

## SKYLAB: A BEGINNING

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"The Eagle has landed; Tranquillity Base here." This simple and now historic message of July 20, 1969, marked the attainment of perhaps the greatest peacetime goal in the history of man. It fulfilled President Kennedy's directive issued some 8 short, hectic years earlier, when he proclaimed on May 25, 1961: "I believe we should go to the moon . . . before this decade is out." It marked the culmination of a technically complex engineering accomplishment that began with Mercury and continued uninterrupted through Gemini and prelunar Apollo. The ultimate goal of these efforts was a manned lunar landing. None of these programs had as a major objective the detailed study of man's biomedical responses to the space environment, except in the broadest sense of survival and the ability to live and work effectively in that environment. Nevertheless, throughout each program, information concerning man and his new surroundings was obtained wherever possible and whenever practicable, ever mindful of the time constraints imposed by the lunar landing goal and the weight limitations of the launch vehicles.

In these few days, the preliminary biomedical results of NASA's Skylab effort have been presented to you. A major goal of Skylab was to learn more about man and his responses to the space environment for missions lasting up to 84 days. The results are necessarily preliminary, for in the short time which has elapsed since the end of the program, no in-depth cross-correlation of the voluminous multidisciplinary data has been possible. This will be done through successive future meetings of specialized working groups.

In this 1974 Skylab Life Sciences Symposium, you have been briefed on the results of measurements and experiments that were conceived some six to eight years ago, and which have added immeasurably to our understanding of man, his physiological responses and his capabilities in space.

In one sense Skylab is the *beginning* of an in-depth study of man in this unique environment, for Skylab has resolved some problems while inevitably raising new questions.

## MERCURY 1961-1963

In order to view the Skylab data in their proper context, let us go back for a moment some 13 years to 1961. At that time both the United States and Soviet Union were placing animals, such as chimpanzees Ham and Enos, in orbital flight. The goal of these flights was to refute untested but plausible theories of catastrophic failures in various vital functions if such animals were suddenly thrust into weightless flight. There were, of course, additional stresses to be reckoned with in space, the most important of which are listed in table I and which are by now quite familiar to you.

TABLE I. PRINCIPAL ENVIRONMENTAL STRESSES IN MANNED SPACE FLIGHT

- ° Weightlessness
- ° Ionizing radiation
- ° Temperature and humidity
- ° Accelerations
- ° Circadian rhythm disruption
- ° Noise and vibration
- ° Atmospheric composition

But the factor of greatest concern to man with his many gravity-influenced body systems was and continues to be null gravity. Many dire effects - some of them diametrically opposed to each other - were postulated as direct consequences of exposing man to zero gravity. Some of these predictions are listed in table II and are well known from previous publications (1, 2).

TABLE II. PREDICTED WEIGHTLESS EFFECTS

Anorexia	Demineralization of bones
Nausea	Renal calculi
Disorientation	Motion sickness
Sleepiness	Pulmonary atelectasis
Sleeplessness	Tachycardia
Fatigue	Hypertension
Restlessness	Hypotension
Euphoria	Cardiac arrhythmias
Hallucinations	Postflight syncope
Decreased g tolerance	Decreased exercise capacity
Gastrointestinal disturbance	Reduced blood volume
Urinary retention	Reduced plasma volume
Diuresis	Dehydration
Muscular incoordination	Weight loss
Muscle atrophy	Infectious illnesses

A few of these predictions were later shown to be valid; happily, most of them were not substantiated by subsequent flight experience. During the Mercury Program, NASA scientists made some tentative realistic predictions of their own regarding the time course of certain symptoms should they develop during weightless flight. These are indicated in figure 1 and, except for sensory deprivation and sleep changes, have been generally proved quite realistic.

The first indication of cardiovascular or circulatory impairment related to space flight was the orthostatic intolerance exhibited by Schirra following his 9-hour MA-8 flight and Cooper after his 34-hour MA-9 flight. Cardiovascular data from the last and longest Mercury flight are indicated in table III, including orthostatic intolerance and dizziness on standing, weight loss (dehydration) and hemoconcentration.

TABLE III. FLIGHT MERCURY-ATLAS-9 (MA-9) CARDIOPULMONARY DATA SUMMARY

EVENT	PULSE (bpm)	PRESSURE (mm Hg)	RESPIRATION RATE (breaths/min)
Prelaunch	72	113/79	19
Orbital	89	119/81	15
Postflight	83 (supine)	89/64	--
(1 to 7 h)	123 (erect)	90/73	--
(18 h)	58 (supine)	98/61	--
	80 (erect)	94/68	--

Flight time: 34 h 20 min.

Weight Loss: 3.5 kg (7.75 lb)

Postflight temperature: 310.6° K (99.4° F) (Oral)

Hematocrit: 43 (Preflight); 49 (Postflight)

Subjective symptoms: Dizziness

#### GEMINI 1965-1966

The biomedical studies conducted during the Gemini Program were directed toward evaluating the magnitude of flight-related changes first noted following the Mercury flights, and other physiological changes that might occur in Earth-orbital flights of up to two weeks' duration. Heavy emphasis was placed upon evaluation of the cardiovascular system, since the principal changes observed during Mercury involved alterations

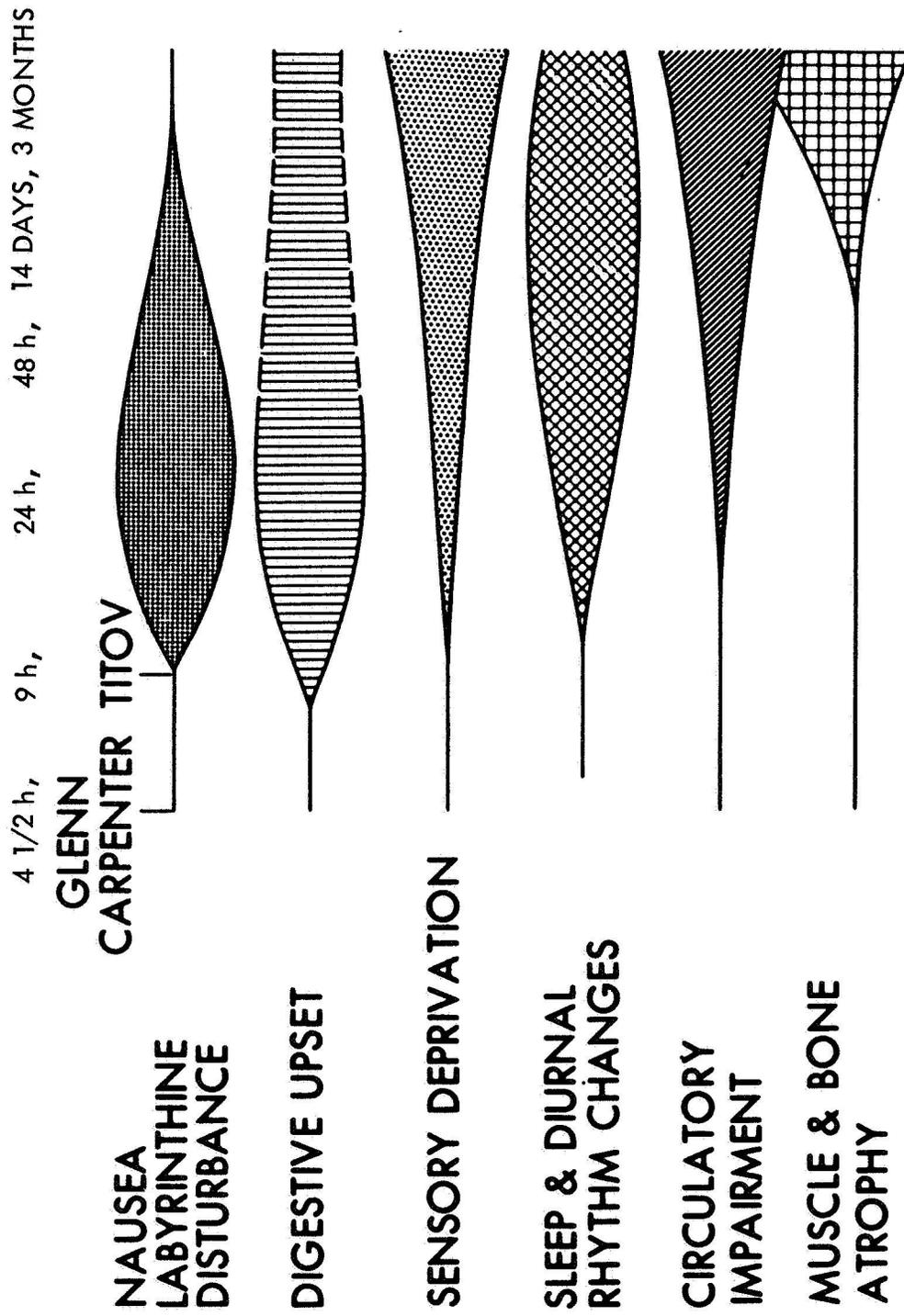


Figure 1. Expected time course of symptoms if they occurred in weightlessness.

in cardiovascular reflexes that regulate blood flow in the face of a continuous hydrostatic gradient in Earth's gravity field.

The preflight, in-flight, and postflight studies conducted during the Gemini Program were intended to detect alterations in the functional status of the principal human body systems with increased flight duration. The results of these studies indicated that some of the major human physiological systems undergo consistent and predictable alteration as a result of space flight. The significant biomedical findings in Gemini are listed in table IV.

TABLE IV. SIGNIFICANT BIOMEDICAL FINDINGS IN GEMINI PROGRAM

- Moderate loss of red cell mass
- Moderate postflight orthostatic intolerance
- Moderate postflight loss of exercise capacity
- Minimal loss of bone density
- Minimal loss of bone calcium and muscle nitrogen
- High metabolic cost of extravehicular activity

It should be emphasized that the principal objectives of the 10 Gemini flights were to perfect the techniques of rendezvous, station keeping, docking and extravehicular activity--all critical to the Apollo lunar landing mission, then only four and one-third years away from Gemini 3. Three flights of the Gemini series were of medical and physiological interest. Gemini 4, 5, and 7, lasting 4, 8, and 14 days respectively. Several in-flight measurements or experiments were accomplished on these missions, as well as preflight and postflight studies. These investigations confirmed the postflight orthostatic intolerance observed in Mercury and extended the findings to include moderately decreased exercise capacity and red cell mass, minimal loss of bone calcium and muscle nitrogen, and the high metabolic cost of extravehicular activity. The medical findings of the Gemini Program have been reported in detail elsewhere (2, 3, 4).

#### APOLLO 1968-1973

Eleven manned missions were completed in the five year span of the Apollo program: four prelunar flights (Missions 7 through 10); the first lunar landing (Mission 11), and five subsequent lunar exploratory flights (Missions 12 through 17). Apollo 13 did not complete its

lunar landing mission because of the unfortunate pressure vessel explosion in the service module. Instead, it returned to Earth after a partial lunar orbit.

As stated previously, biomedical studies in Apollo were limited essentially to the preflight and postflight mission phases, along with in-flight monitoring and observations. Apollo witnessed the addition of vestibular disturbances to the list of significant biomedical findings incident to space flight.

Vestibular disturbances with nausea were noted by Soviet Cosmonaut Titov during his one-day, Vostok 2 flight on August 6, 1961, and by the crews of other later Soviet flights. No astronauts had experienced any motion sickness symptoms until the early Apollo experience. In retrospect, however, the anorexia and reduced caloric intake observed on certain Gemini and later Apollo flights, may have been, in fact, early symptoms of vestibular disturbance.

Apollo 8 and 9 especially were plagued with vestibular problems: five of the six crewmen developed stomach awareness, three of the six, nausea, and two of these six proceeded on to frank vomiting. In Apollo 15 and 17, three of six of the crewmen also experienced stomach awareness. The flight plans of Apollo 8 and 9 required that the certain crewmen leave their couches soon after orbital insertion. All three Apollo 8 crewmen noted some motion sickness symptoms (stomach uneasiness or awareness, nausea, or vomiting), confined generally to the first day of flight. There is some confusion concerning the etiology of the Apollo 8 crew's symptomatology, since the Commander felt that a viral gastroenteritis accounted for (or aggravated) his symptoms. In Apollo 9, the vestibular disturbance lasted for a considerably longer time, and in the case of the most severely affected crewman, necessitated a postponement of the flight plan. And thus an additional problem area was introduced into the American space experience. This disturbance, which had long plagued the Soviets and which had been predicted in the early 1960's as a probable effect of weightless flight, had made its belated American debut. Its late appearance was probably related to the relative immobility of the crews in their spacecraft during the Mercury and Gemini flights and the absence of any rotation of the vehicles themselves.

Other significant biomedical findings in Apollo are indicated in table V. Generally, they confirmed the Gemini findings of postflight dehydration and weight loss, postflight orthostatic tolerance decrease, and postflight reduction in exercise capacity (5).

TABLE V. SIGNIFICANT BIOMEDICAL FINDINGS IN APOLLO PROGRAM

- Vestibular disturbances
- Adequate diet; less than optimal food consumption
- Postflight dehydration and weight loss
- Decreased postflight orthostatic tolerances
- Reduced postflight exercise tolerance
- Apollo 15 cardiac arrhythmias
- Decreased red cell mass and plasma volume

In addition, the decreased red cell masses and plasma volumes noted in Gemini were confirmed, but were less pronounced in Apollo.

One final observation deserving mention was the cardiac arrhythmia episode of Apollo 15. Two of the crewmembers each experienced a single run of bigeminy during the mission - the first significant arrhythmia observed *during* any American space flight up to that time. Two short bursts (9 and 17 beats, respectively) of nodal tachycardia were observed on the postponed MA-6 launch attempt of John Glenn in 1962. At the time of the arrhythmia, he was lying in his couch preparing for the final countdown. No arrhythmias were subsequently observed on Glenn either during flight or following his historic five hour orbital flight. In the case of the two Apollo 15 astronauts, it was first thought that a dietary deficiency of potassium might have been a contributory factor. Subsequent careful analysis of their intake and mission simulation studies failed to bear this out. The etiology remains obscure. Fatigue, following vigorous lunar surface activities most certainly was a factor. Other contributory factors remain speculative and are likely to remain so. It should be noted that one of these two crewmen sustained a myocardial infarction in April 1973, some 21 months after his flight in July 1971. Thus coronary atherosclerosis was very likely a factor in one case at least.

For further details concerning the biomedical results of Apollo, the reader is referred to the final summary report which will be available shortly (6).

## SKYLAB 1973-1974

The three principal objectives of the Skylab Program were the study of man, his Earth and his Sun. This symposium has reported on man's responses to long-duration space flight (7). Reports on the other two study objectives of the program will be forthcoming at a later date.

Before summarizing the salient biomedical findings of Skylab, I should like to stress the sometimes overlooked fact that, in assessing the effects of weightlessness on man during prolonged space flight, we are not examining *absolute* effects or responses. Clearly, man is not vegetating in space, but is actually doing his utmost to maintain a high level of physical fitness and performance. Thus the absolute detrimental effects of null gravity will, in most cases, have to be determined in subhuman surrogates. Other points worth emphasizing are the relative inflexibility of the principal studies or measurements made on space missions, including Skylab, once conceptual design has been finalized; and the fact that space flight investigations are essentially "field studies", fraught with many attendant difficulties, in which the investigator is even farther removed from the experiment and subject than in field studies on Earth. And finally, although the measuring equipment is highly reliable in performance and the astronaut a superbly trained, perceptive scientist/observer in his own right - yet the circumstances fall short of the classical picture of the experimenting scientist in his exceptionally well equipped laboratory, constantly fine-tuning his equipment and personally conducting experimental trials and collecting precious data.

All these factors, notwithstanding, the efforts of the Skylab investigative team have resulted in a major contribution toward understanding man in his new environment.

### Cardiovascular

In the cardiovascular area we have learned that so-called cardiovascular deconditioning does occur during flight, that the change is adaptive in nature and stabilizes after a period of four to six weeks, that this change does not impair crew health or performance aloft and that it is triggered by factors tending to reduce circulating blood volume. These changes are summarized in table VI.

TABLE VI. SKYLAB CARDIOVASCULAR SUMMARY

- Cardiovascular deconditioning was observed during flight; changes appear adaptive in nature and tend to stabilize after 4 to 6 weeks.
- Cardiovascular changes do not impair crew health or ability to function effectively in weightless flight.
- Lower body negative pressure tests provide fairly reliable predictive index of postflight cardiovascular status.
- Cardiac electrical activity as measured by vectorcardiogram was not significantly altered and remained within physiological limits.
- Decreased cardiac output noted in crewmen postflight; thought to be related to reduced venous return.
- Single episode of significant cardiac arrhythmia in one Skylab 2 crewman during exercise early in mission.
- No significant in-flight decrement in work capacity or physiological responses to exercise.
- All crewmen have shown postflight decrease in exercise capacity and altered physiological responses.
- Skylab 3 and 4 crews returned to preflight cardiovascular status by the fourth and fifth day and the Skylab 2 crew on the twenty-first day postflight. Increased exercise by Skylab 3 and 4 crewmen thought to be a factor in improved recovery rate.

The provocative lower body negative pressure test has proved to be a fairly reliable predictive index of postflight cardiovascular status. Cardiac arrhythmias have been rare: only one episode noted early in Skylab 2 during intensive personal exercise interpreted as multiple, unifocal ventricular premature beats with no evidence of coupling.

Other arrhythmias observed have been limited to isolated rare to occasional premature beats. Cardiac electrical activity has been within physiological limits as judged from the vectorcardiographic data.

Exercise tolerance *during* flight was unaffected. It was only *after* return to Earth that a tolerance decrement was noted.

Finally, the rapid postflight recovery of orthostatic and exercise tolerance following two of the three Skylab missions appears to be directly related to total in-flight exercise as well as to a graded, regular program of exercise during the postflight debriefing period.

As indicated in table VII, the postflight orthostatic intolerance and diminished exercise capacity are both related etiologically to a decreased effective circulating blood volume at one-g, with consequent decreased venous return and cardiac output.

TABLE VII. CARDIOVASCULAR SYSTEM

Findings

- ° Postflight orthostatic intolerance
- ° Postflight diminished exercise capacity

Probable etiological factors

- ° Decreased effective circulating blood volume postflight
- ° Diminished venous return at one-g
- ° Muscular imbalance occasioned by functional disuse atrophy of antigravity muscles
- ° Altered internal milieu (fluid/electrolyte dynamic flux) during early postflight period
- ° ? altered venous reflexes/tone
- ° Fatigue

Other factors to be considered are muscle imbalance, altered electrolyte flux, possible changes in venous tone or reflexes and, of course, fatigue. There is no convincing incidence of myocardial damage as an etiological factor; however, transient cellular changes during the period of homeostatic perturbation would not be surprising or unusual. In animal oxygen toxicity studies, we have observed such changes in lung, liver and kidney.

The thrust of future cardiovascular investigations is indicated in table VIII. Continued human studies, as well as critical invasive experiments on animals must be conducted to define the time course of pertinent mechanisms. The Gauer-Henry reflex has yet to be demonstrated. This will not be easy to demonstrate in man, since the critical time-period to be investigated is thought to coincide with the early operationally exacting first day of the mission.

## TABLE VIII. CARDIOVASCULAR SYSTEM

### Rule out

- Permanent myocardial damage (cellular level) - remote

### Candidate future cardiovascular studies

- In-depth, noninvasive cardiovascular dynamics monitoring
- Invasive pressure/volume/flow changes in early flight (animal)
- Demonstrate presence or absence of Gauer-Henry reflex
- Total body exercise regimen to maintain integrity of antigravity as well as major muscle groups
- Assess role of venous (capacitance) vessels in observed deconditioning process
- Assess role of fatigue

Attention must also be given to devising an effective, practicable exercise regimen for all major muscle groups, including the anti-gravity muscles.

Finally, we must assess the roles of the capacitance vessels or veins and the elusive fatigue factor in the deconditioning phenomenon.

### Mineral/Fluid Balance

Findings in this area are summarized in table IX. They include the moderate losses of calcium, phosphorus and nitrogen that have been observed in the first two Skylab missions. Preliminary evaluation of data from these flights as well as from the 84-day mission tends to support the general observation that these losses are comparable to those observed at bed rest or six grams of calcium per month or five tenths percent of total body calcium per month. Complementary mineral losses in the *os calcis* have been relatively low. It would appear from these data that missions of from 8 to 9 months' duration would be feasible without preventive or remedial measures.

The Skylab experience has provided evidence that the caloric requirements of space flight are identical with those for the individual on Earth - at least for high activity missions such as Skylab. From the Gemini and Apollo experience we were led to believe that the in-flight caloric requirements was some 300 calories/day less than Earth requirements. This judgment may have been colored by the relative low

activity profiles of these missions, and the fact that the food provided was often not consumed. In retrospect, as mentioned before, this anorexia may have been a manifestation of early motion sickness and not recognized as such at the time.

TABLE IX. SKYLAB MINERAL/CALORIC, FLUID/ELECTROLYTE SUMMARY

- Moderate losses of calcium, phosphorus, and nitrogen have been observed comparable to those seen in bedrested subjects: 6 grams/month calcium or 0.5 percent/month total body calcium.
- Rate of calcium loss would not preclude extended missions of 8 to 9 months' duration. Longer missions may require remedial measures.
- Significant *os calcis* mineral loss:  
Skylab 3: Scientist Pilot: 7.4 percent  
Skylab 4: Scientist Pilot: 4.5 percent; Pilot: 7.9 percent
- Caloric requirements during flight identical with individual requirements at one-g.
- Renal function unimpaired; however, apparently unique adaptive functional changes observed require further study.
- Skylab 4 anthropometric studies consistent with predicted shift of body fluids during weightless flight.

Renal function was unimpaired during flight through a complex interplay of humoral and possibly hemodynamic factors as we will consider shortly. In addition, anthropometric studies performed on Skylab 4 support a cephalad shift of body fluids at zero-g.

With regard to the musculoskeletal system, the negative balances observed are due primarily to the absence of gravity as shown in table X. However, the correct balance of weight bearing, muscular activity, hormonal influence and circulatory factors required to prevent or arrest mineral and nitrogen loss during bedrest simulations has to date defied definition. Elevated cortisol secretion during flight helps to confound the picture and doubtless contributes to nitrogen and potassium loss.

Continued studies must be pursued--and we are currently active in this area--to define absolute catabolic change in the musculoskeletal system of animals. We also continue to evaluate various countermeasures in bedrest studies in order to determine the most suitable for flight use. More attention must be given to the selection of individuals who are most refractory to catabolic influences of space flight. The prediction formula of Vogel, *et al.*, may be useful in this regard.

## TABLE X. MUSCULOSKELETAL SYSTEM

### Finding

- Moderate losses of calcium, nitrogen, and phosphorus

### Possible etiological factors

- Primary - loss of gravity gradient
- Secondary
  - Absence of weight bearing
  - Absence of hydrostatic venous gradient
  - ? hormonal imbalance (elevated cortisol secretion)
  - Combinations of above

### Candidate future studies

- Absolute catabolic in-flight changes (bone, muscles) in animals
- Countermeasure evaluation
  - Dietary
  - Physical
  - ? Hormonal
- Selection criteria for prolonged missions (Prediction formula)

## Fluid and Electrolytes

Following Apollo and before Skylab a working hypothesis was advanced (5) which provided a logical flow of events outlining the adaptive changes in the fluid, electrolyte and hormonal area. The essential steps in this adaptive process are outlined in figure 2. In brief, the relative hypervolemia (total circulating blood volume) experienced on orbital insertion resulted in decreases in antidiuretic hormone (Gauer-Henry reflex) and aldosterone resulting in a diuresis of water and solute (sodium and potassium). Such a diuresis may have occurred during mission day 1, but was not evident since fractional urine samples could not be obtained due to mission constraints. Thus, a diuresis could have occurred but was obscured by collection procedures or modified by increased insensible loss and sweating which were not measured.

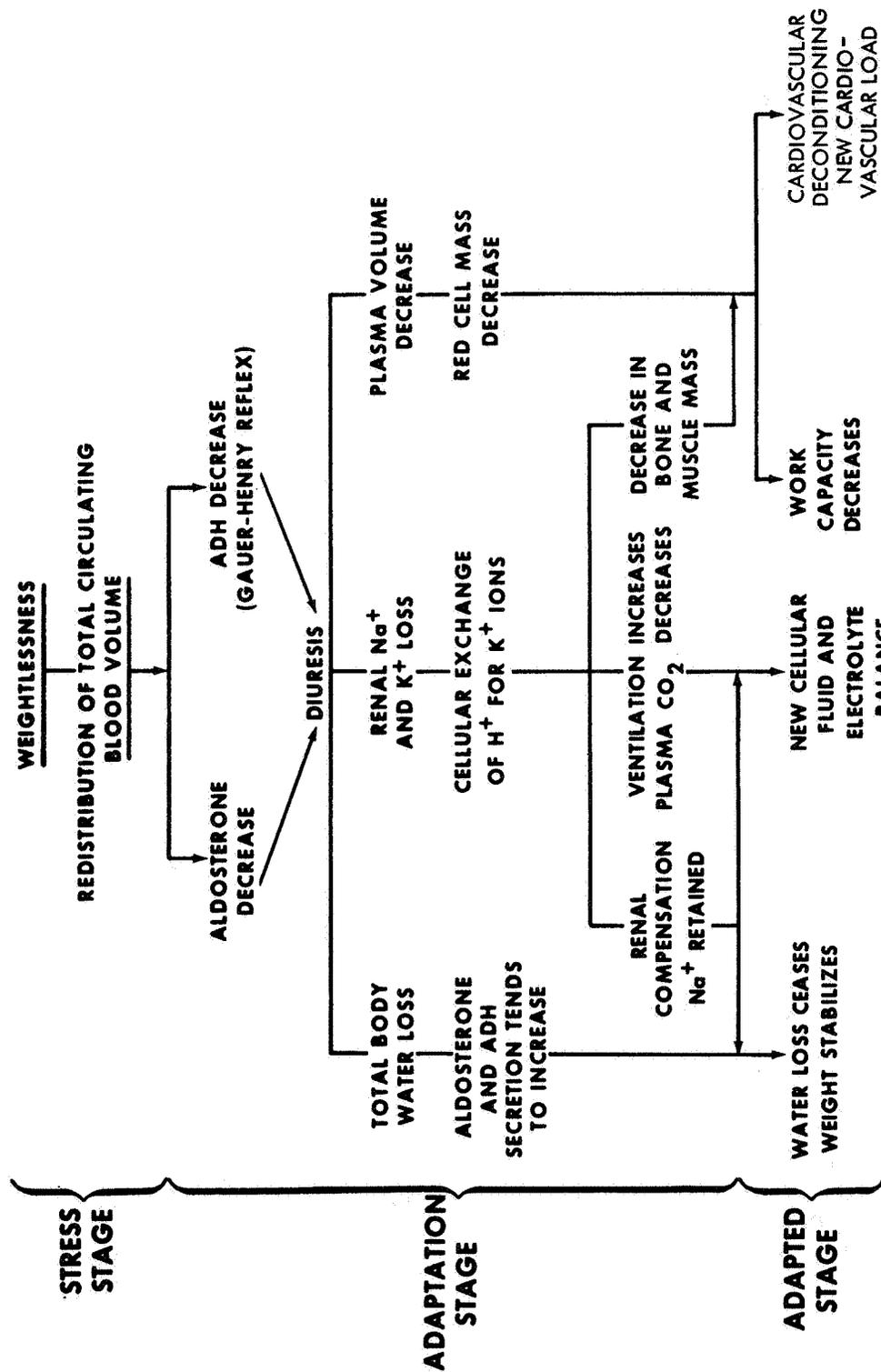


Figure 2. Adaptive responses to weightlessness pre-Skylab hypothesis.

Even assuming the occurrence of a diuresis during early mission, there are some consistently paradoxical findings which are difficult to reconcile with the working hypothesis. These findings are listed in table XI. Antidiuretic hormone secretion was uniformly decreased during all missions with the exception of Skylab 2 in which case it was elevated, especially in early mission following the overheating of the orbital workshop. Also, aldosterone secretion was consistently elevated throughout all missions, and particularly in the early part of Skylab 2 and 3. Despite this elevated aldosterone, solute (sodium and potassium) excretion was consistently elevated and was reflected in the increased urine osmolality. As stated earlier, the consistently elevated cortisol secretion doubtless contributed to muscle catabolism and increased nitrogen and potassium loss. Its overall effect on fluid and electrolyte homeostasis must remain conjectural at this point in time.

In general then, it is evident that internal homeostasis and satisfactory renal function are maintained through complex humoral and/or hemodynamic (physical) factors that await clarification.

Future studies currently being pursued at this Center include demonstration of the presence (or absence) of the Gauer-Henry reflex during early weightlessness, the changes in renal hemodynamics during zero-g; the renal response to provocative stresses such as water loading, salt loading and water deprivation during space flight; and the hormonal interplay involved in these processes.

TABLE XI. FLUID/ELECTROLYTE AREA

**Pre-Skylab working hypothesis**

**Paradoxical Skylab urinary findings**

- + Antidiuretic hormone (+ Skylab 2)
- + Aldosterone secretion
- + Na<sup>+</sup> K<sup>+</sup> excretion
- + Osmolality
- + Cortisol

**Interpretation**

- Internal homeostasis maintained
- Renal function maintained
- Interaction of complex humoral (and ? hemodynamic) factors required to maintain homeostasis during weightlessness

**Future studies**

- Demonstrate Gauer-Henry reflex
- Renal hemodynamics in zero-g
- Renal response to water/salt loads, dehydration in zero-g
- Humoral interactions involved in above

## Hematology

Red cell mass loss was again observed following the Skylab missions. The mean loss in Gemini was about 17 percent; in Apollo, 10 percent; and in Skylab, 8 percent. Further, the mean loss in Skylab 2, 3, and 4 was 9.4 percent, 8.6 percent, and 5.9 percent respectively. Other findings in the areas of hematology, immunology and cellular biology were not consistently remarkable as indicated in table XII.

TABLE XII. SKYLAB HEMATOLOGY, IMMUNOLOGY AND CYTOLOGY SUMMARY

- Loss of red cell mass observed postflight appears to be suppression of red cell production rather than increased destruction.
- Red blood cell mass loss not related to mission duration.
- No significant changes consistently observed in humoral or cellular immune responses.
- Cellular proliferation (tissue culture) normal during space flight.

The red cell mass losses are apparently related to marrow suppression (table XIII), since there is little evidence to support increased cell destruction. The stimulus resulting in marrow suppression is not clear and requires further study. Toxic suppression appears remote; physical factors, such as a pulse of increased bone marrow venous pressure should be investigated. It is apparent that there is no increased red cell mass loss with increased mission duration. The apparent diminution in red cell mass losses from Gemini through Skylab may be a reflection of the distance of the first postflight sampling period from the initial in-flight suppressive stimulus (fig. 3).

TABLE XIII. HEMATOLOGIC SYSTEM

### Finding

- Red cell mass loss

### Etiological factor(s)

- Increased destruction - no evidence
- Marrow suppression

### Toxic

Physical (increased blood volume. Bone marrow venous pressure)

### Candidate future studies

- Ground-based marrow-suppression factors
- Validate Skylab results on longer Earth-orbital flights

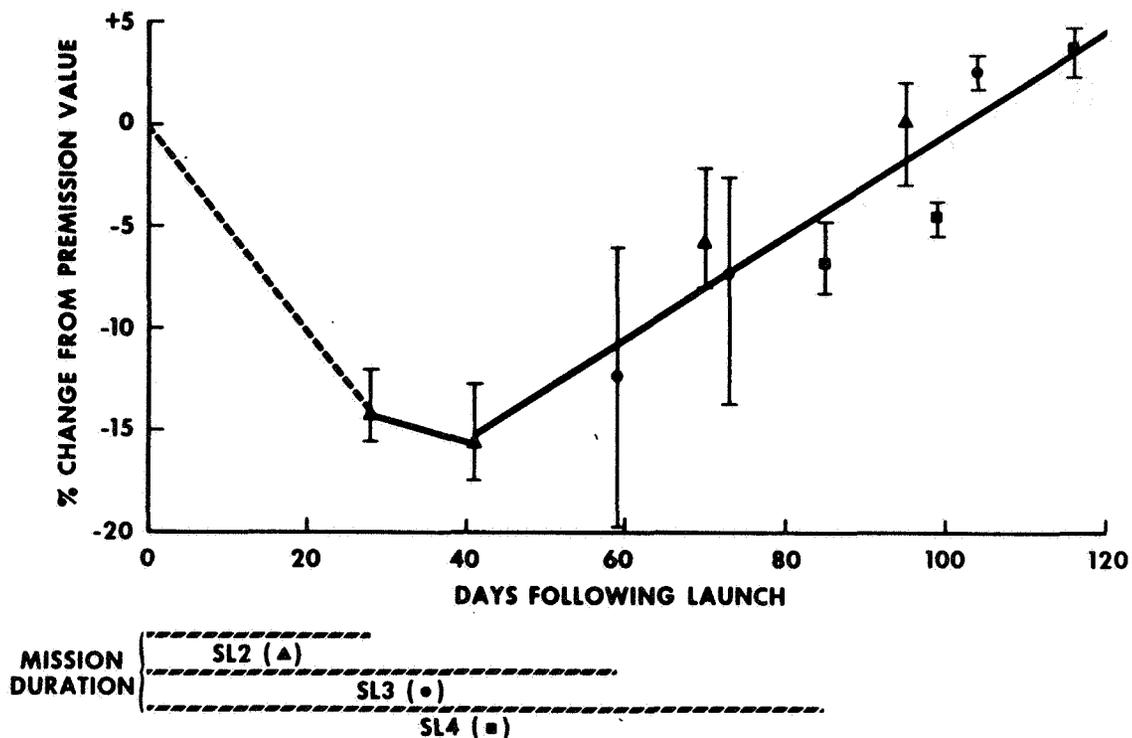


Figure 3. Red Cell Mass/Skylab.

Clearly, ground-based studies regarding the bone marrow suppression mechanism must be pursued. Further validation of the Skylab results should be pursued on orbital flights of longer than 4 months' duration, since the mean life span of the red blood corpuscle is 120 days.

#### Neurophysical and Performance Areas

The salient findings in the neurophysiological and performance areas of Skylab are indicated in table XIV.

TABLE XIV. SKYLAB NEUROPHYSIOLOGICAL AND PERFORMANCE SUMMARY

- After initial in-flight adaptive period, all crewmen show marked increased tolerance to motion sickness measured by rotation and head movements. Tolerance threshold gradually reverted to baseline post flight. Antimotion medications helpful in control of symptoms.
- No major disturbances noted in quantity or quality of sleep.
- Carefully regulated crew work/rest cycles essential for maintaining crew efficiency.
- Postflight hyperreflexia confirmed and quantitated.
- Improved in-flight performance efficiency exhibited by all crews.
- Overlearning recommended for critical tasks on short-duration missions.

Among these findings, the occurrence of motion (space) sickness symptoms during the first few days of space flight is of paramount operational importance for the forthcoming Shuttle flights. Some possible etiological factors are indicated in table XV, although at the present time true etiological factor or factors cannot be specified. It would appear that otolith function is profoundly influenced by null gravity and its modulating influence perturbed; sensory inputs are accordingly distorted and appropriate responses are not forthcoming, since these are based on a one-g environmental memory store. Presumably, a repatterning of this central memory network must perhaps occur, so that new and unfamiliar zero-g sensory inputs are correctly interpreted and appropriate motor responses elicited. This repatterning of the central memory core is, we believe, the end result of the process of habituation or adaptation. Other contributory factors should be considered such as hypervolemia or increased venous pressure effects on the vestibular system.

Future studies in this area should address the problem of space sickness susceptibility and the development of a reliable predictive test for this susceptibility in candidate crews and passengers. Basic studies should be pursued relative to etiological factors involved in the space sickness syndrome and the role of one-g training in its prevention or mitigation. Finally, improved medications should be sought for more effective prevention or control of the vagal manifestations of this vestibular disturbance in space.

**TABLE XV. SKYLAB VESTIBULAR FINDINGS**

**Possible etiological factors**

- Otolith receptor physiological deafferentation
  - + Modulating influence on canals
  - Direct interaction with canals

**Rule out:**

- Influence of hypervolemia  
(Transient + pressure) on vestibular system

**Candidate future studies**

- Role of altered cues: visual, kinesthetic other sensory
- Effect of overhydration, dehydration and increased venous pressure on motion sickness threshold
- Predictive test for zero-g space sickness susceptibility (? parabolic flights)
- Basic studies regarding etiology
- Role of one-g training in prevention
- Improved medications for prevention/control

## GENERAL SUMMATION

Table XVI lists the general conclusions reached as a result of the Skylab biomedical experience. In substance, the findings indicate that man adapts well to and functions effectively in the space environment for time periods approaching three months. Appropriate dietary intake coupled with adequate, programed exercise, sleep, work and recreation periods are essential to crew health and well being. No untoward physiological responses have been noted that would preclude longer duration space flights, but more research is required in order to understand the mechanisms involved in the observed responses.

Finally, remedial or preventive measures may be required for Mars-type missions, and further study of man in Earth orbit for an uninterrupted six-month period should ideally precede this Mars-type mission - truly the gateway to exploration of the Universe: a step which may bring man closer to answering the eternal questions of whence he came, why he is here, and whither he goes.

TABLE XVI. SKYLAB GENERAL SUMMATION

- ° Biomedical results show that man can adapt and function effectively in weightless environment for extended periods.
- ° Daily in-flight personal exercise regimens coupled with appropriate dietary intake and programed adequate sleep, work and recreation periods essential for maintaining crew health and well-being.
- ° No untoward physiological changes noted that would preclude longer duration manned space flights; however, research required to understand the mechanisms responsible for many observed changes.
- ° Remedial or preventive measures may be required for mission durations in excess of 9 to 12 months (*e.g.*, bone demineralization countermeasures)
- ° Ideally, further observations of man in Earth orbit for an uninterrupted period of 6 months should precede a Mars-type mission.

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## SYMPOSIUM PANEL DISCUSSION

Charles A. Berry, M.D., M.P.H., Moderator  
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Health Science Center at Houston  
Houston, Texas*

DR. BERRY: Could we ask the panelists to please come up and take a seat at the table?

Well, colleagues, ladies and gentlemen, we've reached that point that we've all been waiting for, to try and decide the total meaning of all the material which has been presented. That's an awesome task. I think Dr. Dietlein did a fantastic job of pulling his material together. I certainly think his summary was excellent and he did a very good job of telling us where we are.

There are a few remarks that I would like to make at the outset, and then I would like to note how we're going to work the remainder of this session. For this period, we have asked the panelists covering various areas, to be a part of this discussion and give their views of the data. They're not limited to their special area of discussion, but they should present their views concerning what they have heard of these results. These statements will be relatively brief so that we don't end up with a whole series of papers all over again. The objective is to have some interchange among those of us on the panel and with you in the audience. We particularly want those who have been investigators, those of you who have been carrying out some of these studies, to address questions you may have to the panelists. It would be interesting to determine if they view the data the same way you did.

Now I think it's very important that we all realize one of the things that Dr. Dietlein said and is well stated in the title of his paper. This point is still a beginning. It's a culmination, though, of many things, as you saw from the slides that he presented; and that there are many people in this room who have had a tremendous amount to do with reaching this point. There are some people whom I think have not been singled out — and this is always dangerous, once you start doing that. I want to say at the outset that there is no way possible that I could single out all the people in this room who have something to do with making today possible, and this day is possible only after roughly the last 15 years of activity in this field — a tremendous effort to get us to the point where we had data to review as has been done today.

I would like to congratulate the entire biomedical team for the development of this symposium. As you know, this team is composed of members from both inside NASA and from the scientific community. Within NASA we have people from the Johnson Space Center, from other Centers and Headquarters. My congratulations are directed to this entire group, and in particular, to the Johnson team who worked so earnestly in organizing the program in which we are participating this afternoon. Now some of the individuals who are in this audience are people who have formerly worked with this team in one form or another. They've had activities tied with the team — trying to get data for one area or another or working with the operations teams. Many of you are here because of those particular interests and we're thankful to all of you. There are some people here, though, who have played a particular role in some of our activities over the years because they've taught many of us and led many of us down these productive paths. Dr. Strughold I see sitting over here. He's been with us for many, many years and really led us into space medicine. I think we owe a particular debt to him. We also have a couple of people in the audience who were quite active in leading the team of us who were involved at the very beginning of the program back in the Mercury days. They have since moved to other areas, one of them only recently, but they are still very tied to our area of interest. I'm referring to Stan White and Bill Douglas, who are here in the audience. We have Dr. Hitchcock down here in the very front of the room, and it's people such as he who have helped to teach us along the way and have made great imprints upon the capability to develop data such as you've seen here. Dr. Bjurstedt and Dr. Gauer from across the oceans are here with us in the room. You've heard Dr. Gauer's name mentioned so many times during the symposium. Drs. Luft and Sam White from Lovelace started very early in the program working with us, and they have continued with that activity. We could go on and on and on with people like these. There is another thing I would like to emphasize — there are a number of panelists here who went through some very trying times with us.

I saw Herb Hultgren out in the audience during the last three days, and I'd like to say something about the role he and some other fine people played with us. You've heard many very fine comments about what great teamwork we had; what a great job everyone has done and how happily it's all ended. Today, everyone is bouncing and full of joy. I'd like to tell you that this last year has not always been bouncing and full of joy for the people who have been working on this program. At times, I tell you very personally, I considered it hell. And I'm not sure that some other people on the team didn't consider it that way also. So while it has all turned out great, I don't want anyone to go away from here with the idea that it's easy and that it all just sort of happens, because it doesn't just happen.

There were daily problems, and these were alluded to in some of the opening morning speeches when some of our key people in the Program Office mentioned that there had been some of these early problems. Some of the people who were talking about the program operations mentioned these, and there was daily some sort of difficulty in trying to work out the problems which were occurring on a minute-to-minute and hour-to-hour basis. These problems and their resolutions were important to the outcome of these data which you've heard discussed here. While some of them may have sounded not important at the time, they had great importance; and those decisions required were not always easy to reach, and they always weren't made to everyone's satisfaction, of course. There was severe management concern, and Dr. Dietlein, I think, led up to that very well in some of the things that he was telling you about past history.

I'd like to call to your attention the fact that the cardiovascular system, while it was the first system that was ever noted to show measurable changes and with which we had problems, certainly remained one of concern. This concern was augmented by our problems with Apollo 15 — the arrhythmias which were mentioned — and then a great deal of data which we obtained from our Russian cohorts. I would just make one parenthetical statement here; that we have come a long way in our dealing with our Russian colleagues over these years. A great deal has changed in the last 15 years. We've exchanged a significant amount of data directly. They're looking at many of the same problems and questions as we are. They're not always looking at them in the same way that we are, but they're searching for an understanding of the physiological mechanisms.

These concerns of top management surfaced to the point that we were required to get decisions weekly, for medical purposes, as to whether we would continue to extend the mission or not. I can tell you that those weekly meetings were deadly serious; that the Administrator was very, very serious about what he was going to do, or not do, and he required that he be reassured by evidence. It was fine to try and give that reassurance on a personal basis, backed by our NASA team such as we had conducting these missions, but we needed other assistance. We formed two particular consultant groups. One group was a cardiovascular group. And John Shepherd, who's here on the panel, spent a great deal of time with that. Scott Swisher, who is also a member of this panel, was on that group. This group met many times during the course of the program. They met with others and gave of their time unstintingly to help us convince management; I needed that support and I'm deeply grateful for it. We also had a group that was organized to try and look at the vestibular area, and one of those people is here on the panel, Melvill Jones. It's hard to find many vestibular experts once you get past Ash Graybiel. We went to great

lengths to try and find vestibular people to come. They did meet and we appreciate the guidance they provided.

I've reviewed the remarks that I had a chance to present in trying to sum up this program on two previous occasions; namely, the Fifth-Man-in-Space Symposium last December, and then again in May at the Aerospace Medical Association meeting. In December, we were still flying the last mission and in May, we were at the point where the missions were completed and we were sort of able to sum up, at least with data as they were revealed at that point in time. I don't think that I would change anything that I said in any of those remarks, and so I'm not going to repeat them here today. I think that Dr. Dietlein has summarized very well the status that we all believe exists and that man has shown adaptive changes to a unique environment. In some cases, these changes are definitely going to require some countermeasures. I think in the calcium balance area we're going to have to use countermeasures. I suspect even in the cardiovascular area we're going to continue to look for these procedures.

There is one observation that I would like to leave you with, and that is the fact that we are defining many new norms as we look at these findings. There's no question about that. We're looking at man, normal man, placed into this very unique environment. As we make our observations, we know we can't look at the absoluteness of weightlessness because man is going about his mission activities. Still I believe that we are conducting an unparalleled experiment in man's adaptation. As we derive these new norms, we are able to look at the hypothesis that we've developed. There are some gaps in this hypothesis and they lead to the future research that needs to be done. I hope that our panelists are going to identify a good deal of that needed research in their discussions.

I'm left with the feeling that while we have probably come up with more questions than answers, still we have gained a lot of answers. And certainly, if you look back at the time of the beginning of Mercury, we've come a long way in deciding what's really happening to man in this very unique environment. Now I'd like to begin our panel discussion. The cardiovascular system was mentioned first. To save time, I'll not introduce everybody on the panel until we come to them. First, although listed on your program, Neal Bricker is not with us. Nor is Ted Cooper. I'm going to call on Dr. Epstein in a moment, as he is replacing Dr. Cooper. I'd first like to call on John Shepherd, because of his interest in the cardiovascular system which we've mentioned so frequently and most recently in our elaborations of the last day and a half. And so, John, I'd like for you to take a few minutes and give us your views about how you sum this all up, as far as the cardiovascular system is concerned.

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For those of us from the biomedical community who have followed the progress of the manned space program from its inception, this symposium has been a great occasion, and Mr. Richard Johnston and his colleagues at the Space Center deserve our congratulations. Over these years you, our colleagues in NASA, have been receptive to suggestions and tolerant of our lack of understanding of the lead time which is essential for the proper implementation of experiments to be conducted during manned space flight, and the constraints that are necessary to meet the overall objective of each mission. By the cooperation you have achieved between the astronauts, the in-house NASA scientists and the scientific community, we now have, as Dr. Larry Dietlein said in his excellent summary of the symposium, objective data of man's ability to adapt to the space environment, and hence of his potential for extended space missions. As Doctors Kerwin and Musgrave so aptly put it, "just feed us, house us and let us exercise".

Dr. Berry has reminded us that all this has not come about easily, but rather as a consequence of a logical progression of knowledge and appropriate adjustments as we moved through the missions from Mercury, Gemini, and Apollo to Skylab. Many of you will recall our long-past panel discussions at Woods Hole, Cape Cod, as we talked wisely of cardiovascular deconditioning, without much idea of what we were talking about in coining this term. We worried about potassium loss and cardiac arrhythmias in the later Apollo missions. Today for those interested in the cardiovascular system, you have provided a clear picture of the physiological changes in space flight, which can fit into an accepted and logical pattern of normal cardiovascular adaptation.

With the achievement of the weightless state, fluid shifts quickly from the lower to the upper part of the body. Evidence for this has been given by the astronauts. Doctors Gibson and Kerwin have described to us the fullness of the head which they experienced, the distension of the head and neck veins, the congested sinuses and the facial puffiness. Leg measurements have demonstrated a rapid decrease in leg volume. With this transfer of blood and tissue fluid from the legs to the central circulation (one might estimate the amount to be around 700 milliliters) the volume of the heart and the cardiac filling pressure is increased. This results in a small increase in cardiac output, due mainly to an increase in stroke volume because of the greater end-diastolic volume of the ventricles (Frank-Starling mechanism). At the

same time the activity of the mechanoreceptors in the cardiopulmonary region is increased; this results in a greater inhibition of the vasomotor centers with a resultant reduction in sympathetic adrenergic outflow. Consequently the peripheral blood vessels dilate so that the total systemic vascular resistance is decreased. Evidence for this was provided by Dr. Johnson, who showed that during weightlessness there was a widening of the arterial pulse pressure and by Dr. Thornton who indicated from measurements made on the calf of the leg by venous occlusion plethysmography that the blood flow to the legs may be increased.

Even though the cardiopulmonary receptors are strongly activated by the increased volume of blood in the heart and lungs, the magnitude of the peripheral vasodilatation is limited by the counterbalancing effect of the carotid baroreceptors. In cats and dogs these latter receptors are more effective in opposing the increase in muscle blood flow and the glomerular filtration rate will be increased. Diuresis is facilitated by the reduced reabsorption from the renal tubules, since stimulation of the cardiac receptors results in a diuresis which is brought about by a blood-bone agent.

At the same time the amount of renin released from the kidney is reduced because these cardiopulmonary receptors act continuously to inhibit its release and the more so when they are strongly stimulated. As a consequence less angiotensin II is secreted. Thus there is a loss of fluid from the body as a consequence of this normal response to an increased central blood volume. Somehow, as I hope Dr. Scott Swisher will tell us, the red blood cells are reduced in proportion to the decrease in plasma volume. The astronauts have reported that exercise relieves the fullness of the head. With the severe exercise which they undertook the blood flow to the active muscles is increased as the arterioles dilate. This causes an increase in pressure in the capillary and post-capillary vessels in these muscles so that fluid passes from the capillaries into the interstitial spaces and more blood is accommodated in the post-capillary bed; as a consequence, the distension of the vessels in the thorax and head is lessened. With the application of a given set of negative pressures to the lower part of the astronaut's body during the Skylab missions, there was a greater increase in heart rate and in diastolic blood pressure (indicative of a greater reflex constriction of systemic resistance vessels) than when the same stimulus was applied on Earth. In the weightless state, with less blood and tissue fluid in the legs, and more in the central circulation, more blood is pulled into the lower body with application of the same negative pressure than in a gravity environment. The reduction of the stimulation of the cardiopulmonary mechanoreceptors is greater, the inhibition of the vasomotor centers is less, and hence the increase in sympathetic adrenergic outflow is more than that with the same test preflight.

If we could amputate the legs, which have little use and indeed may be an inconvenience in space flight, these shifts in blood volume would not occur. In fact, the major question for prolonged space flight is what to do about the legs. The bones in the legs lose calcium as they no longer perform their normal function of weight bearing. Exercise seems the best answer and the astronauts described an ingenious plastic platform they used that slips backwards with each step, so that as the subject walks he stays in the same position.

Immediately on return to Earth gravity these changes are reversed. There is more blood in the legs and less in the upper part of the body. Since both the plasma and the red cell volume are slightly reduced, the system as a whole must adjust to a smaller total blood volume. The filling pressure of the heart is decreased, the heart volume is less and as shown by the excellent echocardiographic studies of Doctors Henry and Epstein, the stroke volume and diastolic volume are reduced. With exercise under these conditions the increased cardiac output to meet the increased oxygen requirements is achieved by a faster heart rate and a smaller stroke volume. Also, the hemodynamic response to lower body negative pressure will continue to be exaggerated until blood volume which is customary for Earth's environment is restored. Again it is important to emphasize that these are the normal compensatory physiological responses to changes in blood volume and its distribution within the vascular system. At this time, immediately postflight the astronauts report that they are thirsty and drink freely.

As we turn from the studies of Skylab and look to the Shuttle era, the success of the former has provided the stimulus for gaining new understanding of man in the latter. There is much still to be learned from well-conceived animal experiments and complimentary studies on man, both on Earth and at zero-g.

For example, the presence of mechanoreceptors in the heart and lungs has long been known, and many investigators are active in studies designed to elucidate their function and morphology. Complex unencapsulated sensory endings are present around the junctions of the pulmonary veins and of the caval veins with the left and right atrium respectively. It has been postulated that there are two types of these receptors, one type having its bursts of activity coincident with the a-wave of the atrial pressure pulse, and the other with activity related to the v-wave. Others conclude that their characteristics are similar. They are connected to medullated vagal afferents and their stimulation causes an increase in heart rate, a decrease in activity in nerves to the kidney and a diuresis caused by a blood-bone agent. Discussion continues as to whether the diuresis is caused by a decrease in the concentration of antidiuretic hormone or an increase of an unknown diuretic substance. By contrast with these receptors

with medullated afferents, there exists in the left ventricle and in the atria a diffuse and large population of receptors connected to slowly-conducting non-medullated vagal afferent fibers. Activation of these receptors causes bradycardia, a generalized vasodilatation, and especially an augmentation of the vagal outflow to the heart receptors, probably located in the left ventricle and with unmyelinated afferents in the vagi. Thus it is possible that a similar mechanism in man contributes to the sickness experienced by the astronauts. The lung too, like the heart, is a source of reflexes which modify the cardiovascular system and which merit further study. The role of left ventricular receptors in the causation of the vasovagal reaction also needs elucidation; it has been suggested that the vigorous contraction of the ventricles when their volume is reduced might excite these receptors and induce a reflex bradycardia. Perhaps this might occur in susceptible subjects with the reduction in central blood volume that follows the application of negative pressure to the lower body. The Shuttle too with its increased facilities for observations in man will permit a more detailed analysis of the rapid adaptations in the body systems which occur within the first few hours of weightlessness and which provide the explanation for the subsequent responses to various stresses.

Thus the wealth of data which has been accumulated on the adjustments of man to space travel, and which have been so well described in this symposium, truly establish his future role in the exploration of our universe.

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(The following list of selected references was furnished by Dr. Shepherd for the use of interested readers seeking further details of statements made by him here.)

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[Note: Although Dr. Otto Gauer was not a Panelist *per se* his comments together with illustrations and references fit most appropriately into the panel discussions at this point, and are therefore included.]

I was much impressed by Dr. Kerwin's vivid description of the severe engorgement of the cephalad circulation characterized by extended neck veins, a puffy face and nasal congestion. These findings are corroborated by Dr. Thornton's report of a dramatic loss of extracellular fluid and blood volume from the thighs and calves in the order of two (!) liters. This figure is based on foolproof anthropometric measurements. Although venous pressure was not recorded, we can safely assume, that the intrathoracic circulatory compartment, which has to accommodate the lion's share of this volume, was greatly distended. In the weightless condition the cephalad fluid displacement was in all likelihood greater than that induced by whole body immersion in a thermoneutral bath. It is therefore not surprising that similar effects on circulation and fluid balance in the weightless condition (1-6) and in whole body water immersion have been observed. Upon immersion, intrathoracic blood volume increases by 700 milliliters (1), and the heart volume by 320-120 (mean 180/milliliters) (5). (Figure 1, table I.)

This engorgement is reflected in an elevation of central venous pressure to 12-15 mm Hg (3) (fig. 2). The distension of the heart has a primary effect on cardiac dynamics and secondary reflex effects on the arterial and capacitance systems (table I). Thus an increase in cardiac output, a fall in total peripheral resistance (TPR) and a reduction in the tone of the capacitance system were well established during immersion and weightlessness. Furthermore the volume control reflex is activated for the relief of the central engorgement. This reflex is by no means adequately described by the sequence: left atrial distension, reduced antidiuretic hormone (ADH) secretion, diuresis. Numerous factors are involved (2,4) (fig. 3). Although the final results, namely, plasma volume loss, impaired orthostatic tolerance and reduced working capacity are the same after exposure to immersion or weightlessness there are considerable differences in the behavior of the effector mechanism. For example; during immersion a negative fluid balance is effected by excess urinary excretion, in weightlessness this effect is attained by deficit drinking. During immersion the attenuation of plasma volume

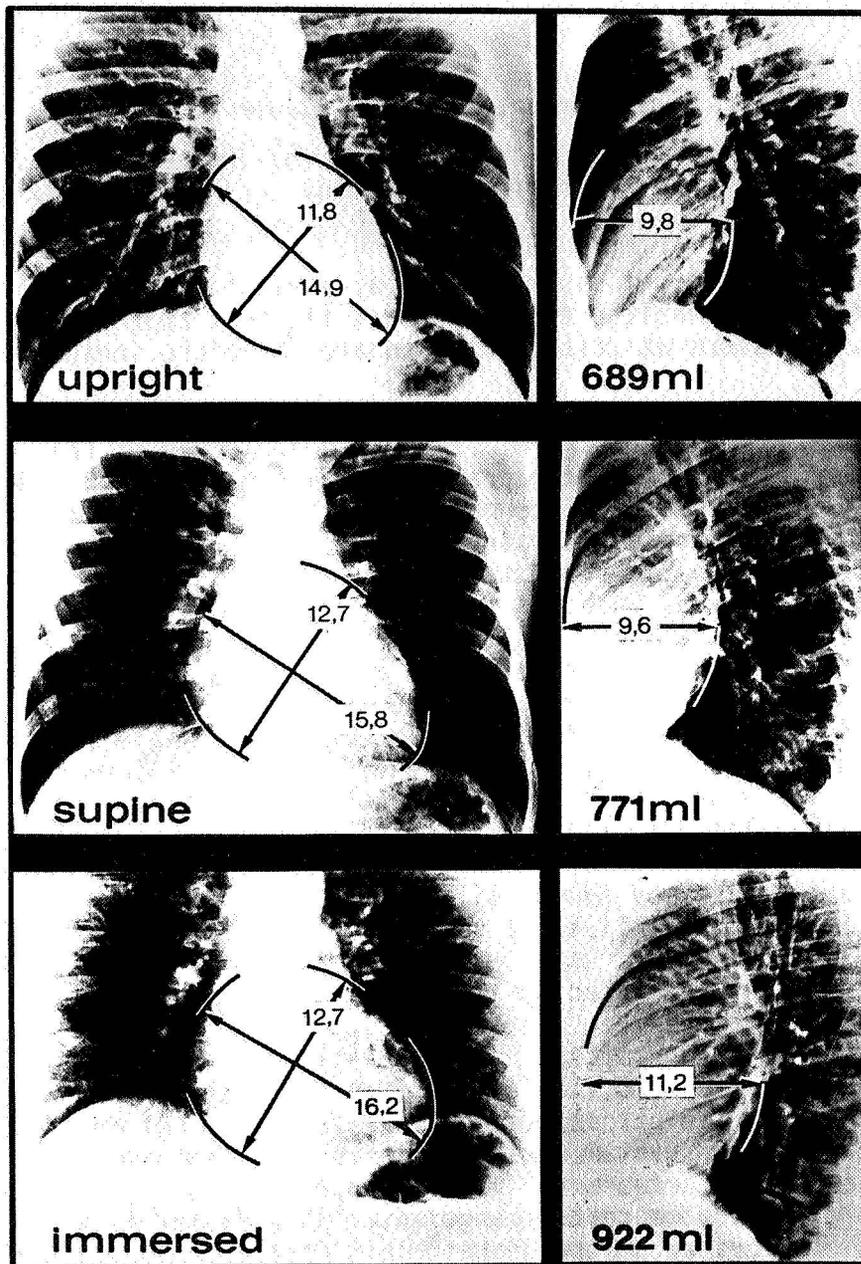


Figure 1. Roentgenometric demonstration of the change of heart size in relation to posture and immersion in a bath. The lines to calculate heart volume from the postero-anterior (left) and the lateral projection (right) have been drawn. With immersion of the subject standing in air heart volume rises by 233 ml. Considering the severe congestion of the cephalad circulation in the weightless condition a similar increase in heart volume can be expected. (Lange, L. *et al.*, 1974.)

TABLE I. CIRCULATORY CHANGES INDUCED BY WHOLE BODY IMMERSION\*

Primary and secondary effects on the circulation induced by whole body immersion. (Data from Arborelius *et al.* 1972, Echt, Lange and Gauer 1974 and Lange *et al.* 1974)

Primary Effects

Δ Central Blood Volume (L) <sup>†</sup>	+700 ml
Δ Heart Volume (G) <sup>†</sup>	+180 ml
Δ Central Venous Pressure (G,L)	+12 to +18 mm Hg
Δ Intrathoracic Pressure (G,L)	+ 4 to + 5 mm Hg
Δ Transmural Pressure (G,L)	+ 8 to +13 mm Hg

Secondary Effects

Δ Stroke Volume (L)	+35% <sup>‡</sup>
Δ Cardiac Output (L)	+32% <sup>‡</sup>
Δ Total Peripheral Resistance (L)	-30%
Δ Peripheral Venous Tone (G)	-30%
Δ Arterial Pressure (L)	+10 mm Hg <sup>§</sup>

\*Subject standing or sitting erect in air versus standing or sitting in water.

<sup>†</sup>(G) Gauer and co-workers; (L) Lungren and co-workers.

<sup>‡</sup>Heart rate was unchanged.

<sup>§</sup>The arteriovenous pressure gradient was not changed since CVP was increased by the same amount.

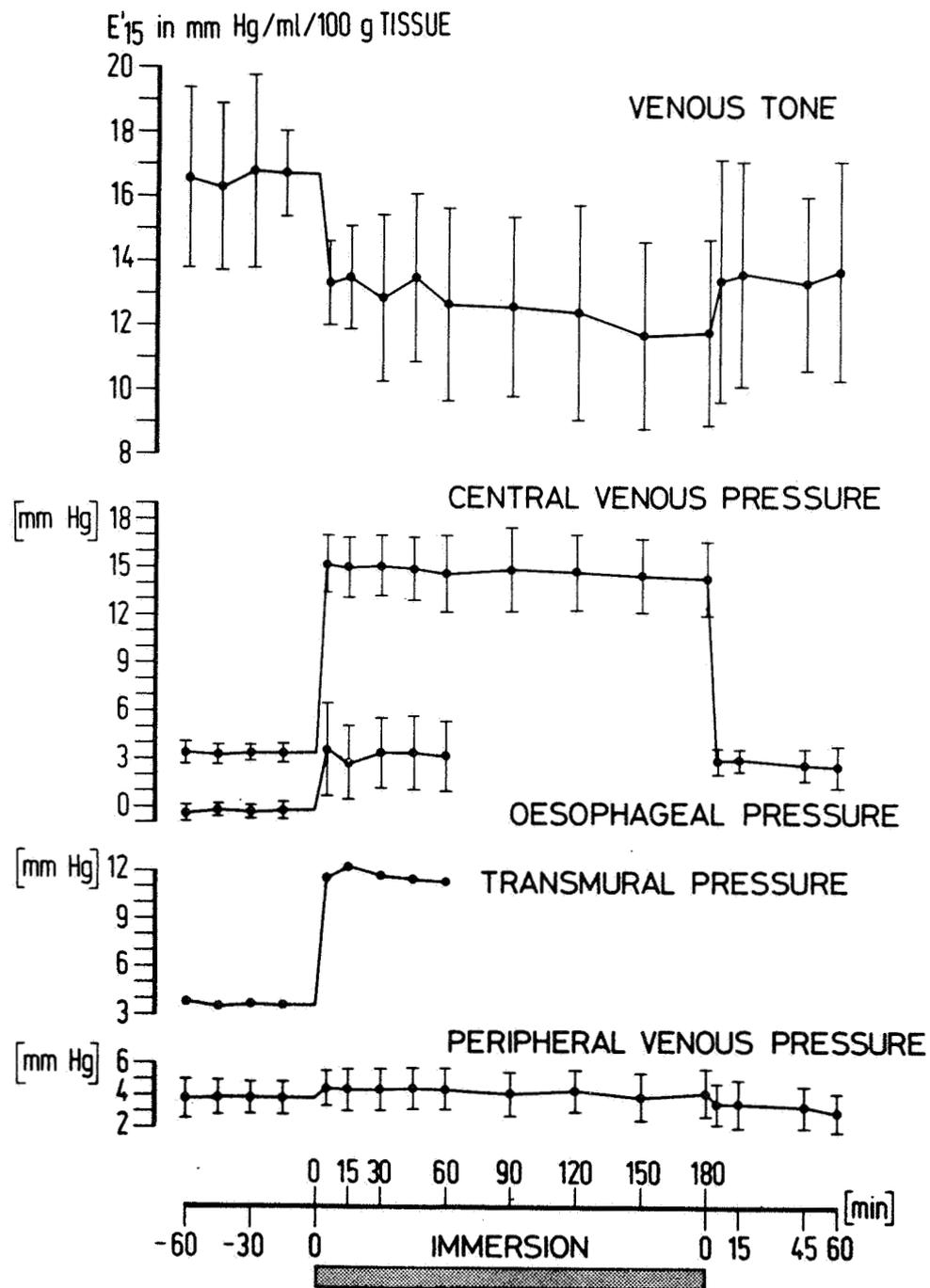


Figure 2. The effects of whole body immersion on various parameters. From above: peripheral venous tone; central venous pressure, oesophageal pressure, central venous transmural pressure, peripheral venous pressure. Recording of oesophageal pressure was discontinued after 1 hour immersion. N=5. (Echt, M. *et al.*, 1974,)

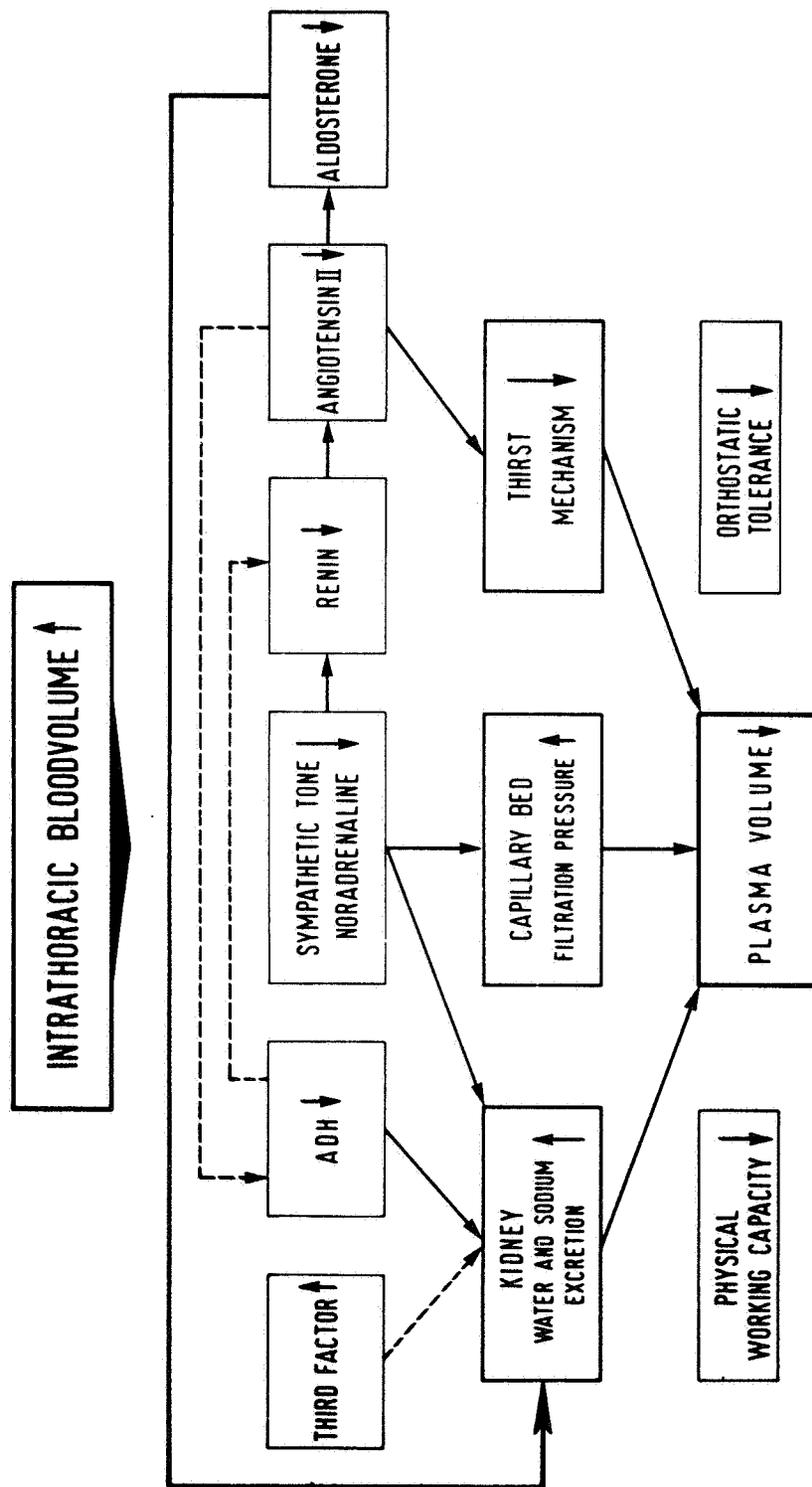


Figure 3. Intrathoracic vascular distension induced by whole body immersion and plasma volume control. With an increased intrathoracic volume the combined effect of several hormonal mechanisms leads to an increased renal excretion of water and sodium, a tendency towards outward filtration in the capillary bed and (probably) an attenuation of the thirst mechanism. The three effects combined (or single) lead to a reduction in plasma volume. (Gauer, O.H., 1973.)

is supported by an increased outward filtration (6), which is probably distributed over the whole body (2). In the weightless condition this outward filtration is obviously confined to the cephalad regions. Not easily explained is the observation presented by Dr. Leach, that sodium loss in the weightless condition occurs in spite of an increased aldosterone activity. Of particular interest is the adaptation of the red cell mass to the reduced plasma volume. In summary, numerous problems have been presented by the Skylab results. If they can be solved, our knowledge of the overall regulation of circulation and fluid metabolism will be greatly augmented.

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Dr. Shepherd painted quite beautifully the broad strokes of what can be derived from the data you've heard over these past few days. What I'd like to do now is to focus on a few specific questions I believe still remain to be answered regarding the long-term effects on myocardial function of prolonged space flight.

The results of the excellent paper presented by Dr. Bergman on systolic time intervals led him to the conclusion that there seemed to be at least some depression of myocardial function following return from space. However, it is quite clear from the studies of Dr. Bergman and his associates that systolic time intervals are exquisitely sensitive to preload; that is, during lower-body negative pressure (when, as our echocardiographic data show, left ventricular end-diastolic volume decreases), measurements of the systolic time intervals change. Therefore, interpretation of the meaning of changes in systolic time intervals is complicated, and distinction between alterations in intrinsic myocardial function from changes in the loading conditions of the heart may be impossible. However, on the basis of the ventricular function curves we were able to perform with echocardiography, we found no evidence of deterioration in intrinsic myocardial function. Parenthetically, I'd like to suggest that it might be interesting to relate the changes in systolic time intervals to the existing left ventricular end-diastolic volume. We know what left ventricular end-diastolic volume was at the time Dr. Bergman was measuring the systolic time intervals. Thus, we might be able to conclusively demonstrate whether or not changes in these intervals are caused by changes in ventricular volume.

Although I would like to state that the echo studies unequivocally demonstrate that there is no impairment in myocardial function, I don't think we can be absolutely definitive. After all, we studied only three astronauts, and we studied them only under resting conditions. The exercise studies, presented by Mr. Ed Michel, *et al.*, indicate that there is depression in cardiac output and stroke volume during *sub-maximal* levels of upright exercise that returns to normal in a rather brief period of time after splashdown. It seems reasonable to ascribe these transient changes to the decreased left ventricular volume we measured by echocardiography. However, one of the limitations of the exercise studies is that post flight, only submaximal levels of exercise performance were studied. The crucial measurement that still

must be made is what the *maximal* performance of the heart is in late postflight, compared to preflight. For example, if an impairment of myocardial function exists, measurements made at submaximal levels of exercise may be entirely normal and not necessarily reflect an impairment of the maximal pumping capacity of the heart.

One other aspect of myocardial function that has not been touched on at all is whether there is any alteration in myocardial compliance. This possibility occurred to us when we found that during the echo studies, although there was a decreased left ventricular end-diastolic volume post flight, we were unable to increase end-diastolic volume back to preflight levels by subjecting the astronauts to lower-body positive pressure, or by elevating their legs. One of the explanations of such a finding is that the mission led to a decrease in cardiac compliance. If this were the case, it could be due to a change in the heart muscle itself, or to a change in the dimensions of the pericardial sac. For example, if fluid volume is diminished during space flights and the heart is functioning at smaller volumes, it is possible that the pericardium adapts to this change by shrinking and decreasing the volume of the pericardial sac. The pericardium may thereby act as a restricting membrane postflight so as to keep the heart from returning the preflight volume until increased intracardiac pressures generated by the normalization of intravascular volume slowly distend the pericardium. It would be relatively easy to measure compliance changes in the heart by combining echocardiographic studies with more invasive techniques.

In summary, I think it would be important during future space missions to obtain more echocardiographic studies with ventricular function curves. Perhaps such studies could be performed in-flight, in which case it would be interesting to test Dr. Shepherd's hypothesis that left ventricular volume is increased during flight and only in transition to one-g does volume decrease. I also believe that maximal exercise testing would be essential to perform and that compliance studies of the heart should be considered to ensure that no other deleterious change in myocardial function has occurred that we have neglected to look at.

As a final comment, I would like to say that this has been a very fruitful collaboration for all of us at the National Institutes of Health. We already have begun to employ some of the techniques we have used on the astronauts to study the patients we see in our clinics and wards, and I'm optimistic that new data and insights will be generated using in patients some of the techniques we've helped develop and learn about here at NASA. Thank you.

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It was worth restating that Dr. Berry said the program is the culmination of 15 years of effort. This is about half or a good portion of the lifetime of many members of this audience. This period of time has involved extensive work in many fields of physiology and "space medicine". After the very detailed and excellent review of only one kind of problem, namely, the cardiovascular responses to weightlessness we should move away from that and picture what was one of the very first physiological concerns and which has not even been mentioned yet during this symposium. This is the exchange of gas with the respirable environment that is transported from Earth for the astronauts to breathe. This evidently has become an entirely manageable aspect of manned space flight. However, I would like to restate one of our earlier concerns, namely, that if individuals became ill with diffuse pulmonary disease (such as viral pneumonia), that this might generate peculiar kinds of circumstances such as diffuse atelectasis in a weightless state in the handling of pulmonary debris and secretions. It will still be wise to keep alert to details of the respiratory gas exchange and pulmonary function as one moves on into longer and longer periods of time where illness may develop or consequences of physical changes such as fluid shifts may progressively modify pulmonary function.

Now going from the still important considerations of respiratory exchange, we could next look at the whole man. Something that has been established is that man himself is able to proceed through the whole pattern of flight and come back. The whole man, including his senses, his vision, his hearing, his ability to react to his environment performed very well. His mind worked all right, so that even if his cardiovascular system could not tolerate all of the specific gravitational stresses on return quite the way we wanted them to, he did quite well with his mentality, his fingers and thumbs and other important parts while he was out there. He could carry out exceptionally useful and intelligent work. This means that gas exchange and factors involved in circulation to his head, and his hands and some of the parts in between were functioning all right. Now if we take the whole individual and examine him a little more closely, his heart probably also got along well because it was exercising all of the time as it normally tends to do in us even when we are at rest. It is normally an

exercising organ and, therefore, probably its muscle was not likely to suffer quite as much from the weightless state as his legs were.

I also saw no sign that the actual skeletal motor mass, the voluntary muscles of the individuals themselves, if they were treated right by being given adequate doses of exercise or of strain, had to experience a decrement at all. Massive work loads and rates of oxygen consumption were accomplished by the whole individual in this space environment - probably larger degrees of oxygen consumption than most of us can even begin to think about performing here and now. Therefore the individuals were certainly not limited in terms of performing hard labor activity in the space environment. Their muscles, therefore, in terms of the exertion of force, were certainly not handicapped. The circulation to the muscles may have been handicapped on return, leading to some of the decrement in exercise capability at one-g. However, it is necessary to distinguish between the intrinsic capacity of skeletal muscle itself to contract and the factors involved in supply of nutrients and oxygen to the muscles during a period of work. Therefore one has to consider the muscle and the circulation separately. If in the circulatory system, the heart itself was not severely in jeopardy, then one would have to look towards the circulatory regulating mechanisms as the limiting system on return. And I think they have been elaborated upon quite enough for now.

The question I have been posing is, then: Can we divide the overall exposure and experience into stages and look at these stages separately? Surely we can. One of these parts is the stage of prolonged exposure to the weightless state. The composite of all the observations described has indicated that individuals can, in fact, go on for long periods and keep themselves in reasonably good shape, even with the fluid shifts and even with the central vascular congestion and calcium loss. In addition, there is clearly a reasonably prompt return to - or adaptation on return to sea level and one-g again, back to Earth's atmosphere. The stage of real problems is that of transition between that harmless exposure in space and the readaptation on Earth. It therefore seems to me that the concentration that those of you directly involved in this work must make is on the stage of transition from one more or less "normal" state in weightlessness to a second normal state after return to one-g again, because the failures really occurred at that point. Actually it is still true that present astronauts are active, working, laborers in space but passive on entry into the Earth's gravitational field. Some day one will require active, self-controlled entry, and it is at that particular point that these questions are going to be most important: Can the individual be fully active during the stress of return, including during the entry; not only can he readapt to life in this atmosphere and at one-g well enough.

It seems now that a good deal of the attention from here on is going to be required to take the excellent observations made in the program to date and modify the experiment procedures drastically in ways that are controllable. I would urge that from this point on more attention be given to long-term studies in which individuals in space are allowed to actually deteriorate naturally, without attempting to sustain their physiological systems so that they can function fully on return. In other words, we now need professional "subjects" in addition to the pilot-commander and other responsible individuals in the spacecraft system. Then, having generated natural failure and studied it, one should study use of low-mass materials, such as drugs as stressors, which may, in fact, be able to modify fluid volumes, modify cardiovascular tone, supplement or replace baroreceptor mechanisms, and modify calcium loss. I think we now have to set up the kind of long-term laboratory in space in which such professional subjects are, in fact, considered not as "astronauts" but as "subjects", with physically competent individuals serving as transport crew for other individuals who are being studied in detail along with other experimental animals. Out of such an approach can come the exact pattern of unmodified deteriorations and adaptations to be dealt with in planning toward the ultimate in manned space flight.

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I believe the crucial problem that this symposium has heard about is that related to red cell mass change. The material presented on the change in red cell morphology may be a fascinating insight into a whole new set of problems, but we are still a long way from even beginning to be able to make an interpretation of these observations. I want to spend most of my time on the first problem.

There's a rather interesting psychological set, if you will, that overlays many of the reported investigations which has had a great influence on the way the observations are now coming together and beginning to make a coherent picture. The NASA Manned Space Flight Program has had a very laudable, and I must say, enviable record of attention to crew safety issues. But one of the things this has done is that it has put many of us who have been either peripherally or directly interested in one or another of the investigative aspects of the program in what might be called a "pathophysiological frame of mind". We tended to look first at changes as possible expressions of pathological mechanisms and possibly rightly so; but, in so doing, I think we have from time to time lost sight of what we were really observing, *i.e.* evolving physiological adaptations. I am delighted to see that this conference had its principal focus on physiological adaptation, and the concerns about pathological processes have been put into second rank.

It seems there is no argument that there is a distinct downward shift in red cell mass. Again taking the view that this is not a pathological process, that it is not a process which thus has the potential of becoming continuously downward in its direction, but that it is the searching for a new adaptation, one can, of course, then take a fairly comfortable position about it, at least insofar as the safety of the astronaut functioning in space. Dr. Lambertsen has raised the question about the flight transitional states, which really are the important ones. Here we have some very interesting data that I think need to be reexamined. The data presented suggest that the red cell mass deficits in the shorter flights, the earlier ones we were able to study, were possibly greater than those encountered in missions of longer duration. There may be some technical explanations for this. This may not be a set of entirely comparable measurements. We must try in retrospect to reconstruct the exact circumstances of those, and see if it's possible

that we were overmeasuring the red cell mass decrement in the earlier flights and that our more recent flights and related observations are those which are closer to the truth. You will notice also that the variability in the measurements were much greater in the earlier flights. But it is also possible, and this would be of great interest, that there is a kind of overshoot in the downward readjustment of red cell mass and that this overshoot is gradually recovered over a longer period of time to a new steady state.

I feel that the formulations we have heard of the mechanisms of re-adjustment are both clear and reasonable. Dr. Thornton's formulation is that the change in central blood volume is the crucial factor that all other changes proceed essentially from it, in a passive or active kind of readjustment. Dr. Johnson's formulation, which you heard, is an interesting one. I would have to raise a question with his formulation which in sense says that there are metabolic changes which favorably shift the oxygen-carrying capacity of the red cell mass and that this in turn permits the downward red cell mass adjustment. That is one way of looking at it in contrast to the way which Dr. Thornton presented these changes in oxygen-carrying capacity. It would seem that a metabolic process which produced the shift rightward in the oxygen dissociation curve might be more likely the secondary event than the causative event in the red cell mass decrease.

It's interesting that the "pathophysiological view" still persists! I notice Dr. Dietlein's slides still had the concept of "marrow inhibition". Maybe we really ought to speak of the marrow that is just turned down or turned off because it's not necessary that its activity remain at the normal earthbound one-g level. With this concept, bone marrow is really just resting and not inhibited.

Before we can really get a picture of what happens in a situation like this and in comparable experiments in animals, (for example, the artificially polycythemic overtransfused animal), we have one very large black box in the canonical diagram of the regulation of erythropoiesis that must be opened up. This contains the sensor system, if you will, the sensor-set point physiology. We know a few things. We know erythropoiesis is a hormonally controlled apparatus. At least there is one stimulatory hormone. The apparatus responded to oxygen, possibly not only to oxygen tension but to oxygen transport, which has something to do with blood flow. The time constants of the system are long, and the rude canonical diagram would suggest that it is a system that is driven upward, then relaxes and passively adjusts itself downward in the absence of the stimulus. Many alternative models of this system are yet to be explored. Is it possible that it is a multihormonal system, that there is some type of driver-antagonist hormonal balance, that there are pro-hormones, and that hormone conversion rates are

important? What is the process of sensing, in biochemical, physical, chemical, or electrochemical terms? Are second messengers involved? Until we can answer these questions not only in the case of man but by fundamental experimental investigation, we will have to accept the rather general picture we now have of the mechanism of space flight induced red cell mass decrease. The best assumption to me seems to be that it reflects a new balance in the circulation and in the perceived blood volume. This formulation certainly is an adequate one to explain what we have so far seen.

On the other hand, we ought to exert every effort to try to develop other formulations of these mechanisms of change, and not accept those which seem reasonable and rational on the basis of our very limited present knowledge. For example, is there some direct mechanism by which erythropoiesis is influenced that may bypass the hormonal system even, or at least bypass much of the regulation in control of the hormonal system, which is directly dependent upon some compartment of blood volume? Many of you can develop notions about how these kinds of hypotheses could be approached investigationaly. There is a possibility of control of the red cell mass change. I wanted to consider this because I feel Dr. Lambertsen is quite correct when he says that the next generation of investigators in space physiology is going to have to put much of their effort into problems of control, compensation and adaptation of systems that get beyond physiological limits in less than ideal subject astronauts. What about phlebotomy? People entering zero-g seem to have about 700 milliliters too much central blood volume, maybe even more. What about just taking that volume from them, preserving it in any one of a number of tricky ways that are now available, and putting it right back when they have to come home?

MODERATOR: Dr. Berry.

Well, the suggestions are getting better and better. We really thought about that, Scott. I want you to know we have thought about the phlebotomy route; we discussed it, but we thought everybody gets scared of needles and scarer of blood, it appears.

SPEAKER: Dr. Swisher.

I would suggest you sell it and not put it back.

MODERATOR: Dr. Berry.

Yes, you'd make a lot more money these days. Anyway, I'd like to ask Dr. Bob Heaney if he'd give us his view of this mineral balance area. I know he's been brainwashed somewhat, I'm sure, by Don Whedon by now, but I know him to be an individualist, and he's not going to listen to all that input and so he's going to give you his own strict view here.

Robert P. Heaney, M.D.

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Two major points stand out clearly from both the Skylab mineral studies and their supporting ground-based projects. These are:

- ° bone loss definitely occurs under zero-g conditions. It is certain that this loss continues for at least sixty days, and it is almost certain that it continues for as long as 84 days. There has been no evidence that this phenomenon shows the type of adaptation to zero-g which has been exhibited in the other systems which have been the subject of this symposium.
- ° bed rest, under one-g conditions is surprisingly suitable as a model for the bone loss of zero-g.

I shall expand, briefly, on both of these points, before going on to a discussion of what lies ahead.

Bone Loss. We now have calcium balance data on six of the nine astronauts, and urine calcium values for all nine. Calcium balance shifted negatively for five of the six (one of the Skylab 2 crewmen showed essentially no change). Urine calcium increased substantially in all nine. This latter change, while highly suggestive of negative balance, cannot be fully assessed without knowledge of calcium absorption, so we must wait for final balance data from Skylab 4. Nevertheless, the continued high values for urine calcium through the entire length of the Skylab 4 study gives us no reason to believe that any kind of adaptation occurred during the 84 days of that mission. Finally, both from bed rest and from in-flight studies, we have no evidence that the exercise program or the physical countermeasures which have been employed to date in any way alter this bone loss. This is not to say that more strenuous measures would not work; it is simply to stress that those which have been tested have not been effective.

Vogel has observed significant *os calcis* bone loss in one of the three Skylab 3 crewmen, and in two of the three Skylab 4 crewmen. He suggests that it may be possible to predict susceptibility to bone loss in advance, but data are still too few to reach a final conclusion about the usefulness of this approach in a zero-g situation.

Bed Rest Model. Despite many initial reservations, one-g bed rest appears to mimic zero-g weightlessness to a surprisingly good extent.

The two situations behave similarly for calcium balance, urine calcium, *os calcis* mineral loss, and hemodynamic effects. Hence this appears to be an entirely suitable, ground-based model.

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With respect to these data and their implications, there appears to me to be three big questions which we must try to answer. These are:

- ° how clinically significant is the bone loss?
- ° what, if anything, can be done about it? and
- ° where do we go from here?

Seriousness of Bone Loss. Here I think the major point is to focus briefly on the distinction between negative balance in-flight and the negative balance shift which occurs between preflight and in-flight conditions. Recall that four of the six crewmembers for whom we have balance data were in substantial positive balance preflight; hence the shift in a negative direction is substantially larger than the actual negative balance. Positive balance is unusual in this age group; for this reason we must ask ourselves why it occurred. I think immediately of two major possibilities: preflight conditioning, or systematic measurement error. If the effect is due to conditioning, then it is only the in-flight negative balance which reflects actual bone loss; if there is a measurement error, then the actual zero balance or equilibrium point may be closer to the preflight situation, and the shift is then a better indicator of actual bone loss.

Skylab 2 showed no really significant negative balances; however Skylab 3 did, with two of the three crewmen demonstrating actual negative balances of pathological severity. We eagerly await the Skylab 4 data. If the balance shift is the better indicator of actual bone loss then four of the six crewmembers had pathological balances. The average shift, for example, in the three Skylab 3 crewmembers, exceeded 200 milligrams Ca/day. This is a really worrisome figure. With respect to bone loss, therefore, I feel we must conclude that it is at least, potentially serious, that it remains a problem, and that it shows little evidence of demonstrating that adaptability which has characterized so many of the other systems studied in the Skylab projects.

What Can Be Done About the Bone Loss? Recall that the relation between bone mass and stress was articulated many years ago and is known as Wolff's Law. Paraphrased, this law states that the mass and configuration of bone change in response to changes in external stress. Loss of bone, particularly in the legs, is an entirely normal adaptation

to reduced gravitational forces. Our rationale in attempting to suspend the operation of this law is that zero-g is not the ultimate environment for our astronauts and we want them to be able to function well once again in a one-g environment. I do not believe we would have the same concern if we were contemplating interstellar voyages at sublight speeds. It is the one-to-three year trips about which we worry.

Basically, therefore, we have - it seems to me - only four ways to go:

- ° We can select people who are sluggish responders to Wolff's Law, *i.e.*, who have a long time constant in their response to altered mechanical stresses. We don't now know how to look for such individuals, but Vogel's prediction term may be a start. I suspect that the urinary hydroxyproline component of his term is its most important and promising feature. Clinical analogs of slow responders are seen in human hypothyroidism and hypoparathyroidism. Incidentally, both hypothyroid and hypoparathyroid individuals would have high prediction terms.
- ° We can develop pharmacological or other treatments which effectively lengthen the time constant of response, *i.e.*, which convert astronauts into sluggish responders. Agents of possible utility include the diphosphonate compounds and fluoride, both of which, used preflight, show considerable promise of retarding in-flight bone loss. They may be useful in-flight as well, but premedication seems especially promising. We also need to look at a whole cluster of factors which, though not primary, may nevertheless frustrate our attempts to lengthen the time constant of bone remodeling response. There are a great many factors which are known to enhance any bone resorptive stimulus. These include such agencies as acidosis (even mild), high tissue oxygen tension, high bone blood flow, as well as the level of hormones such as thyroxin. (We heard yesterday of a tantalizing increase in free plasma thyroxin. We need to know what this means.) I think it is probably safe also to conclude that the diets consumed by the astronauts had a high acid ash content. You may have noted that the protein intake was at least twice the recommended adult dietary allowance. Whereas this is typical of the adult American male, there is some question about whether it is good for him under even one-g circumstances, and I suggest that there is both less justification for its use in zero-g, and even some reason to believe that it may be harmful.
- ° We can select individuals already adapted to something closer to zero-g. Here I refer to sedentary, skinny, small individuals. Perhaps someone more like Dr. Whedon or myself would be better suited than these wiry athletes. I have found myself asking,

repeatedly, these past three days, why there is this quite extraordinary emphasis on physical fitness for function in a weightless environment? Great muscular strength and endurance have obvious survival value in the jungle, are of problematic importance in a civilized environment (except as a means of burning our excess caloric intake), and are all but redundant in a zero-g environment, where it is the human nervous system and cybernetic flexibility which are of crucial importance. Pushing this suggestion even further, I think one must seriously consider selecting individuals who have already developed lower extremity disease osteoporosis, whose legs are already - as in space - nearly useless appendages. I refer to individuals who have a variety of lower extremity paralyses.

- ° Finally, and I suggest this quite seriously, I think sober consideration should be given to selection of amputees. The legs are the major source of our concern about bone loss. At very least, they deadhead with us on these missions. We have seen that they are nearly useless. Their tissue requires food and consumes oxygen, and if we exercise them, they consume even more. The ultimate fuel cost of legs on long missions must be really staggering. There are many double amputees around, and many of them must be veterans of our own wars. Instead of stigmatizing them as less than "whole men", I think we must seriously ask ourselves whether they do not have an important role to play in space.

There is one other theoretical option, namely the development and application of even more strenuous exercise and countermeasures than those employed to date. It is not known that these would work, but they might. I have neglected this option because its cost for long missions would appear to be prohibitive. Hardware weight would be the least of that cost. The food, oxygen, and waste management requirements, and the fuel necessary to orbit it all, would be uneconomical in the extreme. Sooner or later considerations of economy must emerge. When that happens, minimization of caloric intake and expenditure will be seen to be desirable. This may mean longer reconditioning back on Earth, but that is not a serious problem. Running the mile within three days of splashdown is nice, but it's almost certainly a luxury.

The final question is *where do we go from here?* Obviously, the answer is, "Back to space". But we need more answers, and happily the bed rest model appears able to provide them. I thus suggest a significant emphasis on bed rest studies, with particular attention paid to the development of effective pharmacologic countermeasures. I stress once again that, on long flights, the food and fuel costs of drug countermeasures are far less than the cost of maintaining physical conditioning.

Because of the long lag time between experimental design and results, very careful advance planning is vital so as to insure that we obtain the maximum useful information from a set of bedrest experiments. We badly need numbers in this game, and we will not get sufficient experience from actual space flights, particularly in view of the fact that the Space Shuttle Program, for at least the next several years, will be confined to flights of no more than 30 days duration. Ground-based experiments constitute our only reasonable hope. Luckily, as I have already said, bed rest has turned out to be better than we had any reason to hope.

Thank you.

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## ADAPTIVE NEUROBIOLOGY IN SPACE FLIGHT

### Introduction

A characteristic feature of this symposium has been a general re-orientation of research effort away from the earlier "acute" problems of conventional flight, towards longer-term problems of "chronic" adaptive change incurred by exposure of Man to long durations of maintained space flight. In the neurobiological sphere this trend is well exemplified by a change of focus from problems of acute disorientation due to sensory illusions in flight, to long-term adaptive changes in our neuromuscular systems due to prolonged exposure to the zero-gravity environment.

Naturally, faced with the pressing need to meet new goals in a current space flight program, immediate research objectives must necessarily be guided by severely practical objectives. Nevertheless, before discussing more applied aspects it may be helpful to touch upon a few currently emerging basic mechanisms which probably contribute to the adaptive capability of our nervous system.

### Sensory-Motor Interactions

There is good evidence that much of our normal motor control is organised not merely as an on-going interaction between continuously operating automatic Sherringtonian reflexes, but rather as centrally released preformed packages of programmed neural information (1, 2). One might well guess that adaptation to new requirements could be relatively easily met by merely reprogramming relevant patterns of the outgoing central neural discharge. However, there is a growing body of research findings which indicates that even cortically released patterns of motor drive are not devoid of early interaction with corresponding sensory mechanisms. For example we now know that such a central discharge of motor drive is not only destined to activate muscles through relatively direct connections with spinal motoneurons, but also, through collateral branches of central fibers, to act directly upon SENSORY neural relay stations in spinal cord pathways. Thus the corticospinal (Pyramidal) motor tract, not only descends to spinal cord

networks generating motoneurone activity to drive skeletal muscles, but also sends many collateral branches to synapse directly on second order afferent neurones in the sensory gracile and cuneate nuclei of the dorsal columns of the cord. (1,3).

A clue to the functional implication of this rather surprising fact is perhaps to be found in somewhat analogous mechanisms operating in the periphery. For example it is now well established that in many circumstances both alpha and gamma motoneurons, innervating the main (extrafusil) and muscle spindle (intrafusil) fibers of a skeletal muscle, can be coactivated at the same time. It has been proposed that when the combined alpha-gamma program operates "according to plan", the muscle spindles contract (or relax) in just such a way as to null out any change in their sensory discharge caused by mechanical shortening of the main muscle (4). This rather neat arrangement would ensure that it all went well (*i.e.*, according to plan), then the central nervous system (CNS) would not be bothered with unnecessary sensory information. By contrast, if the "intended" response was *not* achieved, then needed sensory information would indeed reach the CNS which, in turn, would presumably modify the next motor command.

What do we know of the ways in which such modification could be brought about? One such mechanism might well be associated with the recently postulated concept of "Cortical Servo-Assistance" in skeletal muscle control (4). Briefly, there is growing evidence pointing to the probability that many muscular and other related afferent neural discharge from peripheral sensors bypass the sensory cortex of the cerebrum and project more or less directly to associated areas in the cerebral MOTOR cortex. These in turn relay suitably time (5) motor signals to relevant muscle groups (6) in a highly localized quasi-reflex manner. However, passing through cortical levels in the CNS, presumably responses of this nature could be subject to conscious, or even subconscious, modification (7) in such a way as to reestablished an acceptable match between corresponding motor and sensory signals associated with a given action.

Similar properties may apply to other sensory-motor systems. For example it has been proposed on the basis of neurophysiological experimentation that the vestibular primary afferent neural response to an INTENDED head movement may tend to be nulled out by a suitable outgoing efferent discharge to the end organ (8). In this case involuntary vestibular stabilizing reflexes in the neck and/or body muscles would only arise when unintended or perturbing head movements occurred. Again, the normal exercise of voluntary control would include the generation of an appropriate combination of neural signals to both the relevant motoneurons and the associated sensory systems. Mismatch between these

two informational neuronal systems due to changes in the environment would then bring about appropriate changes in their relationship so as to reestablish acceptable conformity in the new environment.

At a lower, more automative, level in the CNS, other mechanisms have recently come to light in a series of experiments specifically designed to investigate habituated adaptation in the adult human brain (9). During normal head movements, autostabilization of the eyes relative to space is brought about by two complementary physiological processes namely, visual tracking and the vestibulo-ocular reflex. By the simple process of optically *reversing* the "seen" visual field, these two processes are forced into direct opposition: during head rotation to the right visual tracking then supplies a *right-going* oculomotor drive, whilst the vestibulo-ocular reflex continues to supply what is now an opposing left-going drive. Obviously, the residual vestibular drive then disturbs, rather than aids, visual fixation during head movement. The question now arises whether or not central habituated adaptation can reorganize the available sensory-motor mechanisms to restore complementary interactions serving the common goal of image stabilization on the retina during head movement.

Remarkably, through a rather complex sequence of detailed changes, radical reorganization of the vestibulo-ocular reflex occurs such that after about 10 to 14 days of continued vision-reversal, the adult human vestibulo-ocular reflex becomes effectively reversed, thus once again serving a complementary function with visual tracking (10). Recent and current findings in this field from several different laboratories point strongly to cerebellar involvement in these autoadaptive changes (11,12,13). Although in this case cerebellar involvement may be hard to equate with the cortical servo-assistance mechanisms outlined above, yet a common factor remains in the outcome of these latter experiments. Peripheral sensory retinal signals generated specifically by undesirable (*i.e.*, blurring) movement of the image on the retina tend eventually to be nulled out by consequent readjustment (*i.e.*, reversal in this case) of the automative vestibular drive to the extraocular muscles which control eye movement.

#### Astronaut Adaptation

Turning to the astronaut's problem of sensory-motor adaptation to the space environment, one may guess that on setting out to make a movement in his normal earthbound environment he formulates a motor program, as a result of which the EXPECTATION is:

- ° a particular magnitude, direction and speed of limb and/or body movement, and
- ° an anticipated set of afferent sensory signals which would be generated had that movement been successfully achieved as planned.

In zero-gravity space environment, not only is the actual movement for a given neuromuscular program going to be changed, but so also is the compatibility of the evoked sensory response, since the pattern of the sensory message itself will also be modified by absence of the gravitational acceleration vector, even had the movement occurred as intended. Presumably the CNS is then forced to work through a series of successive organization readjustments which might in their simplest form be conceived somewhat along the following lines: first there would be a mandatory call for changed associations between patterns of intended motor command and the actual patterns of efferent, or outgoing, neural discharge generated by that command. Then there would be a logical need for compatible readjustment in the meaningful interpretation of informational content in the resulting patterns of evoked sensory discharge. In turn there would presumably have to be habituating, or goal-directed, modification of requisite automotiv "reflex" responses (*e.g.*, ocular stabilization) to those changed patterns of sensory discharge.

Seen from this viewpoint it is little wonder that on entering the space environment an astronaut is faced with a more or less traumatic experience of habituating adaptation. Indeed in this symposium such adaptation has been shown to carry a significant practical penalty sometimes manifest as a temporary reduction in acceptable work load, and even on several occasions overt "habituation" sickness, together with potentially serious accessory penalties of endogenous malaise with its subtle changes in motivation and the loss of appetite familiarly associated with ordinary "motion sickness".

Fortunately, after 7 to 10 days all Skylab personnel appear to have adapted well to the new environment, even to the point of becoming remarkably agile in the organization and management of their daily movements through the Skylab interior. Nevertheless, this very fact necessarily implies that some form of readaptation must occur on return to Earth.

Important questions then arise concerning the rate and nature of readaptation to the normal Earth environment. Certainly, immediately after return both postural equilibrium and locomotion are seriously impaired. At first it was felt that return to near normal was only a matter of a day or so. But quantitative tests of postural balance control showed that readaptation probably occurs along a similar time course to the initial adaptation after entering orbit, namely 7 to 10 days. It could be argued that the measured difficulty of balance was merely a manifestation of diminished strength in the leg muscles. However, although disuse atrophy of leg muscles was shown to occur, this could hardly have been the only source of disequilibrium, since with *eyes open* normal balance tended to be restored very quickly; it was only with eyes shut that prolonged postural inadequacy was revealed.

Numerous other observations, such as dizziness on shaking the head, occasional misjudgements of footing, difficulty in walking round corners *et cetera*, collectively seem to indicate that the CNS does not simply "click back" to its remembered regimen before takeoff. Rather the evidence, both objective and subjective, points to a progressive re-organization in the nervous system which has to "unravel" the adaptive changes incurred in space, probably by means of habituation mechanisms akin to those responsible for the original space adaptation. In the present author's view this conclusion is strongly supported by the very striking findings of Dr. Ashton Graybiel and his colleagues from the Human Vestibular Function tests of experiment M131. Controlled head movements performed on the earthbound rotating chair produces a characteristic onset of motion sickness even with eyes shut. This could be attributable to sensory conflict between the thoroughly misleading semicircular canal signals which then arise and other more normal non-visual sensory inputs such as activation of the vestibular otolith organs by the gravity vector and/or proprioception from the neck.

Of very great interest is the finding that on performing similar head movements with eyes shut during rotation on the orbiting Skylab turntable, subjects were essentially free of the expected signs and symptoms of motion sickness. Since the essential difference between the two conditions is absence of a fixed gravity vector in space, it could be argued from the above finding that the earthbound phenomenon with eyes shut is due specifically to internal conflict between canal and otolith components in the vestibular system, rather than other sensory sources such as neck proprioception.

From the data presented in this symposium an even more striking observation seems to have been temporary retention of immunity to head movements with eyes shut, performed on the turntable after return to Earth. Dr. Graybiel has cautiously reserved judgement on this apparent finding on account of changes in his planned schedules of tests imposed by such imperative factors as changed preflight schedules of the astronauts. Nonetheless, the evidence is sufficiently strong to persuade the present writer that the postflight immunity mentioned above will eventually prove to be real. In that case there would appear to be two alternative conclusions:

- the space environment generally reduced susceptibility to motion sickness, or
- central adaptive changes of the kind discussed above left the CNS temporarily unresponsive to otolith stimulation by the steady "g" vector.

The fact that some astronauts were made seasick shortly after splash-down into moderately rough sea would seem to contravene the first conclusion, leaving one with the view that the time course of return of normal motion sickness on the turntable represents some index of genuine habituated readaptation; in this case perhaps reacquisition of a meaningful sensory perception of the gravity vector through the otolith-mediated afferent neural signals.

The reader could reasonably detect an inconsistency in this argument, on the grounds that seasickness after splashdown would probably be attributable to periodic stimulation of the otolith organ (14). However, in this context, it is important to appreciate that *changing* linear accelerative stimulation of the otolith organ must continue to be experienced during head and body movements in the orbiting Skylab; but the *constant* gravitational field is nevertheless consistently absent in space. Perhaps in the context of these combined observations we may be seeing additional evidence in favour of an earlier suggestion of Mayne (15) that otolith neural responses to changing accelerations and the steady acceleration of gravity may be informationally separated by "high-pass and "low-pass" filtering respectively in the CNS; as indeed is the case in some forms of man-made inertial guidance. In this case it would be easy to reinforce the earlier conclusion (*i.e.*, CNS temporarily unresponsive to otolith stimulation by the steady "g"-vector) that one form of adaptive change in space would amount to a "learned" ability to disregard the presence of those neural signals carrying information about a constant "g" vector. Such a conclusion would not be out of line with the observed difficulties of postural control after return to Earth, recovery from which would appear to run an almost parallel time course with the return of normal motion sickness induction during eyes-closed head movements on the turntable.

Of course these views on basic mechanisms must be treated as highly speculative. Still, without speculation there would be little chance of progress in subsequent experimental designs having more applied objectives.

### Applied Considerations

Bearing in mind the relative imminence of Space Shuttle we should perhaps consider first any relevant implications to that program from this symposium. In the context of the present article a prime question must surely be: Could adaptive phenomena of the kind discussed above prejudice "fly-home" of a Space-adapted Shuttle pilot? Of course it may well turn out that continued maintenance of a high standard of training in the use of instrument aids will suffice to offset any unexpected disorienting factors; as indeed has proved to be true in most circumstances encountered in conventional instrument flight. However,

although one may hope for this we have to face the fact that for reasons discussed above it seems that Skylab adaptation was uniformly associated with a new form of more or less profound reorganization of the body's orienting mechanisms. It would therefore seem negligent to disregard the problem. Unfortunately the paucity of intervening space flights leaves little opportunity for full interrogation of this question. Nevertheless the very serious consequences of an adverse outcome encourages the urgent design and development of a suitable battery of experimental tests for inclusion in the forthcoming Apollo-Soyuz mission, despite the potentially limited space-adaptation offered by its short duration and relatively small internal volume of the combined vehicle. Indeed perhaps the practical urgency of the matter warrants the additional inclusion of a "try and see" approach in which the returning Apollo astronaut is immediately exposed to dual-control real instrument flight in a familiar high-performance aircraft.

A second feature bearing directly on the Shuttle program is the protracted period of space sickness malaise and loss of appetite encountered by a sizeable proportion of Skylab astronauts. Bearing in mind the short duration of the average Shuttle mission, it seems inevitable that effectively novice personnel engaged in research or other activities will be penalised by reduced work potential unless some form of successful preconditioning regimen is discovered. The difficulty of doing so has been highlighted in this Skylab symposium by the notable lack of correlation between space sickness and both personal motion sickness histories and immediately preflight habituation measures. Even pharmacological therapeutic measures did not always suffice. Consequently there would seem to be an urgent need to search for effective means both of selecting suitable personnel and for their preconditioning and/or therapeutic treatment.

#### Preconditioning

Presumably the major source of space sickness must be directly related to the sudden absence of gravity, with the somewhat uncertain implication that changed patterns of vestibular otolith stimulation may offer the most likely source of disturbing afferent signals concerned with generating space sickness. It is true that other afferent sources such as kinaesthesia and muscle proprioception will also be affected by zero-"g". But such evidence as has been discussed above in connection with experiment M-131 does not encourage the view that these alone can provoke space sickness. Furthermore the habituation associated with readjustment of motor-eye coordination due to simple angular displacement of the visual scene is not apparently associated with vegetative symptoms of "motion sickness" (16).

Perhaps a fruitful approach might be to explore the possibility of employing strictly linear oscillatory stimuli in a low frequency range known to be highly provocative of motion sickness (14, 17). Probably motion should be constrained in the vertical direction to avoid directional changes in the resultant acceleration due to vectorial summation with gravity.

A further point to bear in mind is the potential need for prehabilitation to a high gravity environment after long periods in space, as for example when landing on Mars. It would seem advisable in any case to search for means by which an astronaut in space might not only maintain his leg muscle mass, but also exercise his postural equilibrium systems. One might for example envisage bodily control, perhaps even through the legs and feet, of a suitably unstable mechanical device simulating the normally standing man.

### Otolith Dynamics

On a long-term basis, it would seem important to learn more about the basic dynamic response characteristics of the vestibular otolith organs. After many years of research, corresponding response characteristics of the semicircular canals have become well understood and this knowledge permits accurate prediction of boundaries encompassing movement profiles beyond which they feed misleading information to the brain (18). However, much less is known about the mechanical and neural dynamic response of the otolith organs (19,20,21) and there is an obvious need to make good this deficiency by insightful combinations of human and neurophysiological animal experimentation.

### Habituation

Although some of the adaptive phenomena referred to as habituation have been extensively studied (22,23,24) the nature of the processes involved are yet far from understood. For example it has been customary in the past to consider the habituation process as essentially an attenuating one, whereby repetitive stimuli progressively cause less effect in the CNS. However, it is now clear that this is too simple a concept. For example in animal experiments it has been shown that after unilateral labyrinthectomy the spontaneous activity of ipsilateral second order vestibular neurones falls drastically, probably causing the resulting persistent ocular nystagmus. But as the animal adapts (habituates) to the point of relatively normal behaviour (no spontaneous nystagmus), so the spontaneous activity of those neurones rises again to normal. The functional advantage of this is that they can then be adequately driven by inhibitory commissural connections from the normal, contralateral, vestibular system (25). Again, we have already seen that

optical reversal of vision in the adult human subject leads progressively to active reversal of the involuntary vestibulo-ocular reflex, rather than its mere passive attenuation to zero gain (9, 10). It now appears from a number of difficult sources that not only can visual afferent signals from the retina influence vestibular afferent activity in both excitatory and inhibitory ways (11,12,26,27) but furthermore vestibular afferents can similarly modify the activity of visually evoked responses in the tectum of the mid-brain. Evidently there are multitudinous ways in which intersensory, and sensory-motor interactions can bring about change in the adult central nervous system. One must presume that eventually the rational use of these powerful adaptive facilities for our own ends must depend upon basic knowledge of their mechanisms and functional capabilities. In particular, it would seem important to learn how to define the physiological goals towards which one may wish the habituating change to be driven, since as already emphasized it appears that the habituation mechanism characteristically acts in the manner of a goal-seeking process (9).

### Postural Equilibrium

A clear-cut feature of return to Earth is the transient postural disequilibrium already discussed in other contexts above. Thus the combined outcome of experiment M-131 and the "rail" tests of postural equilibrium suggest to this author that more profound adaptive changes are at play than mere deconditioning of postural muscles. However, the detailed nature of such change is by no means clear and since the matter has both basic and applied implications further experimental investigation would seem to be called for.

First, with the background supplied by M-131, advisably carried out in Skylab without vision, it would be of great interest to employ the same methodology to further explore the role of vision. Even in space, the cross-coupling canal "errors" introduced by head movement in the rotating chair would presumably drive the oculomotor system according to those "erroneous" canal signal. Consequently with eyes open the retinal image of the workshop interior would then be destabilized, very much as on Earth. Would the added sensory conflict from vision restore the otherwise absence of motion sickness?

Next, one could envisage development of the postural equilibrium test, using a servo controlled "postural" platform to make quantitative assessment of both normal static control of equilibrium and the postural response to unexpected perturbations. Furthermore, following the example developed in Dr. L. R. Young's Man-Vehicle Laboratory, M.I.T., it should be possible to extend the use of such a system to interrogate the component part played by changes of proprioceptive muscle feedback in the post-return postural disequilibrium (28).

Indeed the versatility of this general approach has been further developed, using galvanic stimuli to generate artificial vestibular stimulation. Thus a particular galvanic stimulus causes a sensation of head yawing, say, to the left, due presumably to preferential stimulation of the horizontal semicircular canals. Moving the head onto the left shoulder carries this sensation with it, so that the subject now feels he is "tilting" forwards. A quickly acting backward tilting reflex response can then be demonstrated in postural muscles acting on the ankle joint. If the head is then moved onto the right shoulder, the *same* electrical stimulus to the vestibular system generates a *sensation* of tilting backwards, because the planes of the relevant canals have then been turned through 180 degrees. The corresponding reflex response in the limb muscles is then appropriately *reversed*, despite the *unchanged* nature of the peripheral vestibular stimulus (29). Evidently in the Earth-adapted subject, vestibulospinal responses are automatically adjusted for maintenance of postural equilibrium according to the instantaneous attitude of the head (*i.e.*, the vestibular system) relative to the body. Would this versatile flexibility of basic vestibulospinal postural reflexes disappear in the space-adapted subject? And if so what time course would be taken by their reappearance during readaptation on Earth?

#### Concluding Remarks

The extensive Life Sciences program in Skylab has revealed that the zero-gravity environment of space induces a wide range of adaptive changes extending throughout the biological systems of the body. The detailed physiology behind some of these changes has been clearly defined for the first time by experiments described in this symposium. Other ingenious experiments have demonstrated adaptive changes which raise more questions than they answer, leading to a continuing challenge for further research.

However, taking an overview of the program as a whole, two outstanding features have emerged. First, Man can adapt to, and live in, the zero-gravity space environment for extended periods of time. But second, and therefore above all, none of the measured changes so far seen in missions extending up to 84 days have proved irreversible after return to Earth.

Nevertheless, these two salient and rewarding conclusions leave no room for complacency since this symposium has raised a wide range of new and varied problems needing urgent solutions. If the high quality of research reported during these past three days has anything to say for the future, we may indeed hope that these new problems will be tackled with equal energy and imagination.

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