, J.F., Jr. 1982. Space physiology and medicine. NASA SP-447. Washington, DC: National Aeronautics and Space Administration. 324p.

Park, S.K.; Brody, J.I.; Wallace, H.A.; Blakemore, W.S. 1971. Immunosuppressive effect of surgery. Lancet 1:53-55.

Parkinson, A.J.; Muchmore, H.G.; McConnell, T.A.; Scott, L.V.; Miles, J.A.R. 1980. Serologic evidence for parainfluenzavirus infection during isolation at South Pole Station, Antarctica. Am. J. Epidemiol. 112:334-340.

Pestov, I.D.; Geratewohl, S.J. 1975. Weightlessness. In: Calvin, M.; Gazenko, O.G., general eds. Foundations of space biology and medicine. Vol. 2. Book 1. Washington, DC: National Aeronautics and Space Administration. p.317, 327, 330.

Pierson, D.L. 1983. Medical microbiology of crew members and spacecraft during OFT. In: Pool, S.L.; Johnson, P.C., Jr.; Mason, J.A., eds. Shuttle medical report: summary of medical results from STS-1, STS-2, STS-3, and STS-4. NASA TM 58252. Johnson Space Center: National Aeronautics and Space Administration. p.49-52.

Plotnikoff, N.P.; Murgo, A.J. 1985. Enkephalins-endorphins: stress and the immune system. Fed. Proc. Fed. Am. Soc. Exp. Biol. 44:91.

Poteliakhoff, A. 1985. Emotion and immunity. Lancet 2:327.

Rebuck, J.W.; Crowley, J.H. 1955. A method of studying leukocytic functions in vivo. Ann. N.Y. Acad. Sci. 59:757-793.

Riley, V. 1981. Psychoneuroendocrine influences on immunocompetence and neoplasia. Science 212:1100-1109.

Ritzmann, S.E.; Levin, W.C. 1973. Investigation of man's immune system (M 112), part B. Skylab Medical Experiments Altitude Test. Johnson Space Center: National Aeronautics and Space Administration.

Rose, R.M. 1980. Endocrine responses to stressful psychological events. Psychiatr. Clin. North Am. 3:251-276.

Sawyer, R.; Sommerville, R.G. 1966. An outbreak of Mycoplasma pneumoniae infection in a nuclear submarine. J. Am. Med. Assoc. 195:958-959.

Scheja, A.; Forsgren, A. 1985. A skin chamber technique for leukocyte migration studies: description and reproducibility. Acta Pathol. Microbiol. Immunol. Scand. Section C. 93:25-30.

Seed, T.M.; Fritz, T.E.; Tolle, D.V.; Poole, C.M.; Lombard, L.S.; Doyle, D.E.; Kaspar, L.V.; Cullen, S.M.; Carnes, B.A. 1984. Survival patterns and hemopathological responses of dogs under continuous gamma irradiation. In: Broerse, J.J.; MacVittie, T.J., eds. Responses of different species to total body irradiation. The Hague: Martinus Nijhoff Publishers. p.137-159.

Simmonds, R.C.; Wrenn, R.T.; Heimpel, A.M.; Taylor, G.R. 1974. Postflight analysis of Bacillus thuringiensis organisms exposed to spaceflight conditions on Apollo 16. Aerospace Med. 45:1244-1247.

Sonnenfeld, G.; Morey, E.R.; Williams, J.A.; Mandel, A.D. 1982. Effects of a simulated weightlessness model on the production of rat interferon. J. Interferon Res. 2:467-470.

Spector, N.H. 1983. Anatomic and physiologic connections between the central nervous and the immune systems (Neuroimmunomodulation). In: Fabris, N.; Garaci, E.; Hadden, J.; Mitchison, N.A., eds. Immunoregulation. New York: Plenum Publishing Corporation.

Springer, T.A. 1985. The LFA-1, Mac-1 glycoprotein family and its deficiency in an inherited disease. Fed. Proc. Fed. Am. Soc. Exp. Biol. 44:2660-2663.

Talas, M.; Batkai, L.; Stoger, I.; Nagy, K.; Hiros, L.; Konstantinova, I.; Rykova, M.; Mozgovaya, I.; Guseva, O.; Kozharinov, V. 1983. Results of space experiment program "interferon". Acta Microbiol. Hungarica 30(1):53-61.

Tansey, W.A.; Wilson, J.M.; Schaefer, K.E. 1979. Analysis of health data from 10 years of Polaris submarine patrols. Undersea Biomed. Res. Submarine Suppl.:S217-S246.

Taylor, G.R. 1974. Recovery of medically important microorganisms from Apollo astronauts. Aerospace Med. 45:824-828.

Taylor, G.R.; Dardano, J.R. 1983. Human cellular immune responsiveness following space flight. Aviat. Space Environ. Med. 54(Suppl. 1):S55-S59.

Taylor, G.R.; Graves, R.C.; Brockett, R.M.; Ferguson, J.K.; Mieszkuc, B.J. 1977. Skylab environmental and crew microbiology. In: Johnston, R.S.; Dietlein, L.F., eds. Biomedical results from Skylab. NASA SP-377. Washington, DC: National Aeronautics and Space Administration. p.53-63.

Unanue, E.R. 1981. The regulatory role of macrophages in antigenic stimulation. II. Symbiotic relationships between lymphocytes and macrophages. Adv. Immunol. 31:1-136.

Vorobyev, E.I.; Gazenko, O.G.; Genin, A.M.; Egorov, A.D. 1983. Medical results of Salyut-6 manned space flights. Aviat. Space Environ. Med. 54(Suppl. 1):S31-S40.

Vorobyev, Ye. I.; Gazenko, O.G.; Genin, A.M.; Gurovskiy, N.N.; Yegorov, A.D.; Nefedov, Yu. G. 1984. Main results of medical studies on Salyut-6-Soyuz program. Space Biol. Med. 18(2): 27-31. [Translation of Kosmicheskaya Biologiya i Aviakosmicheskaya Meditsina 18(2):22-25].

Voss, E.W., Jr. 1984. Prolonged weightlessness and humoral immunity. Science 225:214-215.

Watkins, H.M.S. 1970. Epidemiologic investigations in Polaris submarines. In: Silver, I.H., ed. Aerobiology. New York: Academic Press. p.9-53.

Weiss, A.; Stobo, J. 1984. Requirement for the coexpression of T3 and the T cell antigen receptor on a malignant human T cell line. J. Exp. Med. 160:1284-1299.

Whedon, G.D., chairman. 1978. Future directions for the life sciences in NASA. A report of the Life Sciences Advisory Committee of the NASA Advisory Council. Washington, DC: National Aeronautics and Space Administration. 44p.

Wiskocil, R.; Weiss, A.; Imboden, J.; Kamin-Lewis, R.; Stobo, J. 1985. Activation of a human T cell line: a two-stimulus requirement in the pretranslational events involved in the coordinate expression of interleukin-2 and γ-interferon genes. J. Immunol. 134:1599-1603.

Wright, D.G.; Meierovics, A.I.; Foxley, J.M. [1986]. Assessing the delivery of neutrophils to tissues in neutropenia. Blood In press.

Yegorov, A.D. 1979. Results of medical research during the 175-day flight of the third main crew on the Salyut-6 and Soyuz complex. Academy of Sciences, USSR, Ministry of Public Health, Institute of Biomedical Problems, Moscow. NASA TM-76014. Washington, DC: National Aeronautics and Space Administration.

Yegorov, A.D. 1980. Results of medical research studies during long-term manned flights on the orbital Salyut-6 and Soyuz complex. Presented during the 11th meeting of the Joint Soviet-American Working Group on Space Biology and Medicine, Moscow. NASA TM-76450. Washington, DC: National Aeronautics and Space Administration.

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