HUMAN ECOLOGY IN SPACE FLIGHT

Proceedings of the First International Interdisciplinary Conference

Edited by

DORIS HOWES CALLOWAY

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PREFACE

This book presents a report of the proceedings of the first conference on the general subject of "Minimum Ecological Systems for Man in Space" (retitled "Human Ecology in Space Flight"). These conferences were initiated by Dr. Orr E. Reynolds and Dr. Frank Fremont-Smith, who selected the Chairman and obtained the necessary financial support from the National Aeronautics and Space Agency. The plan was begun actually before Dr. Reynolds had any official connections with NASA.

The initiators of the plan, together with the Chairman, organized the First Conference and selected permanent participants who form a Planning Committee. The First Conference turned out to be very broad in scope and serves as a sort of exploration of the field. The Committee helped in the selection of much more specific topics for the later conferences. The subject of the Second Conference was concerned with physiological results of prolonged inactivity, with special reference to calcium balance. The Third Conference scheduled for October, 1965, will discuss the problems of food and drink for man in space flights. With these more specific topics, it becomes possible to bring in more experts who can discuss the subject much more exhaustively than was possible in the meeting reported in this volume.

Since this plan was initiated there have been many symposia on the manifold problems of space flight, but probably not one of them has had quite the same characteristics as the informal gatherings so frequently arranged by Dr. Fremont-Smith, who refuses to allow the presentation of formal lectures, and insists on nothing but open discussion with frequent interruptions. The hope is that this method will provide a better exchange of ideas, and will extract more information from the multidisciplinary group as a whole. Spontaneous reactions often divert minds into new channels and thus generate new and fruitful ideas; and in the progress of science, there is nothing more rare and harder to obtain than a really new idea.

Because of this policy, which was followed rather rigorously during the three days of this Conference, the reader must not expect to find in these pages an orderly text-book presentation of the subject, such as those in several recent books in this field. Discussion leaders were instructed to present only enough material to ensure that all the important aspects of the subject were brought up for discussion. However orderly the subject may have been in the speaker's mind, he was interrupted so frequently that the final result, much to his dismay,

probably bore little relation to his well-laid plans. All of the discussion was faithfully transcribed, and was then corrected by the participants. The revised transcript was then carefully, expertly and, we hope, drastically edited by Dr. Doris Calloway, in order to make the published record as orderly and comprehensible as possible.

Many of the participants feared that the discussion contained so little that was new that it did not really deserve publication. The discussion, however, was useful to the participants, and it is likely that it will be useful to others in unexpected ways. Publication certainly avoids the charge that the Conference had limited usefulness because it could not reach a larger audience. It is published, therefore, for what it is worth, as a record of the spontaneous reactions of a group of competent experts to a series of questions and problems related to man in space. It is the earnest hope that the reader will find here some idea that will "click" in his mind, and lead him to take some steps to advance our understanding of the subject. It is our earnest hope that there may be enough "clicks" of this sort to make the whole enterprise worth the time, money, and effort expended upon it.

Although it is manifestly impossible to measure the success of a conference or a book of this type, most of the participants returned home feeling that the time had been well spent. Much of its success depended upon the careful organization of the mechanics of the meeting by Dr. Fremont-Smith, Mrs. Elizabeth Purcell and their assistants. It is a pleasure to express to them the gratitude of the participants.

W. O. FENN
Conference Chairman

INTRODUCTION

Ever growing numbers of scientists today are rapidly extending the frontiers of knowledge. From outposts of research, streams of new information are pouring into already overloaded channels of communication. New methods of investigation lead to increasing specialization and to esoteric vocabularies difficult to understand outside the specialty of their origin.

Yet many of the crucial problems in medicine and biology require for their solution a multidiscipline orientation and often multiprofessional teamwork. Thus, in the search for the cause, treatment or prevention of disease, or in the effort to achieve a "breakthrough" in such basic fields as genetics, homeostasis, or growth and development, the research scientist may find the needed clue unexpectedly in a new advance in one of the branches of biology or medicine, or in a new method derived from bioengineering or computer research, provided only that he has the breadth of knowledge to grasp its significance.

The Interdisciplinary Communications Program was organized to counteract the narrowing effect of excessive specialization and to make available systematic opportunities for cross-discipline communication by means of informal group discussion.

These conferences are organized to facilitate the advance of science. Within this broad frame of reference they have several interrelated purposes. A major one is to provide an opportunity for communication within a group of scientists who, while belonging to different disciplines, share a common field of interest. A second goal is to provide an opportunity to thresh out and discuss in depth, problems that arise out of difficulties of communication and, thus, to narrow and specify the areas of disagreement. A further goal is the development of lasting friendships and cooperative efforts among the participants.

I should like to state here my basic assumption that nature is all of one piece and that the branches of science are branches of *one science* and not separate sciences. Science is man's effort to understand the laws of nature. The different disciplines or university departments are fragments of science. These tend to be too isolated from one another. Usually they are built up around a method, technique, or a point of view. But each of these disciplines is only one window through which man looks at nature. Each window permits the passage of only certain rays of light and also, inevitably, has some distorting lenses. If one wants to see nature whole, one must look at it through many windows. This is why there is a great need for multi-disciplinary orientation for

the optimum advancement of science.

We are in a kind of information crisis. We are being overwhelmed by so much information, so many data, that we are inclined to limit ourselves to the study of those fragments that fall within our own narrow discipline. Important new developments in science have repeatedly come through a combined operation of several disciplines in exploring an area which had been previously neglected, an area lying between sharply specialized lines of previous advance. This conference is an effort to facilitate interdisciplinary communication in the field of Human Ecology in Space Flight.

We would like to express warm appreciation to Dr. Doris H. Calloway, Department of Nutritional Sciences, University of California, Berkeley, California, for undertaking the arduous task of Scientific Editor.

FRANK FREMONT-SMITH, *Director*
Interdisciplinary Communications Program
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CABIN ATMOSPHERE

Discussion leader:
ARTHUR DUBOIS
Department of Physiology and Pharmacology
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DUBOIS: The problem of gases in the capsule applies more to man than it would to some other biological systems, because man has lungs, and from the medical viewpoint if the lungs do not work very well, the brain will not work very well either. All the blood goes through the lungs to the brain; therefore, this morning, I am afraid, has some medical orientation.

I am supposed to list five or six factors which we might consider; for instance: (1) bends, (2) oxygen toxicity (at the cellular level), (2) atelectasis due to absorption of gas in the lungs, (4) the effects of acceleration on lungs—and here remember that there will be another session on acceleration later, (5) problems of instrument cooling and fire hazard. This has to do with heat conductivity and with the unusual conditions of burning in oxygen, and (6) the CO_2 level allowable in the capsule. At this point I would like some discussion. Perhaps we could deal with the first topic as a means of getting into the subject. The Russians use air at sea level in their space capsules. Consider the following question: Why do we not use air in our space capsules? We use oxygen at a third of an atmosphere. There is no nitrogen in it.

FREMONT-SMITH: No CO_2?

DUBOIS: There must be some Co_2. It is a rebreathing system, which means that no matter how fast you exchange the air to scrub out the CO_2, there is always going to be a little bit there, but it might be an upper limit of a fraction of a per cent of CO_2.

Carbon Dioxide Effects

FREMONT-SMITH: Does this kind of atmosphere provide for over-ventilation, or is pulmonary ventilation at about the usual minute volume in the capsule as you describe it? May I explain why I asked this question? I did an experiment, many years ago, when I was measuring spinal fluid pressure in a patient who was breathing 10 per cent CO_2, 90 per cent oxygen, and of course over-ventilating strikingly as a result of the CO_2; the arterial pulsation in the column of spinal

fluid that I was measuring was so striking, so much larger than normal, that I thought to myself there must be a vasodilation taking place. Then it occurred to me to look at the retinal blood vessels, which are cerebral blood vessels. To my great surprise when I used the ophthalmoscope the patient's retinal veins were bright red, which indicated that the arterioles in the retina were dilated to the point that arterial blood was pouring into the veins; i.e., the rate of blood flow through the retinal capillaries was greatly increased.[1]

Then I remembered that earlier experiments, carried out by Wolff and Lennox,[2] had shown that this was also true in animals. If you have a high CO_2 in the inspired air you get a very marked vasodilation of the arterioles in the brains of monkeys, cats and other animals, and the obverse is true—that is, if you overventilate an animal you get a vasoconstriction, and you get a more marked vasoconstriction of the cerebral blood vessels from diminished CO_2 in the inspired air or over-ventilation than from almost any drug that one can use; and the most marked vasodilatation, which means the most marked increased rate of blood flow through the brain, takes place with a higher level of CO_2 in the inspired air.

From that point on, I have been very much interested in something which tends, in my judgement, to have been neglected in the high altitude flying, and that is that perhaps you must provide enough CO_2 so that you not only have oxygen saturation of the arterial blood, but also are delivering this blood at an appropriate rate through the brain.

Every doctor knows that when he says to a patient, "Take a deep breath," while he is listening to the chest, with the patient sitting up, after fifteen deep breaths, one after the other, the patient is likely to keel over because of cerebral anoxia. The cerebral anoxia results from depletion of the CO_2 in the arterial blood from over-ventilation leading to cerebral vasoconstriction. So, this is the reason for my question concerning over-ventilation: If these people are over-ventilating in an atmosphere that has no CO_2, they are diminishing their cerebral capacity because they are diminishing delivery of oxygenated blood to the capillaries of the brain.

DUBOIS: It is a very relevant question and worth pursuing.

HELVEY: For my own clarification—considering the low CO_2 in the atmosphere, isn't the CO_2 produced by the body the primary trigger unless you hyperventilate?

FREMONT-SMITH: That is right, but if you hyperventilate you get rid of it.

HELVEY: In our studies with more than adequate oxygen, there was no hyperventilation.

FREMONT-SMITH: Breathing a high level of oxygen usually does produce hyperventilation.

RAHN: But this is only a slightly higher than normal oxygen pressure, even though it is 100 per cent, because of the lower total pressure.

FREMONT-SMITH: Yes, that is why I asked: Is there hyperventilation or not?

DUBOIS: Doctor Helvey, did you measure ventilation in your confinement studies?

HELVEY: Not minute volume. Of course, we measured respiration, and we measured the P_{CO_2} on a couple of occasions.

FREMONT-SMITH: The situation sometimes affects ventilation. The person's breathing, over-breathing, is under cortical control. That is, you can voluntarily increase your breathing, and you can increase it reflexly from outside nervous stimuli. Can you tell a little about the situation in which the arterial bloods were measured and how they came out?

HELVEY: The psychological environment?

FREMONT-SMITH: The total environment.

HELVEY: Briefly, we exposed groups of six young men in an altitude chamber to various pressures and levels of oxygen, including 100 per cent oxygen at five pounds per square inch (psi), approximately one-third atmospheric pressure. We had the men in there around the clock for a two week period, and arterial blood samples were taken on the fifth and last day.[3]

This was a new experience for them but they adapted rather readily. They were graduate students. Other than the idea of an arterial puncture, there was, I think, no particular anxiety after the initial experience.

The gaseous environment was controlled by pumping in oxygen but instead of recycling, we exhausted the gases out of the chamber so there was a constant flow through the chamber, which was the manner in which we controlled CO_2 and any other contaminants.

The chamber has two cylindrical rooms. It was not a study in constriction or confinement. One room was 18 feet long and it had a diameter of 13 feet and the other room was eight feet long, so they had reasonable room to walk around.

DUBOIS: Let's go back to CO_2 a minute, because there is a practical question as to whether the CO_2 should be allowed to increase to a perceptible level in the capsule—perhaps one-half per cent or one per cent. The basic advantage would be that it would cause some cerebral vasodilatation and, therefore, perhaps improve the state of consciousness of the person whose cerebral function was impaired because of acceleration effects or desaturation of the arterial blood from shunting through collapsed parts of lungs.

FREMONT-SMITH: It might be impaired by over-ventilation and if they are made a little anxious by the situation, they are very likely to over-ventilate.

DUBOIS: Yes. This is thought to be a practical problem in fighter pilots at low altitude level. Some of them have lost consciousness and it has been proposed that perhaps it is due to over-breathing.

BJURSTEDT: The question of the relationship of CO_2 and pulmonary ventilation during acceleration is quite interesting. We are coming back to that in another session, but I would like to mention that we have measured the CO_2 tension during headward acceleration, and although there may be a tremendous amount of hyperventilation, the arterial CO_2 level may remain almost constant.

RAHN: How can you have hyperventilation and have the P_{CO_2} stay constant?

BJURSTEDT: This must, of course, be due to pulmonary shunting of blood and perhaps some other mechanisms, but the arterial CO_2 tension and pH really showed only insignificant changes.

RAHN: I would like to know what Doctor Wood has to say about that. Have you measured this?

WOOD: We have not measured P_{CO_2} in arterial blood - just oxygen saturation, which decreases because of shunting. It is true that hyperventilation occurs both in normal men and anesthetized dogs during exposures to transverse acceleration.[4,5] It is possible, however, that a combination of over-ventilated superior and under-ventilated dependent alveoli could occur during acceleration which would cause no change in the P_{CO_2} of mixed arterial blood.

ODUM: May I interject? Looking to the future and a self-contained ecological system, CO_2 will be needed by plants, so there won't be excess CO_2, if we can devise a true self-contained system in the very distant future. Is that not right?

DUBOIS: There is always going to be CO_2. It is a question of at what level you are going to stabilize. The reason there will always be CO_2 is because if we have a man in a box, or a capsule, he is producing CO_2 at a certain rate, perhaps 200 or 300 cubic centimeters a minute; and let's say we have a fan that mixes this evenly throughout the box, the CO_2 is at a certain level. Attached to this there is a system with a CO_2 absorber and a fan that draws the air to the absorber. The level which is finally reached in the box will depend on how fast our man is putting CO_2 out and on the rate of removal, and this will stabilize. We have this simple equation: The amount equals the concentration times the volume. The amount he is putting out equals the concentration in the box times the volume of ventilation.

If you scrub out a rate of, say, 12 liters a minute, if a man is breathing six liters a minute, if the CO_2 he is breathing out from the alveoli is six per cent, and if you then ventilate this system and scrub out from the six liters a minute of air all the CO_2, then you will stabilize at say three per cent, from this equation.

If you stabilize at three per cent, something will happen. The man will increase his breathing because CO_2 at three per cent stimulates the breathing. He will breathe, say, 12 liters a minute. If he breathes 12 liters a minute, and if you were to scrub out at the rate of 12 liters a minute, you would then restabilize at 1.5 per cent CO_2.

You would have to scrub out at an infinite ventilation of the capsule to keep the man's ventilation normal, which means you would have to have a big pump and a low resistant bara-lime system if you were to keep the level of CO_2 in the chamber approaching zero.

Now let's suppose that you allowed the CO_2 concentration to drift up to 1.5 per cent in the chamber in order to save your blower and have a smaller cannister of bara-lime or sida lime, what would the effects of CO_2 be on this man over a two-week period?

BROWN: We have quite a bit of field data in submarines on just this sort of thing. The atomic submarines have a CO_2 removal system which takes essentially all the CO_2 out when it is operating optimally, but the size of the crew compartments and the number of crew members is such that when the whole thing stabilizes it comes out very close to one per cent.

The only way to improve this and to lower the CO_2 content would be to have fewer crew members, which is technically impossible, or completely to change the scrubber. In World War II, one per cent frequently was not achievable for long periods of time, and sometimes the concentration went to astonishingly high levels. The tolerances that were put on this from the medical standpoint were then much higher than today and as technology improved, the specs gradually went down, and now by a remarkable coincidence one per cent is considered safe. One per cent is all that is achievable.

DUBOIS: I believe that perhaps there was more done on this in World War I than in World War II, because in World War I the methods of removal were more primitive, and there were some submarine medical officers who were interested in this at that time.[6] Again, they came up with figures of one per cent to 1.5 per cent, as being a reasonably tolerable limit, and three per cent as being as much as you would care to put up with for any short number of days.

ROTH: Karl Ernst Schaefer at the New London sub base has been interested in this problem for a number of years. In the fifties this group did a study called Operation Hideout in which they had a number of people in a submarine at dockside and went through some of these points, trying to determine whether there was a biochemical adaptation going on at the 1.5 per cent CO_2 level. The study lasted about 40 days. There was no disturbance in any of the psychological tests that Schaefer performed. There was, of course, a biochemical adaptation in that there were shifts in serum calcium and *p*H over

time. These stabilized at an equilibrium point somewhat different from normal, but there was no gross performance difficulty associated with the shift, so Schaefer likes to set 1.5 per cent as the level at which you do not get performance changes, but do get changes in equilibrium.[7]

FREMONT-SMITH: What I don't think we know is whether there is an adaptation of the cerebral blood vessels to a prolonged increased percentage of CO_2; whether they stay dilated or whether they come back after a certain length of time to a normal degree of vasoconstriction in spite of the CO_2 concentration would make a difference. As far as I remember, Schaefer didn't pay any attention to cerebral blood flow.

ROTH: No, I am sure he didn't. He gives one-half per cent as the level where there are no obvious biochemical changes. Below a half per cent, he found no changes in the blood value.

BJURSTEDT: Isn't there a CO_2 level in the inhaled gas above which you get vasodilatation, but below which you don't get any effect at all? I believe I read an article in the *Journal of Clinical Investigation*[8] some years ago stating that there is no effect below 3.5 per cent of CO_2.

FREMONT-SMITH: In the earlier work in animals that was done in Stanley Cobb's laboratory by Wolf and Forbes, it seemed to me there was a continuum. The animal was overventilated by artificial respiration, and a very sharp vasoconstriction resulted. The level of vasodilatation was a function, or largely a function, of the percentage of CO_2 in the alveolar air. But that was under anaesthesia and that may make a difference.

DUBOIS: To go back to this report of Doctor Schaefer, he indicated that at the end of the 42 days, there was a large alveolar-arterial CO_2 difference in the subjects; that is, that the alveolar CO_2 measured in millimeters of mercury, was lower than the tension in arterial blood, whereas in the control samples, values were equal, roughly. When you get such a large alveolar-arterial difference, it can mean serious impairment of certain functions in the lung, and so we can't ignore it.

FENN: Schaefer didn't record arterial CO_2 tension continuously.

SCHWARTZ: May I ask a completely uneducated question? Where does carbonic anhydrase or the enzymatic system fit into the total body balance? Your equation only takes into account the CO_2 that comes out in respired air, but CO_2 can go to carbonate, be handled in other ways. Is this a significant factor in CO_2 balances?

DUBOIS: In this equation we were considering the man in a black box that was part of a closed system, so the equation governing the concentration of CO_2 in the air around him in terms of his CO_2 output

and the rate of removal from the system is independent of mechanisms going on in the body.

If you get to the body itself, the equilibrium between CO_2 in the arterial blood and in the alveolar air depends upon the blood coming to equilibrium as it passes through the capillary, and that reaction, without carbonic anhydrase, would require roughly two minutes to go to 90 per cent completion, whereas the time spent in the capillary is approximately one second.

FREMONT-SMITH: This is capillaries of the lung?

DUBOIS: Lung capillaries. So, to have the reaction go to equilibrium between the arterial blood and the alveolar air, you must have this enzyme present in high concentration. If the enzyme is inhibited you can have a situation in which the arterial CO_2 tension comes to equilibrium in the plasma going through the lung; the partial pressure at the end of the capillary is equal, but not in equilibrium with that in the red cell where the carbonic anhydrase acts, because most of the buffers are inside the red cell.

FREMONT-SMITH: And does this mean that the CO_2 comes off the hemoglobin after it has passed through the capillaries, and that the hemoglobin then doesn't get its oxygen content because it has already left the capillaries where the oxygen might be available to it?

DUBOIS: The CO_2 in the hemoglobin will impair the uptake of oxygen due to the Bohr effect to some extent, and I believe that is what you are referring to. Doctor Margaria could comment on this. As I remember, the Bohr effect accounts for about a third of the oxygen uptake by the hemoglobin, so if you were to impair the Bohr effect, you could impair the oxygen transport mechanism slightly.

MARGARIA: Those are two different mechanisms. One is the combination of CO_2 with hemoglobin and this is a very fast process, but I thought we were speaking of the delay in hydration of CO_2 that takes place in the corpuscles after they have left the capillaries, and this is a process that may go pretty fast. I don't think that it takes a long time—there cannot be a great delay in the hydration of CO_2 in the blood corpuscles. The concentration of carbonic anhydrase in the blood corpuscles is very high and I believe there is a great excess.

DUBOIS: Yes, under normal conditions you wouldn't expect any of these difficulties to occur, but there are certain drugs that will inhibit carbonic anhydrase.

MARGARIA: Yes, and in that case you may see a very large effect by supplying "Diamox."

DUBOIS: Yes, this started partly through the use of the sulfonamides, which were found to inhibit carbonic anhydrase; the strongest of this group is acetazolamide, which has the trade name "Diamox"

and is used clinically for this purpose. This will cause an A-a CO_2 difference.

MARGARIA: There is another thing about CO_2 concentration in the inspired air: I get the impression that the increased circulation takes place only at very high CO_2 concentration; if you increase the CO_2 in the inspired air only one or two per cent, the effect of the increase of CO_2 is very low because of the compensation due to hyperventilation. It takes at least four or five per cent CO_2 in inspired air to increase effectively the washing out of nitrogen, as experiments demonstrating the effectiveness of CO_2 in relieving the bends during decompression show.[9]

FREMONT-SMITH: But this doesn't tell us what is happening to the rate of blood flow through the brain, does it? In the animal experiments, even a small increase of CO_2, if I remember correctly, increases the vasodilatation of the arterioles. It seems to me this is the crucial thing. The point that I am trying to make is that if there is hyperventilation which washes out CO_2, so that you get a low CO_2 content, then you get vasoconstriction and this is the deleterious thing that I think has perhaps to be watched for.

If there are experiments to show that you can get a certain degree of hyperventilation without any vasoconstriction in the brain, then we are relieved of any anxiety on this score, but it seems to me this is the question that has to be settled in any human-capsule situation. If we have a hyperventilation, is it lowering the rate of blood flow, the delivery of arterial blood to the key centers of the brain, the cortical centers, and if it does, is this deleterious? Maybe you answered this question and perhaps I misunderstood you.

MARGARIA: If we have hyperventilation, what we are interested in finding out is what the P_{CO_2} is of the arterial blood. Does this hyperventilation decrease the P_{CO_2}, or does it just keep the P_{CO_2} at the normal level?

FREMONT-SMITH: But the P_{CO_2} could be kept at a normal level as a result of a decreased blood flow, could it not? Really, the crucial question is, what is the blood flow through the brain, isn't it?

MARGARIA: Yes, but this is directly related to the P_{CO_2} in the blood, not to the hyperventilation, and I believe that the arterial P_{CO_2} keeps pretty constant unless the CO_2 in the inspired air is very high. Generally, when we make the experiments in animals we increase the CO_2 so as to increase very gently the P_{CO_2} in the arterial blood; in man an increase of one to two per cent CO_2 in the inspired air does not lead to an appreciable increase of the arterial P_{CO_2}. It seems that we give a lot of CO_2 to the men, but as a matter of fact, if we measure the arterial blood, we see that it has not increased appreciably.

FREMONT-SMITH: Maybe the absence of anesthesia in the man ex-

periment may make a difference. The animal experiments have usually been done under anesthesia, whereas humans don't need this.

MARGARIA: And in this case when we give two per cent CO_2 to the man and he over-ventilates so as to keep the CO_2 of the blood constant, we don't improve the condition of the man at all. On the contrary, we just make it worse because we force the subject to overbreathe, to maintain the same chemical conditions as before, so we are just stressing his respiratory center.

FREMONT-SMITH: If we go to the other level where he is over-ventilating without CO_2, and he is over-ventilating from either a high concentration of oxygen, anxiety, or cold, all of which lead to over-ventilation, then we may get a reduction of P_{CO_2}, may we not, in the arterial blood; and then you have a reduction in blood flow through the brain. It is this other side, the over-ventilation with loss of CO_2, that I refer to.

BJURSTEDT: There is probably a continuum in the responses of the cerebral vasculature to changes in the CO_2 level, but the effect might be very slight around the normal CO_2 value. Also the dynamic characteristics of these responses have to be taken into account: when you overventilate you might not get very much of an effect in the beginning, but when the CO_2 tension has fallen down to a very low level you get drastic vasoconstriction.

FREMONT-SMITH: It seems to me that this question should be clarified. We have methods but I don't know of any information that settles the question. I keep bringing it up for this reason. Is there an experiment that can be done?

GRAYBIEL: Is the critical measurement the oxygen uptake by the brain? You might have lots of variation in blood flow, let's say, and yet oxygen utilization would remain within normal range.

FREMONT-SMITH: Not if the blood stops, to carry it to an extreme.

DUBOIS: You can carry it still further and say that one of the critical levels is not only the rate of oxygen consumption by the brain, but also the question as to whether the brain put out lactic acid during certain periods, indicating an anaerobic metabolism.

This was used as a criterion last year. Investigators hyperventilated an animal as much as possible and took samples of blood leaving the brain, to see if there were increased lactic acid due to hypoxic metabolism in the presence of cerebral vasoconstriction, and no matter how much they hyperventilated the animal they were unable to find any increase in the lactic acid level.[10]

RAHN: I would like to look at the oxygen tension of the cerebral venous blood, rather than the CO_2. There must be a critical venous O_2 tension below which one will obtain certain changes in EEG pattern indicating anoxia and dysfunction of the brain cells.

DUBOIS: I think it is very good to define a particular mechanism affecting cerebral function, but there must be several things that affect cerebral function and some of them may be additive—such things as the P_{O_2} in the tissues, and also perhaps the *p*H in the tissues. Wouldn't these act in such a way that, if you got a disturbance of *p*H, you would become more sensitive to a disturbance of P_{O_2}?

RAHN: Very likely. I might reword my question. If I became dizzy after hyperventilation, would this be due directly to the changes in P_{CO_2}, or to the lowered venous P_{O_2} resulting from the vasoconstriction triggered by the CO_2 change?

DUBOIS: The cells in your brain want a certain environment. They want a transmembrane potential which depends on several things: on the amount of calcium ionization, on the potassium concentration, on oxygen tension and how much ATP there is, and other factors.

RAHN: I would pick the oxygen pressure as the important factor.

BROWN: What is the answer when you do the experiment? Hyperventilation is easy, but is the whole syndrome independent of the P_{O_2} at which you do it? I can't believe that it is.

RAHN: I don't know.

BROWN: It must have been done thousands of times.

ROTH: Both simultaneously changing, though.

BROWN: Yes, but experimentally, it is easy. You hyperventilate breathing air and breathing other oxygen tensions.

BJURSTEDT: The pure effects of a lowered tissue CO_2 level could be studied by hyperventilating the subject and regulating the tissue O_2 level by adding oxygen in the inhaled gas mixture as needed. However, I think your point is well taken. These two parameters should be controlled by measurements in the cerebral venous blood.

DUBOIS: There is another point at which they can be measured. This is done by Britton Chance[11,12]; he measures the reduction of the DPN to DPNH by a fluorometric method. By changing the inspired oxygen tension, you can get a certain percentage reduction of DPN to DPNH. He gets 50 per cent reduction, when the inspired oxygen is at a certain level which is around four per cent.

He gets complete apnea when the reduction is 90 per cent. The animal is so impaired in its function that it is unable even to breathe when the DPN is 90 per cent reduced, and this is another way of measuring, inside the cell, the effect of hypoxia in the inspired air on the metabolic processes in the cell.

FREMONT-SMITH: Anesthetized animals, presumably?

DUBOIS: The animal can be prepared and then the anesthesia allowed to wear off.

FREMONT-SMITH: I might also comment that the electroencepha-

logram is a rather rough measurement and a lot of cerebral fuction can be impaired, I think, without showing up on the electroencephalogram, at least in the ordinary measurements.

GRAYBIEL: It seems to me that it is an important thing to be able to understand thoroughly the mechanisms of the lightheadedness that you get from over-ventilation. It seems almost incredible that we can't here decide how it occurs.

DUBOIS: One of the issues is as follows: if hyperventilation decreases cerebral blood flow, the tissue oxygen tension (whatever that is) in the brain would diminish and, therefore, your cortical functions would diminish and you would feel lightheaded.

But there is this other proposition—that the CO_2 decrease itself would change the stability in the membranes of the brain cells and, therefore, that that might cause some impairment. Now we are unable at this point to decide which of the two issues is the more important. That is what you are saying.

ROTH: There is a good model for carbon dioxide requirements in heterotrophic bacteria. When you are trying to grow bacteria in an aerated culture medium, the culture will not grow unless you have a given level of CO_2 to prime the metabolic pump at the oxalacetate decarboxylase level.[13] Once the bacteria have started growing, however, enough endogenous carbon dioxide is produced so that you cannot limit growth by the absence of ambient carbon dioxide. The intracellular P_{CO_2} cannot drop to a point where this priming step in metabolism of CO_2 compounds is limiting. The bacterial model would suggest that intracellularly there is an optimum CO_2 level. This priming step is at the junction of the Krebs and Embden-Meyerhof cycles. This may a theoretical point where CO_2 might be critical in the energy metabolism.

FENN: This seems to say that CO_2 is more essential to life than oxygen.

BJURSTEDT: We have been talking about cerebral blood flow and brain function. It is a pity we don't have a psychologist here who might know whether experiments have been done to find out if the level of CO_2 in the brain causes rather specific action on performance. Are higher functions, such as judgment, more sensitive than, say, functions of a type similar to the simple reaction time? It would be very interesting to find out which kinds of functions are especially sensitive to changes in the oxygen and carbon dioxide levels.

FREMONT-SMITH: We had hoped to have Doctor Livingston here and, most unfortunately, he couldn't come. He might have answered some of these questions. I think a pure effect is improbable, since we are dealing with a very complex interaction system, aren't we? So, if you change one parameter, several other parameters change simul-

taneously. How to come to grips with such complex effects upon cell function is a difficult question.

BJURSTEDT: Of course, there is interaction. This is always the case; you can not do anything to the body without changing a lot of things at the same time.

FREMONT-SMITH: Yes, but I think there are probably some psychological studies on this, although I don't know of any since I have not followed the literature. I think it would be very interesting, however, to know in a normal human being at sea level, who is overventilating at a certain rate, what kinds of functions, psychological functions— judgement, memory, whatnot—are affected.

I would suspect that the first effect is going to be on the more complex cerebral functions, because these are the ones which require the greatest degree of interaction of neurons and of systems and, therefore, one might anticipate that the first effects would be at the more subtle levels.

I will give you an example of this. A good many years ago the Soviets reported that irradiation affected the central nervous system at very low levels and we, being quite sure that the Russians are wrong on almost everything, said, "Oh no, of course not. This is not possible."

However, the Russians were using very subtle conditioned reflex studies coming out of Pavlov's work, and we don't really know how to repeat their work. Very recently, at the Naval Radiological Defense Laboratory, the Russian work was confirmed. Very low radiation does affect the central nervous system; the Russians were quite right. Since we don't know how to repeat their experiments, we didn't use their method, but the point I make is that with radiation to the central nervous system, the effect is first shown up in the most subtle most complex relationships, and I would expect that low oxygen would affect first the more subtle relationships and probably at the high cortical level.

BJURSTEDT: And not the more deeply engraved functions which are inborn or acquired at a very early stage?

FREMONT-SMITH: In general, as far as memory is concerned, experience is that very recent memory is much more vulnerable than old memory.

BROWN: May I ask a question for information? It is my impression that if you control the hyperventilation factor by using CO_2-enriched gas, you cannot reproduce the symptoms of low CO_2 by changing the oxygen tension. It is not simply an oxygen-tension phenomenon regardless of how complicated. The symptoms are simply different. Is this correct?

DUBOIS: There is a picture of hyperventilation in which if you

overbreath 15 minutes you get giddy, and you get carpopedal spasm; the skin gets cold and sweaty. These symptoms are different from those which you get with simple hypoxia. At least, as I remember the overall picture of a person who has hypoxia, it is different from that of a person who has been hyperventilated.

ROTH: Not in the borderline situation. In a borderline situation you get gradual degradation of function so that in fighter pilots it is rather difficult to determine which is which. There are three tests that have been used in CO_2 studies. I think Doctor Fenn, at one time you did a hand steadiness test as opposed to a contrast discrimination test and Bruno Balke[14] did the very same hypocapnia tests on a multiple complex coordinator. I reviewed the figures not too long ago and I believe you found degradation at a higher CO_2 level than Balke found in his complex coordination test.[15] I don't know how good the numbers are in that range.

FENN: More sensitive to CO_2 tension?

ROTH: Yes, the visual test was more sensitive than a complex coordination test.

Bends

DUBOIS: Turning to some other aspects of the gaseous environment, what about the bends? Can we state very briefly what the position is? We have to get the man off the ground and he has been breathing air. Over the course of two minutes, you decompress him in those conditions, won't he get the bends?

HENDLER: Our experience with bends has been primarily with a decompression from an atmosphere of 50 per cent oxygen-50 per cent nitrogen at 7 psia to the space suit atmosphere of 100 per cent oxygen at 3.8 psia.

DUBOIS: What I mean is, in your chamber you had people at 5 psi and you had medical officers going in and out to see them and, as I understand it, some of them got the bends going into this atmosphere.

HENDLER: Yes, some of the medical officers did, who hadn't preoxygenated sufficiently. Occurrence of bends depends upon the physical condition and age of the medical officers, as well as other factors. In our case, the one having the most trouble was the oldest. Unless he preoxygenated for about two to three hours, he ran into difficulty.

BROWN: Can you predict a predisposition to get bends?

HENDLER: To a certain extent. I think, in general, obese people and older people are more prone to get bends.

BROWN: Why?

HENDLER: Possibly because of the greater amount of fat available to dissolve the nitrogen.

HELVEY: Pertinent to the 27,000 foot mark, Arthur; you can, of

course, get bends at that level but it wouldn't be unusual for people to go up that high and not get bends. Many times you have enlisted men working around the chambers at pressures up to 20,000 or 30,000 and they have a standard operating procedure to preoxygenate, but sometimes when they are busy they don't. But taking fighter pilots, who are supposed to preoxygenate but often do not, I think there is a case of bends on record at 18,000 feet and another at 22,000, but generally they are well over 25,000 or 30,000 feet, before there is an incidence of bends.

Of course, when you are planning for a space craft you have to be conservative, but I think people can go up to 25,000 or 27,000 without getting bends. Ed, would you agree with that?

HENDLER: We had a young pilot in our place who seemed to be especially bends-resistant, in fact, he was well known for this and he went along for quite a while this way. But once he did get the bends, so it can strike unexpectedly. I am sure we have to take all precautions.*

DUBOIS: You have to wash the nitrogen out of the tissues before you decompress in order to keep bubbles from forming.

RAHN: May I ask what advantage or disadvantage the Russians have, who apparently have air of one atmosphere in their satellites? If we had the capability, should we stick to one atmosphere of air?

HENDLER: A change from breathing air at one atmosphere pressure to that of the space suit atmosphere of 100 per cent oxygen at 3.8 psia, such as could occur if capsule integrity were lost, would almost certainly lead to bends.

RAHN: In other words, you are saying that possibly in terms of the factors that we will discuss, one atmosphere of air is probably preferable. However, in case of an emergency, that is, pressure loss of the cabin, or if you want to get into a pressure suit and leave the ship, then it is a disadvantage and a great hazard, in effect?

ROTH: We have tweaked several Russian people on this recently. They are the first to admit that they are at a disadvantage in using the one atmosphere cabin in event of decompression. Actually, their pressure suits are at 7.5 psi, rather than five. They still believe in the magic number two and therefore take the disadvantage of mobility decrease to protect them in this situation.

They also feel that for these early missions where there is no egress from the cabin and things are rather stable, it is fine; but as soon as they begin dealing with rendezvous and leaving the cabin, I am quite sure they are seriously thinking of changing their pressure.

**Note added by Hendler:* In light of more recent experience, present opinion is that occurrence of bends below altitudes up to 30,000 ft., or even below 25,000 ft., is fairly common. New reports of low altitude bends are becoming more frequent, and our laboratory experience with enlisted men acting as subjects certainly confirms these reports.

HENDLER: Doctor Roth, you used the magic number two. Have you evidence that the number is no longer magic or that there is some other number to be considered?

ROTH: I didn't say it in a derogatory fashion. Haldane, I think, was the first one to come up with this in the Caisson studies, and the Navy diving tables[16] haven't really stuck to two. They have been a little more conservative. They have a problem, of course, in duration of the dive as well as exercise and other problems. During a dive, they are slowly taking gas into the body fluids and these all become a factor in modifying the tables, as a general rule.

The rule of two has held up very nicely because scuba divers leaving the water and going into an aircraft have developed bends at around 12,000 feet, and if you determine the depth they were at and the actual pressure changes, the figure two holds pretty well.

HENDLER: Our experience has been that two is a pretty good figure for some reason.

HELVEY: Except by experience, I think.

HENDLER: Because of the lack of any other guide, I think we are forced to use what we have so far, since we have found it to work.

DUBOIS: But that is like sticking your head in the sand.

NEUMAN: It is only when you don't know the mechanism that you can find a number. When you have a mechanism, you have too many qualifications.

HENDLER: I know the number would never be a nice round one like two.

FREMONT-SMITH: It will be a variable number, depending on circumstances.

ROTH: What is your criterion for bends—visual bubbles, increase in metabolism, decrease in motion?

HELVEY: Maybe it will be no more than a little gastric distress. If it doesn't impair their performance, let them have the bends.

DUBOIS: If you take X-rays of joints, some people have bends and they don't know it. Isn't that the situation?

HENDLER: They have bubbles in the joints.

ROTH: Are you actually concerned with bends, that is, joint pains, or are you concerned with the problem of cerebral vascular collapse and scotomas and things like this, which I think will be more serious? Whereas bends are quite incapacitating, you can still survive and bends are a transient affair, you see. You get over the bends as you get rid of the gas in your body. Bends aren't a permanent thing so that you can actually plot a time history of bends.*

*Prediction of the effects of different inert gases depends on the symptoms or tissues sites in question.

I got involved with this back in '55 when I was trying to determine the relative seriousness of inert gases in the bends problem[17] and what I did was take a model of a bubble using Laplace's bubble theory, Newton Harvey's work,[18] and Leslie Nims' work[19] and I tried to write an equation that would determine the actual life history of a bubble with the individual inert gas factors plugged in. Past equations predicted bends to be a transient affair and I think Air Force experience in World War II demonstrated, with many thousands of people, that it was a transient affair and Anthony[20] actually plotted a very nice curve of a population response to this bends situation. I had a problem of choosing the critical symptoms. In most operational cases you would not like to pay the penalty of even transient symptoms. In an emergency situation, however, one could tolerate most of the symptoms except possible cerebro-vascular collapse.

What I did was to assume that the cerebral problem and the cerebral lipids would be significant in terms of the liquid gas solvent phases involved. The critical inert gas factor determining the hazard turned out to be the square of the solubility of gas in oil times the diffusion in oil, divided by the solubility in water. That is the factor that you could use to compare the inert gases in terms of decompression hazard. One has to think of the cerebrovascular problems rather than just classical joint bends.

HENDLER: There is an appreciable disadvantage in maintaining an earth-like atmosphere in a space capsule, since a thicker hull is necessary to compensate for the greater pressure differential across the spacecraft walls.

ROTH: We recently received a report from several people at North American Aviation who were doing a study on how much weight it would take to go up to a half atmosphere cabin, say, as opposed to a quarter atmosphere cabin. The thickness of the wall actually isn't a problem. It is the thickness of the welding, they claim.[21] They came up with a trade-off of eight pounds of metal to make the difference between 5 psi and 7.5 psi. It seems low, but this is the figure they came up with.

There is another twist to this in terms of future missions, and this is the use of a "Fiberglas" cabin wound the same way that the solid fuel rocket cabins are wound. Using "Fiberglas," you can get away with incredibly low weights. The pressure problem is solved this way, and you beef up your cabin structure at sites involving attachments to the rest of the vehicle. The air-frame industry is looking at these higher pressures without much of a weight penalty, I think. The original impulse was to stay as low as possible, but on second thought I think you can get away with much higher pressures if it is deemed necessary or desirable.

FENN: I thought to some extent higher pressure was an engineering help because it would give more rigidity to a sphere that was reinflated. It gives it reinforcement to keep its shape.

ROTH: The ultimate question in terms of the weight usually turns out to be in a trade-off study the beefing up of the cabin required for the loads of acceleration and deceleration; i.e., the attachment of the cabin to the wall as you are reentering. As far as rigidity goes, you get adequate rigidity even at lower pressure. In other words, at those pressures, you are not really contributing very much to the rigidity of the wall. Rigidity is a problem in the fuel tanks of some boosters. The fuel tanks in rockets actually supply rigidity. The basic rigidity of the booster is determined by the pressure within the fuel tanks. There, it is a problem; I don't think it is so in the cabin.

BROWN: There is another source of increased weight if you go to one atmosphere of mixed gases and that is the more complicated controls that are needed. Capsules are somewhat leaky and you can't assume you won't have to replace the nitrogen or helium, so you need dependable monitoring and dependable systems automatically to regulate pressure and composition. This is going to take some pounds.

ROTH: Fifteen pounds is what Garrett Corporation has now calculated for the Apollo mission. If you take the Apollo mission at the present state of the art, present oxygen detectors, valving and signal conditioners, weight of the nitrogen source, etc., it works out to be about 15 pounds.

BROWN: Which is greater than the structural change.

ROTH: Right. This is what rather surprised me, but their current thinking is that it is 15 versus eight for the welding.

FENN: It depends on how long you are going to stay up.

ROTH: The North American study was for the Apollo 14-day mission.

HELVEY: On this matter of engineering weight, it is hazardous to generalize. We recently looked into the questions of cabin atmosphere. A study was made by competent people who determined that for an eight-man space craft, if you increased the pressure from a half atmosphere to one atmosphere, you tripled the weight, from 3000 to 9000 pounds. But consistent with what Doctor Fenn stated, some of our own engineers, studying different space vehicles, concluded that for reentry pressures, sometimes there is an advantage to higher internal pressures; but in addition to impact which Doctor Roth mentioned, meteoroid shielding and other structural needs, in one case for one vehicle they decided there was no weight cost, not even the eight pounds, to provide a pressure of one atmosphere.

Pertinent to Doctor Brown's comment on the life support systems, I believe Garrett quoted the difference between a one- and two-gas

system in actual control, not the gas, as costing 10 per cent in weight and eight per cent in volume for two-gas over a one-gas system, which gives another idea of the value.

With a rapid or explosive decompression of the cabin, the one-atmosphere cabin is a hazard in that your relative gas expansion in the air-filled organs will be greater and the likelihood that you will tear a lung or something of a serious nature will be higher with the higher-pressured vehicle.

JENKINS: Bill, can you say anything about the leak rates?

HELVEY: Wasn't the measurement about 300 cc.?

JENKINS: It started out higher. Wally Schirra's was 528.

RAHN: Are these standard temperature and pressure volumes that you are mentioning?

HELVEY: They may have been converted to STP I don't know how they did it.

RAHN: In other words, what you are saying is that the leak rate is twice as fast as the oxygen consumption of the pilot? Is that one way of putting it?

FENN: It means you have to supply as much nitrogen as oxygen.

JENKINS: But with a loss rate for a period of two weeks or a month, which we are interested in, this is not very practical. They assured us that if we used the Mercury capsule for the biosatellite program, they could cut it down to 300 cc. per minute by coating the interior with plastic. In our biosatellite program we are using normal air, 14.7 psi.

HELVEY: Leak rates in space suits are not far removed from this. They try to get down to 100-200 cc./min.

HENDLER: The leak rates are usually determined on new suits under static conditions, so as a suit ages, and especially with a man moving around in the suit, I am sure that the rate must get up close to a liter or two a minute, and maybe more than that.

HELVEY: And depending on how you zip it up that day, actually it varies, up to a liter a minute.

BJURSTEDT: With the present know-how, would it be possible to increase the pressure in a suit to near one atmosphere and still have some degree of mobility?

HENDLER: I think people are relatively immobilized at even a third of an atmosphere pressure in a flexible, fabric suit.

HELVEY: It is quite an experience to see a man in a 5 psi pressured suit get on the floor and try to get up. He is quite immobilized.

Oxygen Toxicity

DUBOIS: With the general pace of things we should try to discuss oxygen toxicity, atelectasis, acceleration, a little fire and then some-

thing about inert gas, whether it is necessary and what the actions are—.

BROWN: The partial pressure of oxygen is normally about one fifth of an atmosphere but the capsule is to have one third of an atmosphere. The reason it is a little above the pressure of oxygen at sea level is because this extra pressure gives a man some reserve. In case of a hole in the capsule, he has time to put on his helmet and look things over before he blacks out. But does this high partial pressure of oxygen produce toxicity at the cellular level and, if so, what is the evidence?

GILBERT: According to the ideas of Gerschman[22-24] the toxic effects of oxygen will be noticed even at very low levels. It is known that enzymes can be inhibited just by the presence of oxygen and we think that oxygen toxicity is present with us at all partial pressures. Therefore, it would be a good idea at least to consider the prolonged effects on man of any possible capsule atmosphere which contains more than 158 mm. Hg oxygen pressure.

Actually, when we discuss the effects of oxygen, we should keep in mind the various gradients which exist in the animal organism. The oxygen pressure is 158 mm Hg for the sea level environment. The oxygen pressure in the alveoli is only 100 mm Hg, and the transport of oxygen from the lungs to the tissues via the blood circulatory system represents another barrier which further decreases the oxygen pressure. Finally, there is an additional oxygen gradient which results in a very low oxygen pressure at the cellular sites where oxygen is utilized. I don't know what the pressure is, but it could be below 10 mm Hg. These barriers actually act as a defense against oxygen toxicity. Increasing the oxygen pressure in the environmental atmosphere from 158 mm Hg to 253 mm Hg corresponds to a 60 per cent increase. At the cell site, the percentage increase would be much less due to these defense barriers. Just what it would be I don't know, but these barriers should be taken into consideration.

DUBOIS: On the venous side, oxygen drops to a low tension because of the shape of the dissociation curve, so you will not raise tissue oxygen tension very much by raising oxygen concentration in the inspired air. But the lung tissues are exposed to the oxygen on the arterial side, and the blood leaving the lungs is in equilibrium with the alveolar oxygen tension. The walls of the chambers on the left side of the heart and the red blood cells and white blood cells would be exposed to the elevated arterial O_2 tension. Once the blood goes through tissue, the P_{O_2} drops right down the dissociation curve, almost to a venous P_{O_2} level.

RAHN: I would like to reemphasize the changes in O_2 tensions which occur when 100 per cent is breathed at a pressure of 258 mm Hg. If one subtracts 47 mm for water vapor and 40 for CO_2, we have an

alveolar O_2 of 171 mm. Thus the arterial O_2 is 170 but the average venous O_2 tension is probably not raised by more than 1-2 mm.

If oxygen toxicity effects are produced by changes in arterial O_2 tensions, then we have here a change from the normal value of 100 to 170. If oxygen effects are initiated by changes in the venous blood tension, then we have only a change of about 1 mm.

GILBERT: That is what I would like to emphasize. As I mentioned before, these barriers resulting in an oxygen gradient between the environment and the cell act as antioxidant defense mechanisms. A large percentage increase in the environmental oxygen pressure results in a small percentage increase in the cellular oxygen pressure.

NEUMAN: Isn't the point of all this that the relatively small change in environmental P_{O_2} causes a large change in the P_{O_2} of the arterial side?

RAHN: On the arterial side, but we don't know whether this is important. It may be that the venous or the tissue oxygen is the important thing.

GILBERT: At the Federation Meeting in Atlantic City this year, Welch and coworkers[25] reported on the deleterious effects of low level oxygen pressure exposures to man. The relatively inert nitrogen pressure was not maintained at the normal 0.8 atmosphere. Thus, there are two factors to be taken into consideration: one, the increase in oxygen pressure above 0.2 atmospheres and two, the decrease of nitrogen pressure. The inert gas can act as an antioxidant in inhibiting oxidation. The point I would like to emphasize is that we have to face the possibility of oxygen toxicity even at very low pressures.

BROWN: Is toxicity, even in the singular, appropriate? What about the mechanisms? We must be beyond the stage where it is a matter of strictly empirical, of challenge-the-system-and-see-what-happens study.

GILBERT: According to the "Gerschman theory",[26] toxicity is due at least in part to the effects of oxidizing free radicals. Oxygen is normally sluggish. However, once it gets activated to a free-radical state, then oxidation of cellular constituents can occur which results in oxygen toxicity.

BROWN: What is the mechanism of free radical formation induced simply by changing oxygen tension?

GILBERT: One mechanism would be by oxygen reacting with a reducing free radical. FIGURE 1 simplifies how oxygen can oxidize some substrates. We have present in the system a reducing free radical designated by $R^{\cdot}$ which can activate molecular oxygen to produce an oxidizing free radical, $RO_2^{\cdot}$. The $RO_2^{\cdot}$ radical can react with some substrate, RH, to produce the peroxide RO_2H and to replenish the R radical. This is an example of a propoagating chain reaction. An increase in

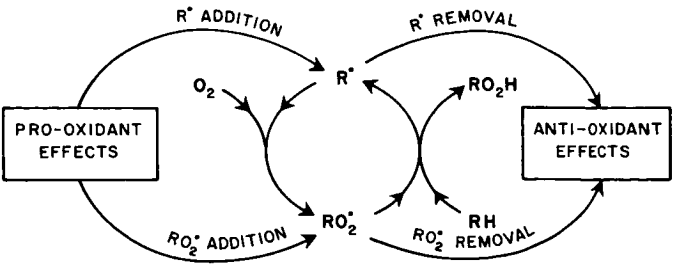


FIG. 1. Chain reaction. (From Gilbert, 1963.[50])

the free radical concentration results in an increase in the rate of oxidation of the substrate, RH. Thus, decreasing the free radical concentration is an antioxidant effect and increasing the free radical concentration is a pro-oxidant effect. The free radicals are very reactive and can destroy cellular constituents. For instance, ionizing radiation induces a large increase in the free radical concentration. Therefore, the deleterious effects of ionizing radiation may be looked upon as merely catalyzing the inherent toxic effect of oxygen—as releasing the brake of the inherent oxidation energy within the cell. Of course, it should be pointed out that the individual ionizing particle contains a considerable amount of energy, but there are relatively few particles. To produce an unstable chemical species, such as a free radical, usually requires a considerable amount of energy which can come from a few packets of intense energy such as from ionizing radiation.

FREMONT-SMITH: Don't we in our biological systems have a whole series of biological antioxidants all the way through, and isn't knocking out antioxidants one of the ways in which we increase oxidation effects?

GILBERT: There are various types of antioxidant mechanisms.[27] For example, in the red blood cell, glutathione peroxidase is important in inhibiting the oxidation of hemoglobin to methemoglobin.[28]

FREMONT-SMITH: What I want to emphasize is that, really, the whole life process depends upon a series of biological antioxidants, which keep us burning at a low flame—that is the extraordinary thing about the life process—and that, therefore, it seems to me we ought to emphasize as much as we know about what are the biological antioxidants involved and to what extent they can be increased or decreased in their activity, aside from the increase in the tension of oxygen, which is only one phase of it.

GILBERT: Yes. The braking action of the various antioxidant mechanisms against the toxic effects of oxygen cannot be overemphasized.[22,24,27] Oxygen toxicity becomes more apparent in the absence of these mechanisms. Substances such as vitamin E, catalase,

peroxidase, and glutathione are cellular antioxidants.[28] The antioxidant defense can be aided by administration of commercial antioxidants such as nordihydroguiaretic acid, propylgallate, and trihydroxyphenones. Cations can sometimes exert a pro-oxidant effect, and it has been observed that chelating agents (which remove free cations) can possess an antioxidant effect.

It seems that cobalt[22,23,27] might possibly be considered a fairly effective antioxidant for moderate increases in oxygen pressure.

If we take a look in nature and observe where the oxygen pressure is above 0.2 atmospheres, we might get some clue as to what type of chemicals might be considered as potential agents for decreasing oxygen toxicity. Offhand, I can think of only two.

One area where the oxygen tension is above 0.2 atmospheres is in the cellular sites, which produce oxygen during the process of photosynthesis. We do know that plants have very special antioxidant mechanisms. Carotenoids and phenols are very effective antioxidants in plants.[24] Actually, photosynthetic production of oxygen by plants has been implicated in inhibiting mosquito breeding.[29]

Another area where there are tremendous increases in the partial pressure of oxygen is the swim bladders of fish in the deep ocean. Here, the partial pressure of oxygen in the bladder can exceed well over 100 atmospheres.[30] I don't know how the bladder resists oxygen toxicity, but it is worthy of investigation.

FREMONT-SMITH: This would apply to whales' lungs, too, wouldn't it?

GILBERT: I don't know what the oxygen pressure would be. It seems that whales can dive to 100 m where the increase in total pressure would be 10 atm, corresponding to a total pressure of 11 atm.[31] A gas phase at this depth would have an oxygen pressure of 2.2 atm. if the gas phase were composed of 20 per cent oxygen. A whale has been reported at a depth of 900 m, corresponding to an increase in total pressure of 90 atm.[31] If a gas phase at this depth contained 20 per cent oxygen, the oxygen pressure would be 18.2 atm. The whales would be consuming oxygen so that the per cent oxygen in the lungs would be much less than 20 per cent. Thus, the consumption of oxygen would tend to lower the oxygen pressure, which would be compensated by increasing the total pressure during the dive.

RAHN: Yes, but that would be a rather temporary one.

ROTH: Twenty to thirty minutes, probably, at the most. There is one point, however, and this brings up the interesting nitrogen factor. The deeper you go in sea water, the lower the per cent oxygen. There is a gradient of decreasing per cent oxygen with depth.

GILBERT: It is not always that simple. The oxygen concentration

can many times increase as the depth increases.[32] If you go very deep, then the oxygen concentration will decrease.

ROTH: Yes, it does, I believe.

GILBERT: The oxygen concentration will depend upon convection currents and areas of oxygen production and consumption.

HELVEY: This has been plotted by oceanographers. There are notable exceptions. There are evidently vertical currents. I think Beebe and others have noted sharks at very deep levels, deeper than one would expect.

ROTH: In relatively still water, as you get away from the plankton area and go down, your per cent oxygen begins decreasing, which means that the nitrogen-oxygen ratio possibly is increasing, and when you say five atmospheres of oxygen, you also have many more atmospheres of nitrogen relative to the surface. I just wonder how much of a nitrogen buffer there really is.

GILBERT: It appears that the large oxygen pressures in the swim bladder are due to the secretion of gaseous oxygen into the bladder.[33]

ROTH: But the peripheral tissues still have a nitrogen buffer.

GILBERT: There is no gas phase here.

ROTH: It is dissolved, and you are concerned with the intracellular oxygen. In terms of the oxygen toxicity, you are concerned with the intracellular oxygen being countered possibly by high intracellular nitrogen at depth. In other words, this might be a factor in protecting fish against cellular oxygen toxicity.

FENN: The oxygen tension isn't much higher at great depths than it is on the surface, and if it is being used by organisms, it would be considerably less.

GILBERT: Why should the concentration of physically dissolved nitrogen in the lower depths increase? That is the point. It is going to be the same at lower depths.

ROTH: No; I don't know what the figures are, but I know the oxygen ratio decreases with depth. How it compares with the surface, I don't know.

NEUMAN: I would like to ask a couple of questions about the radical mechanism. Is this a demonstrated mechanism or an inferred mechanism?

GILBERT: At the present time I would say that it is mainly inferred. Electron spin resonance studies have shown that free radicals do exist in biological systems.[34] Actually, increases in free radical production have not yet been demonstrated. An attempt to detect an increase in free radical concentration in tissue upon exposure to high oxygen pressure using electron spin resonance spectroscopy was reported last month by Doctor H. S. Mason. Doctor Mason reported

that he has been unable to show such an increase so far, but that he is still investigating this problem.[35]

NEUMAN: The reason I bring it up is, if you are going to evolve a radical mechanism using oxygen, then you are involving energies of a certain limiting value, something of the order of one hundred electron volts, I would guess. This would require an energy input. An oxygen tension per se without the energy input, wouldn't do anything. It seems to me there is a necessary additional postulate.

GILBERT: From a thermodynamic point of view, it is very simple. Thus, when oxygen oxidizes sugar to form carbon dioxide and water, there is a release of energy. This would also be true of other types of cell constituents which would tend to go to the reduced form.

NEUMAN: But you have an activation energy that stands in the way.

GILBERT: The activation energy is important in considering the actual mechanism of oxidation. This activation energy can be regenerated by a chain reaction.

NEUMAN: It seems to me that the radical mechanism implies also a source of continuous energy of the order of the quantum levels big enough to produce free radicals.

GILBERT: No. One can use as an analogy a water movement from one level to a lower level by means of a siphon. It requires energy to move the water from the high level to a still higher level in the siphon tube. This higher level in the tube corresponds to an activated state. Once energy has been added to the system to drive the water from the high level to the activated level in the tube, then water will flow from the activated level to the lower level continuously until all the water has been transferred. The energy released in going from the activated level to the low level is used in part to drive the water from the high level to the activated level. In the chain reaction, the free radicals act as the activated states. Once they are present, they are continuously being regenerated.

DUBOIS: If you just take some of the enzymes in the Krebs cycle and expose them to oxygen, they become oxidized. You don't necessarily have to have a perpetuating source of high energy or free radicals to do it. They just oxidize irreversibly.

GILBERT: How do they oxidize? What is the mechanism of oxidation? I believe it is a free radical mechanism.

ROTH: I got interested in this subject several years ago when I took a course in free radical chemistry at Harvard. The final exam question was actually a theoretical discussion of the biological autooxidation problem. I would like to go over a few slides since we are involved in all this discussion on the actual mechanism.

I think the basic problem, in terms of these low pressures, is the

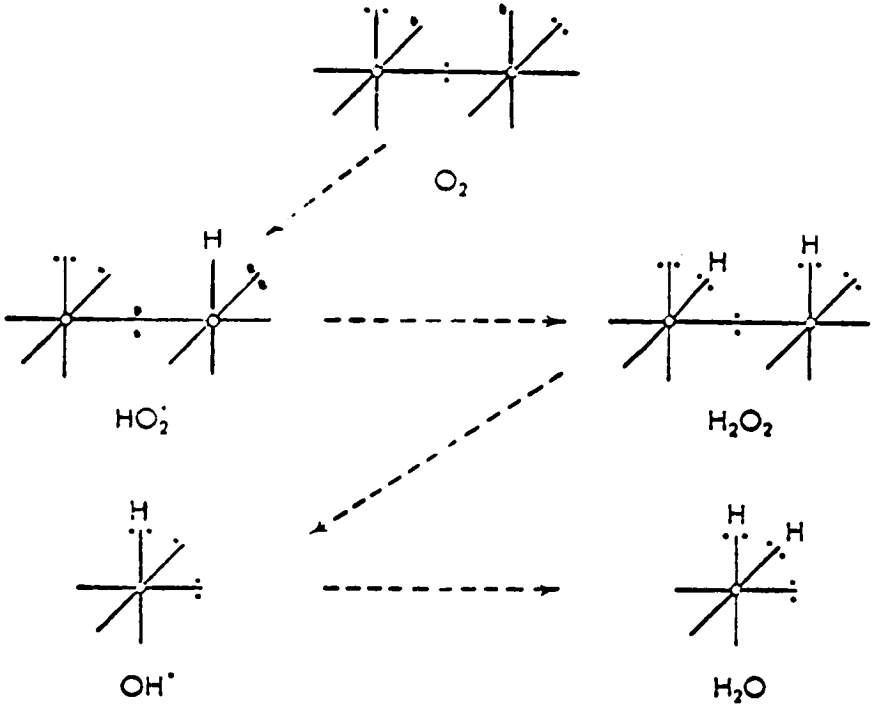


FIG. 2. Hydrogen-Oxygen species. (After Gerschman, 1962.[23])

fact that free radical reactions occur at very finite threshold, and once you get a given level of free radicals in a system, the chain reaction will cannonball to a complete free radical oxidation.

In the plastics industry, polymethacrylate and polystyrene chemistry, depend on these critical thresholds. The final product of oxidation is very, very sensitively determined in reality by sulfhydryl compounds in the gimisch that they start the reaction off with.

FIGURE 2 is from Gerschman's paper[23] but indicates that oxygen itself is a free radical (a di-radical) in that it has two unpaired electrons in the molecule and the reduction of the oxygen system to water involves another free radical, a hydroperoxyl which goes through hydrogen peroxide on to a hydroxy radical, and then is further reduced to water. So, this is a fact of life that every cell is exposed to whenever oxygen enters the system.

FIGURE 3 shows the energy barriers that you spoke of. This is also from Gerschman's paper. Michaelis,[36] I think, was actually the first to point out that there are activation barriers—in other words, to get from oxygen to the next step, H_2O_2, activation energy is required. I think this is one of the reasons why oxidations themselves don't go as

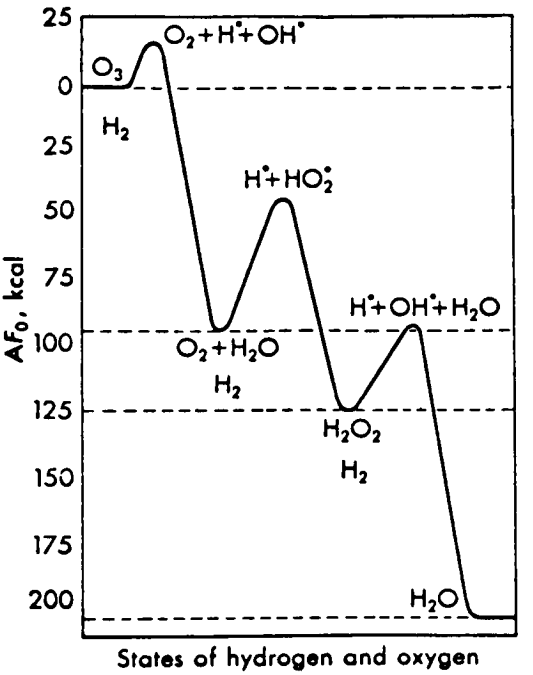


FIG. 3. Reduction of oxygen by hydrogen. Dotted lines refer to stable or quasi-stable states. (After Gerschman, 1962.[21])

rapidly as the theoretical energetics would predict. These activation energies for each of the reactions actually tend to slow down the free radical cascade.

I took this diagram from Gerschman's paper and added a few more twists to it. The reaction scheme proceeds through these steps:

I. Initiating Steps
  A. Ionizing Radiation
    1. Indirect (via water)

$$H_2O \xrightarrow{h\nu} H_2O^{\cdot} + E$$
$$H_2O^{\cdot} + H_2O \longrightarrow H_3O^{\cdot} + OH\cdot$$
$$E + H_2O \longrightarrow OH + H\cdot$$

    2. Direct Effect on Biological Molecules (RH = normal carbon-hydrogen bonded organic molecules)

$$RH \xrightarrow{h\nu} R\cdot + H\cdot$$

  B. Biological Reduction of O_2

$$O_2 \xrightarrow{H} HO_2^{\cdot} \xrightarrow{H} H_2O_2 \longrightarrow OH\cdot + H_2O \xrightarrow{H} 2H_2O$$

C. Oxidation of R· by O_2
(R· = normal active biological free radical intermediate)

$$R\cdot + O_2 \longrightarrow RO_2^{\cdot}$$

The next step is the damaging step, the chain reaction.

II. Damaging Steps (chain reactions)
(RSH = Normal biologically active thiol group on an organic molecule.)
(RH = Normal carbon-hydrogen bonded organic molecule.)

A. $RH + HO_2^{\cdot} \longrightarrow R\cdot + H_2O_2 \longrightarrow$ Step IC $\longrightarrow$ Chain Reaction

B. $R'O_2^{\cdot} + RH \longrightarrow R'O_2H + R\cdot \longrightarrow$ Step IC $\longrightarrow$ Chain Reaction

C. $RSH + HO_2^{\cdot} \longrightarrow RS\cdot + H_2O_2 \longrightarrow$ Step IC $\longrightarrow$ Chain Reaction

Step IIIC $\longrightarrow$ Permanent damage or chain termination

These are the steps that continue the cascade. RSH would normally be an active, thiol-group-containing organic compound, such as glutathione, cysteine, any other system that you want. A nonthiol critical group would probably be a totopherol-like compound, which seems to show an antioxidant type of action even though it has no sulfhydryl.

It must be remembered that these reactions have never been shown directly in biological systems. They have been inferred from electron spin studies. Group III is the damaging or chain terminating reaction.

III. Chain Terminating Reactions—Permanent Damage or Protection by Stopping Free Radical Chain.

A. $R'O_2^{\cdot} + R\cdot \longrightarrow R'O_2R$

B. $R\cdot + R\cdot \longrightarrow RR$

C. $RS\cdot + RS\cdot \longrightarrow RSSR$

If the normal biological function of a molecule required that it be in transient free radical form, Steps III. A, B, and C would permanently interfere with its reactions.

In his review Billy Welch[25] listed the average time of onset of oxygen toxicity symptoms as a function of ambient oxygen partial pressure. Above 760 mm Hg, the central nervous system is the primary site of defect with symptoms such as nausea, dizziness, convulsions, and syncope. In the range of 400 to 760 mm Hg, respiratory and nervous system symptoms predominate. These are substernal distress (bron-

chitis and probably atelectasis), paresthesia, and nausea. In the range of 200 to 400 mm Hg, symptoms are respiratory and possibly hematological and renal: substernal distress, oxidative hemolytic anemia, and proteinuria have been reported. Studies in progress may clarify the exact cause of symptoms and laboratory findings in this lower range. The role of contaminating gases (nitrogen) and trace vapor contaminants in the oxygen is still unknown.

This confirms what has been known for years, that the critical target molecules within the body vary with the P_{O_2} in question and time of exposure. Specific targets in the central nervous system are still unknown. The British have been working on the lipids as possible primary targets of oxygen in the nervous system and the generation of lipid peroxides.[37]

FREMONT-SMITH: This is human material?

ROTH: This is all human, yes.

In the lower P_{O_2} levels you are running into mostly an atelectasis type of problem, at least symptoms of substernal distress that usually come on in vital capacity tests and are thought to be of an atelectic nature. These take a very, very long time to occur.

The question comes up: Is the atelectasis purely an absorptive phenomenon? Is it a destruction by free radicals of the lipoprotein surface active agent of the lung, or is it actually something to do with the bronchial wall? Exactly what is the initiating site here is still not known.

I think Welch's diagram is a good representation of the general time of onset of the symptoms spectrum in humans at different partial pressures of oxygen.

FREMONT-SMITH: Is there an appreciable reduction in vital capacity?

ROTH: I think in some of Clamman's studies at 578 mm Hg P_{O_2}, vital capacity dropped 30 per cent or so.[38] I think the important thing to remember is that free radical reactions are extreme threshold reactions; Beecher and Williams[39] pointed this out in World War II when they tried to write an equation for oxygen toxicity in various animal systems. They found that everything held well until they got down to the threshold point at about 0.7 atm of P_{O_2}. At this threshold, the constants changed markedly, and I think the threshold point they came up with was, interestingly enough, right at the point where the target organs are changing. This, essentially, is what happens. The change in target organs gives you changing criteria of toxicity.

FREMONT-SMITH: When you say you are changing your target organ, are you not saying that you just haven't got time enough in these brief studies to get the other organs involved because the cerebral symptoms are too acute?

ROTH: Right. I think this is the problem. In some mouse studies, Cook and Leon[40] came up with paralyses and hepatotoxicity. They argued that the animals never came down with pulmonary problems. They were free of atelectasis and so went on to get cellular toxicity in these organs. I think you can explain both symptoms as a hepatocerebral virus being activated by oxygen. Classically, you can activate virus systems, at least in bacteria, by irradiation, and carcinogenic agents that could generate a free radical type of reaction. In bacterial systems, this, essentially, is how you take a lysogenic virus and convert it to a lytic virus with a very low level of radiation. The Russians have actually demonstrated an activation of the cerebral virus by high oxygen tension.[41] I got an abstract but I don't have the Russian paper in hand. But Cook and Leon's results, which are quite contrary,I think, to Doctor Rahn's results[42] under similar circumstances, might be explained on the basis of triggering off of the virus reaction.

This, I think, is quite important in terms of having people in closed systems for long periods of time. You might be avoiding the acute symptoms; you might even be avoiding the atelectasis; but the critical aspects of the free radical reaction might extend to the triggering off of a virus reaction. It doesn't really take very much to start the virus cascade going, so I think we have to be very careful about this area in terms of unusual symptoms. I think this is a very good example of the sort of thing that you could easily hand off as being an artifact of the experiment or a contaminant in the system, but it could just as well be the fact that we are dealing with a very critical site in the spectrum.

The question of the role of nitrogen has been raised. As you go down to these low pressure levels, the ratio of oxygen to nitrogen is increasing remarkably. Doctor Helvey had less than one mm. of nitrogen in his test chamber and Doctor Welch probably a little more than that. How important are these last few millimeters of nitrogen present in atmospheres tested experimentally?

If it is a question of oxygen and nitrogen competing for surface absorption on critical sites, say in mitochondria or elsewhere, you might run into this problem. The only studies I have found of this competition have been in Ebert's work with radiation sensitivity using inert gases, bucking inert gases against oxygen.[43] In order to counteract oxygen effects he had to use over 50 atmospheres of either nitrogen or hydrogen to get a visible radiation effect. This is a tremendous ratio, but as you get down to the lower levels of inert gas, 1 mm. Hg or less, you might be accomplishing this sort of ratio in critical sites in the cell, so I think we can't overlook the potential "inerting" effect of nitrogen. I don't think we can use the same analogy with the burning problem, but I think the fact remains that, according to ad-

sorption theory, you might be getting into trouble even at these low levels of nitrogen.

FENN: Is there any other evidence of a competition between nitrogen and oxygen for critical sites?

ROTH: No, this was the only paper I could find.

FENN: This isn't really evidence. It is just an interpretation. There might be other interpretations.

ROTH: Right. They made no attempt to study the competitive adsorption mechanism as opposed to any other mechanism. They tried to compare the effects of nitrogen and hydrogen in terms of pressures required for reducing radio-sensitivity. Hydrogen, they postulated, may act as a $^{\cdot}OH$ trap as well as displace oxygen. I don't think anything definite came out. They didn't plug the data into any preconceived equation to see if they could predict the effect.

FENN: It seems extraordinary to me if there is any such competition that it hasn't been discovered somewhere else, therefore, the absence of any other evidence of that sort makes me think that that interpretation is just wrong.

ROTH: My intuitive feeling would agree, but I think because we are getting the queer symptoms at the lower end of the curve we might have to think seriously of these final few millimeters. I don't think we can discard it completely as being of no significance.

NEUMAN: May I make the point (before we leave the radicals) that I was trying to make intially—that is, having gone through your reactions, your radicals always start off with an HV. To form a free radical, you have to put in energy.

ROTH: I know, I was trying to compare radiation with normal biological reactions with oxygen. Oxygen itself can be considered a free radical, and oxygen can initiate the system. In other words, if you take a methacrylate system, add peroxide and add sulfhydryl compounds so as to maintain the monomer, all you have to do is bubble oxygen in and the whole thing will polymerize.

GILBERT: Free radicals have been demonstrated in biological systems by the electron spin resonance technique.

NEUMAN: I am going to make my point anyway, because you insist you don't have to put energy in, and I insist that you do. You can say it is reacting with another radical, or that it is a transfer of energy of large order.

DUBOIS: I want to leave here with a clear picture of what a free radical is. It just seems they are generated two or three different ways.

NEUMAN: Doctor Gilbert said that free radicals are formed naturally. In the oxidation chain, of course, we are going from a two-electron change to a one-electron change in the cytochromes. It is my understanding that cytochromes do not involve free radicals but

rather a change in the oxidation stage of iron. We do have in the flavoproteins and in cytochrome oxidase an actual free radical state in electron transfer, in which a one-electron step is mediated. Also in cytochrome oxidase, these are the two free radical steps in the oxidation chain that occur normally as a regular path of metabolism. Isn't that correct?

ROTH: I think it was Michaelis[36] who pointed this out; there was the question of how the two hydrogens come off in any of the steps in, say, fermentation or respiration, whether they come off simultaneously or come off one at a time. If they came off one at a time, it would leave a molecule that had one unpaired electron. By definition, a free radical is any compound that has at least one unpaired electron. According to Pauli's pairing principle, in order to balance the magnetic moments in any one orbital, a pair of electrons is needed. If there is only one electron, a free radical or a paramagnetic molecule is obtained.

The Pauling oxygen meter, for instance, detects oxygen because the presence of oxygen increases the intensity of a magnetic field since it has two unpaired electrons. Oxygen has two free electrons, each on different atoms of the molecule and they are unpaired magnetic-momentwise. Any compound, then, that has an unpaired electron is a free radical and can be detected by an electron spin resonance system or a Pauling-type detector.

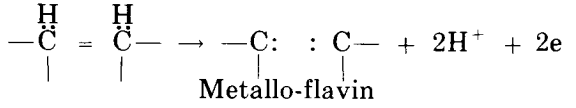
BROWN: Can I make a plea for tidying up our terminology? I don't believe it is helpful to define free radicals in this way. If you want a homely definition, it would be a bond that is unsatisfied; but oxygen is not a free radical. Atomic oxygen could be considered a free radical in this sense. You can make free radicals out of it.

GILBERT: The term diradical has been used for oxygen since it contains two unpaired electrons.

BROWN: Even this is misleading. "Free radical" usually means something else.

NEUMAN: The following is a diagram of the problem:

TWO ELECTRON STEP



$$\text{cyt}-\text{Fe}^{+++} + e \rightarrow \text{cyt}-\text{Fe}^{++}$$

ONE ELECTRON STEP

Let's draw it to a conclusion. When you go from a hydrogenated

molecule to a double-bonded molecule, you will see that there are six shared electrons here and there are four here, so you have removed two electrons as well as two hydrogen nucleii. This is true of all organic oxidations, oxidative decarboxylations, etc. All are two-electron steps. At the end of the cytochrome chain is a one-electron step, and Doctor Gilbert's point was that there had to be some free radical intermediate involving a one-electron step that had a stability in a lifetime that could permit the transfer of one electron at a time to a cytochrome. This is the general concept behind our discussion.

I agree: I think that oxygen should be called a molecule and that the definition of a free radical is an unpaired or unsatisfied valence electron—nascent hydrogen, nascent oxygen.

GILBERT: Let's say molecular oxygen possesses some properties of a free radical, namely, paramagnetism. That doesn't get you into any squabbles.

NEUMAN: A point I wish to get into the record is that you can use radiation and oxygen as a couple. If we go to increased radiation levels, this may very well move the level at which oxygen toxicity would become a problem. You might get a synergism here in raising the oxygen level and the radiation level. The curve that you are sort of extrapolating down to may be in serious error.

ROTH: We did look into this. Thoday[44] showed that at least for his plant systems, the higher the LET radiation you use, the more of a direct response you get and the less of an indirect one involving free radicals.

The Russians published a 600 page volume[45] recently devoted to the oxygen factor in radiation, in which they continually emphasize this, and I have some of their slides. If you compare neutron radiation and gamma radiation, it makes all the difference in the world. Gamma radiation is relatively sensitive to oxygen. Neutron radiation is almost insensitive to the oxygen effect.

SONDHAUS: The oxygen effect is generally considered to accompany low LET radiation. However, I think it is worth mentioning here that efforts have been made in England, as many of you are probably aware, to increase the effectiveness of radiation treatment of cancer by subjecting the patient to a very high oxygen tension. The patient is placed in a tank and irradiated at elevated pressure, and I think that the results so far have shown that there is some increase in effectiveness.

In studies on a bean root or on microorganisms or cells in culture, something of that kind, it is possible to be sure that you have increased the oxygen tension in the environment of the cell itself enough to observe a difference in RBE: that is, an increase in the effectiveness

per unit dose. But in the human whole body irradiation case, I think it would take a considerable increase in oxygen tension outside to show up as a differential radiosensitivity.

Of course, the possible synergistic effect of radiation and increase in oxygen tension resulting in increased probability of oxygen toxicity is another question and I think this should certainly be studied.

DUBOIS: Doctor Helvey, there seemed to be two schools of thought on the effect of oxygen atmospheres on the blood. You found one thing at Republic and Doctor Hendler another thing at the Air Crew Equipment Lab, and I think we ought to have it out, so can you tell us what you found?

HELVEY: Actually, Art, I don't think there is a big difference. In our case, the deleterious effects were seen at half atmosphere and others found that if there was any change in hemoglobin and hematocrit, it was in the same direction as ours.

RAHN: Would you review for us just what the environment was?

HELVEY: Our first group were six young men maintained at sea level pressure on air in the chamber. In the second test we had 5 psi, a third of an atmosphere of essentially pure oxygen; and in the third, one half atmosphere. The last study was at 3.8 psi.

In the first study (control) one of the young fellows, of Italian descent, had a marked drop in hemoglobin although none of the others showed any remarkable change. He went from 15.8 gm. on the day he went in the chamber to, at the end of two weeks, a little over 10 gm. We were concerned and had him worked up at Brookhaven afterwards; electrophoresis of his hemoglobin revealed thalassemia trait.

I might add that this fellow was not clinically detectable. We had examined blood slides and his only history was that his mother was a little anemic. It turned out that his mother was healthy—his father was the carrier.

WOOD: Would you explain thalassemia?

HELVEY: It is, essentially, an abnormal hemoglobin; some people live with this for years with very little problems. Evidently, we precipitated a hemolytic episode by something that occurred in the study. This alerted us to hemoglobin problems. We don't need to be run over by a caterpiller! We had been doing hemoglobin, hematocrits, RBC's, etc., but after that experience we did a few additional tests, like bilirubin. FIGURE 4 summarizes the changes in hemoglobin on these runs. We had a single control hemoglobin value the day prior to the run. In retrospect, we would like to have had a week's work, but we consider the sea level group as the control. Over the two-week span, hemoglobin bounced around and came out about the same at the end of the control run.

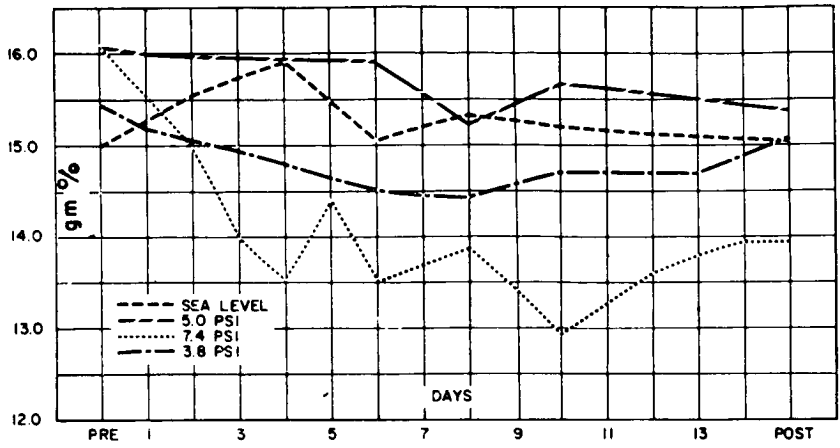


FIG. 4. Average hemoglobin concentration of men in an oxygen environment.

At 3.8 and 5 psi there was no remarkable group change—the hemoglobin and hematocrit went down slightly.

At half atmosphere (7.4 psi), in the first couple of days hemoglobin dropped 2 to 3 gm. After the first days, some subjects tended to return fairly close to normal whereas others did not. Interestingly, one of the medical students who had given blood at times over the period of the preceding year, as a source of income, responded a little better than the others. This may or may not be significant.

We had Doctor John Altman of Columbia University and also a couple of hematologists from Brookhaven, working with us; they believe that the 7.4 psi group experienced a hemolytic episode. Of course, we had to consider at the time that it might have been merely hemodilution. It was a little too rapid to consider an impairment in cell formation and we could not detect any blood loss.

I might say tests for occult blood in the stools were irregularly positive. That just adds a little color to the story; we can't account for that. Perhaps these were falsely positive tests.

In the half-atmosphere group again, the bilirubins spiked on about the second day. The reticulocyte counts on this same group were not too significant. Reticulocyte counts were a little higher in the 3.8 psi group that in the others and the van den Bergh test for bilirubin was slightly elevated.

SONDHAUS: There may be as much variation involved in the control or pretest state as is exhibited here. I would like to ask whether you tested the statistical significance of these.

HELVEY: No, we did not. We had the control data as indicated, and the retic count is probably not as bad as the RBC, but the randomness is significant in this range. We looked at the data but we

feel, as you do, that you can't hang your hat on these particular curves. It is a matter of information in the context of the other related information.

What was the cause of the changes we observed? We intended to do a study on the effects of pure oxygen and we consider this a possible cause. At the end of the study, and even concurrently, we considered that in any sealed capsule a toxicant, detected or undetected, could well be present. These, oxygen and toxicant, may act synergistically. The effects of decreased barometric pressure would have to be considered and then finally one would have to consider the role of nitrogen.

Our chamber is designed for very low vacuums, and we achieved nitrogen levels consistently below about one millimeter. To our knowledge, this is lower than has been experienced for similar durations. However, we have no reason to label nitrogen as a cause, obviously. Independent of this study, we have never really experienced a nitrogen-free environment. Perhaps the astronauts in the capsule will be the first people in a truly nitrogen-free environment, where there is no air to leak in. I think we have to await some scientific experience on a nitrogen-free environment to make a judgement.

I think one has to consider the very interesting experiment that Doctor Rahn has done, where he had mice in low levels of nitrogen—I think he said about four or five millimeters for 52 days. They got along fine and they even had a litter.

Pertaining to our study, I think there is a good case that oxygen shares a portion of the responsibility for this episode. Doctor Altman, who is considerably more qualified than I, sees a comparison between this episode and that seen in primaquine-sensitive individuals, in which you can get hemolysis due to the drug; and in individuals who have a glucose-6-phosphate dehydrogenase defect. From a review of the literature, it appears that this is not inconsistent with other studies; and I think Doctor Roth's comment about the effects of oxygen on enzymatic systems suggests that oxygen could be the mechanism.

This test should, of course, be repeated by someone else, in a different chamber, because if we had a toxicant which is a real consideration—it is likely that in a different chamber they would have different materials present. We did have a continuous flushing system. I think the likelihood of toxic contaminants is much greater if you have a closed or semiclosed regenerative system. We reduced this likelihood, but we don't really know conclusively.*

**Ed. note:* For recent data see Zalvsky, R., F. Ulvedal, J. E. Herlocher and B. E. Welch. Physiologic responses to increased oxygen partial pressure. III. Hematopoiesis. Aerospace Med. 35:622-626, 1964. Small decreases in hematocrit without evidence of hemolysis are reported under slightly different conditions.

DUBOIS: Doctor Hendler, do you entirely agree that your results are compatible?

HENDLER: The results of our study,[46] I think, in which the men were exposed to a simulated Gemini profile, are more or less in agreement with Bill Helvey's. In other words, there was a slight decrease in hematocrit and hemoglobin, but it was also seen in the controls, and we feel it was due to the blood-letting that occurs as part of the experimental procedure.

HELVEY: Actually, in both the 3.8 and 5 psi groups, except for the thalassemic individual there were no significant drops in hemoglobin. The Price-Jones curves in both instances changed contour and flattened. There was anisocytosis, microcytosis, Heinz bodies and a number of descriptive changes. This did not occur in the sea level control group. These were things that, had we had only the little changes that the normal controls showed in hemoglobin and hematocrit, if we hadn't had the thalassemic subject, we would not have been looking for. Bill Welch[25] had noted hemoglobin and hematocrit drops in his group and had attributed it to the blood-letting.

I am not trying to "sell" hemoglobin drops due to oxygen, but it is interesting to note that in a number of other instances this trend does appear, in the same direction, and I think we will have to wait and see when we have more good, solid data.

DUBOIS: This might be one of the by-products of this space program. In other words, doctors treat patients with this degree of oxygen—this is common—and the question is are they causing hemolysis, hemoglobinemia, and anemia by this? Did you say anything about methemoglobin?

HELVEY: No, we did not test specifically for methemoglobin. There was an instance where we felt there might be methemoglobin present, in which our studies of P_{O_2} content varied a little. This could have been laboratory error, and we didn't consider this possibility further. We cannot really say.

DUBOIS: Would you like to say anything about the mechanism of hemolysis?

HELVEY: Really nothing beyond mentioning the possibility of enzymatic inactivation.

DUBOIS: As I understand it, the red cell membrane uses energy to pump sodium out and potassium in, and to keep the ion concentration such that the red cells become neither too swollen nor too shrunken, and this pump depends on enzymes, including glucose-6-phosphate dehydrogenase, and the energy ultimately comes from ATP.

But if you interfere with the energy supply of this pumping mechanism, then you disturb the osmotic balance such that water may leak in and cause excessive swelling and, therefore, hemolysis. Some

individuals may be particularly prone to a loss of glucose-6-phosphate dehydrogenase when it is oxidized by primaquine or, in this case, presumably oxygen.

HELVEY: It does appear that the normal aging of the RBC cell is an oxidative process and the morphology of these cells, the Heinz body formations and others, appears to be similar to that in an aged cell. As a matter of fact, it is the older cells that usually are lysed when you have a hemolytic episode in the primaquine-produced situation, or even, say, aspirin-produced in a person who has an enzymatic defect.

FREMONT-SMITH: Do the senile RBC's swell up before they leak the hemoglobin?

SONDHAUS: No, they do not; they shrink.

FREMONT-SMITH: So, this is a different mechanism?

SONDHAUS: It appears so. At least, there is indirect evidence that the oldest red cells in a population behave differently with regard to sedimentation; some results that I once obtained seem to indicate that although the hemoglobin content is somewhat reduced, the cell size is reduced and the concentration per unit area is increased in the older cells, just as if they had shrunk into a shape approaching a sphere. In the final few moments of a red cell's life, in fact within a very short time, it does form into a sphere. I think this is fairly well accepted by now, but I am speaking of red cells which are not about to disappear, but are simply senescent and form part of the total population.

This is a very complex subject. It does seem as though some of this effect might possibly be explained by changes in the marrow itself, and changes in the production of cells, and one might not necessarily have to invoke a mechanical disruption or a breakdown of the cell membranes. We know, for example, that there is a polycythemia associated with high altitude in which the oxygen tension is lower. This is a stimulation of the marrow to overproduction. It certainly seems reasonable that in this case, increase in oxygen tension will reduce the proliferation of mature red cells by the marrow. One may simply be observing this effect.

HELVEY: This may certainly be true. But, considering the response time and the presence of the elevated bilirubin we could not "make a case" for this mechanism. In addition, on the half-atmosphere study, we did get bone marrows on the six fellows and they were active.

DUBOIS: As I understand it, your main conclusion is that this is not a suppression of the marrow but hemolytic anemia with hyperplastic marrow.

HELVEY: Hemolytic anemia with reticulocytosis.

BJURSTEDT: In these experiments, did you actually measure the

arterial oxygen pressure, or did you simply assume it was higher than normal?

HELVEY: We did measure P_{O_2}'s in arterial blood. As a matter of fact, Doctor Briscoe of Columbia University did that for us. We did them the day prior to the run, on the fifth day and on the last day, as I recall, and they were within normal range.

BJURSTEDT: What do you mean by "normal"?

HELVEY: The range which one would anticipate for the environment.

FREMONT-SMITH: So, they were appropriately elevated?

HELVEY: Yes, they were.

FENN: I can't understand why the 5 psi had no effect on the reticulocyte count and the 7 and 3 did. Is that right?

HELVEY: I believe there was an elevation of the 5, but not as great as the 7.

SONDHAUS: The elevation at 3.8 psi was somewhat higher.

HELVEY: The reticulocyte response for the 3.8 was the highest of all.

CALLOWAY: Did you use the same subjects in all of these runs?

HELVEY: No, we did not. We selected from a large group and had 28 subjects. We would bring seven in for a run, in case one was sick, and then go with six. These were four groups of six men.

DUBOIS: I think this is very exciting work and needs to be pursued. More experiments need to be done on it.

Atelectasis

I hate to stop this morning without saying something about atelectasis and acceleration, and perhaps a little about fire. Could someone else start off on atelectasis? How about Hermann Rahn; would you be willing to say something about this problem and get the ball rolling?

RAHN: What I know was recently published.[47] I can summarize by saying that the rate of collapse of alveoli distal to a blocked airway is about 60 times faster after breathing oxygen than after breathing air. If we now reduce the pressure to 3.5 psi breathing 100 per cent oxygen then the rate of collapse is 360 times faster. These changes in collapse rate are very large, indeed. Thus one would predict that any local interference in the normal gas exchange of the lung of an astronaut could quickly produce a local lung collapse. Such interference could be due to airway blocking by excess mucus production following a respiratory infection or mechanical lung compression during acceleration into orbit.

FENN: How fast is this collapse?

RAHN: This is shown on a slide (FIGURE 5) indicating the minutes

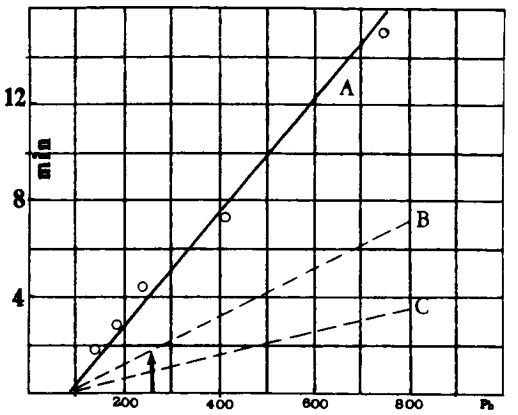


FIG. 5. Time for complete collapse of lung volume after breathing oxygen at various barometric pressures.

required after blocking an airway for producing an airless lung. The abscissa is the barometric pressure. Line B represents the condition for a normal oxygen consumption and a lung volume of 3000 ml. When oxygen is breathed at a pressure of 760 mm Hg, the time required for complete collapse of any or all parts of the lung is approximately six minutes. The arrow indicates that under similar conditions (line B) only two minutes are required at a barometric pressure of 258 mm Hg or 5 psi, the cabin pressure of Mercury capsule. If, on the other hand, the astronaut was exercising and consumed twice the average amount of O_2, then his condition is represented by Line C and the time for collapse is now reduced to half.

DUBOIS: I should think that the astronaut would be in some danger, if he absorbed this gas in his lungs of ending up with meat-like lungs.

RAHN: That's right. On the other hand we also find that you can reexpand your collapsed lung by a deep inspiration. Whether this is always accomplished easily I don't know.

FREMONT-SMITH: But then exercise, which requires much more deep inspiration than normal, would counteract the effect of which you are speaking.

RAHN: I would say so, yes.

FREMONT-SMITH: One of the things that is forgotten about is that during exercise the lung is in an expanded phase for a very much longer time than it is at rest. At rest, the lung is in an expiratory phase for a fairly large portion of the inspiratory cycle, whereas, in exercise—and apparently very little attention has been paid to this—the cycle shifts so that the lung is in an inspiratory phase a very much larger proportion of the cycle.

Anybody who just runs and notes his own breathing will be aware of that. In fact, there is little pause in inspiration during exercise, whereas there is a little pause in expiration during rest, which makes a lot of difference in the percentage of time in which the lung is expanded. This might be a significant point.

RAHN: I would like to comment about this. Both Doctor Hendler and Doctor Helvey have had subjects for many days in simulated space capsule conditions and have *not* noted pulmonary changes which can be ascribed to atelectasis. On the other hand, I like to show in TABLE 1 the figures reported by Green and Burgess[48] and further discussed by Rahn and Farhi.[47] These show large changes in vital capacity in fighter pilots immediately after flying missions in which they were exposed to about 1300 G seconds. Note that the loss of pulmonary function is very much larger when oxygen is breathed instead of air.

TABLE 1
PULMONARY CHANGES AFTER EXPOSURE TO ACCELERATION

	Breathing Air		Breathing O_2	
	No suit	With suit	No suit	With suit
Loss in vital capacity; ml. Average preflight vc = 5,400	349	790	1406	2179

Data from Green and Burgess.[48]

FREMONT-SMITH: It says "no suit" and "suit"; is that reversed?

RAHN: There were four identical mission flown on air and oxygen, with the suit and without a suit.

WOOD: This is an anti-G suit?

RAHN: Yes. I have arranged these in such a way as to show the increasing loss of vital capacity after the flight—350, 790, etc.

FREMONT-SMITH: So, the suit made it worse?

RAHN: Yes, the suit produced greater loss of lung function. Doctor Wood might be able to explain this. It is important to mention that these pilots all regained their full vital capacity within half an hour after landing their craft. Under these circumstances then you can re-expand your lung.

FREMONT-SMITH: In air? They didn't stay in pure oxygen?

RAHN: No, they didn't.

FENN: They should have been able to re-expand in oxygen equally well, with an equally big effort.

HELVEY: I don't know whether it was brought out here that G

loads were present in the aircraft and when this problem first arose it was on a centrifuge. At ACEL they did run folks on the centrifuge before and after maintaining them in this environment, but in our studies, we had no G loads and this may be a major difference.

I wanted to ask Doctor Rahn and Doctor Wood, particularly in the presence of this suit seeming to add to the problem, if the hydrostatic pooling of blood in the dependent portion of the lung may compete for the air spaces. This could perhaps explain why one would get atelectasis with G in oxygen but I was wondering, based on what Doctor Rahn just told us, if a Valsalva maneuver, of itself, even if it weren't in an aircraft, might be a contributor.

With a Valsalva, usually you have expired fairly far, though not necessarily, and then you sustain it. This is a voluntary or involuntary activity of people under G loads, of course. I wonder if you think that might be a major contributor, as well as the hydrostatic pooling of the blood.

RAHN: I will pass that on to Doctor Wood. I want to hear what he has to say.

WOOD: I think anything that increases the volume of the lung, Doctor Rahn would agree, would decrease the tendency for atelectasis. There are variations in the manner in which a Valsalva maneuver may be performed. If the maneuver is begun at the height of inspiration the lung is actually overexpanded. For the best type of antiblackout maneuvers, a type of Valsalva is carried out while continuously expiring and therefore with a continuously decreasing lung volume.

FREMONT-SMITH: Expiring against pressure?

WOOD: Expiring against pressure, yes. The test pilot when he does an anti-G maneuver yells nearly continuously. The yelling is an important feature since it necessitates keeping the glottis open so that air is continuously being expired and lung volume therefore decreases. It has been proved on the human centrifuge that a Valsalva maneuver done with a full chest is a very deleterious thing in relation to withstanding the effects of acceleration.[49] If a type of maneuver is carried out characterized by periods of continuous expiration against a partially closed glottis interspersed with very rapid inspirations, a high degree of protection against blackout due to positive acceleration can be attained.[49]

However, very probably, the atelectatic effects under discussion are not due to the Valsalva but are due to the fact that when an antiblackout suit is inflated, the level of the diaphragm is raised and a decrease in volume of the lungs occurs. This probably increases the susceptibility of the lungs to atelectasis as may the increase in volume of blood in the lungs which results from inflation of the suit.

BJURSTEDT: There is an increased volume of blood in the lungs, so

there would also be a greater tendency toward atelectasis. The Valsalva maneuver would in any case be an effective way of squeezing out some blood from the thorax and would accordingly tend to prevent the formation of atelectasis.

However, it just came to my mind that you could achieve the same thing, and perhaps more effectively, by having some small positive pressure in your mask to prevent accumulation of blood in the lungs. For if the subject is hyperventilating then the mean intrathoracic pressure might become so low as to retain blood in the thorax. It seems to me that this should be avoided, but I don't know whether any experiments along this line have been done.

RAHN: Have you tried continuous positive pressure breathing?

WOOD: Yes. At first blush it would seem that positive pressure breathing would be advantageous for this situation, but, really, the problem in the lung is due to the gradient of hydrostatic effects from above downward, and when you over-inflate the lung, you do it with air which has a specific gravity of practically zero. Therefore, although you can increase the mean level of pressure in the airway, you cannot prevent the hydrostatic pressure gradient. Very probably what happens when this is done is that the pressure in all body cavities increases almost in direct proportion to the increase in level of the airway pressure. As a matter of actual fact, in experiments in healthy men, pressure breathing has not prevented the drop in arterial oxygen saturation, that is, the supposed pulmonary arterial venous shunting due to the effects of acceleration.

In a certain percentage of subjects, pressure breathing does give a feeling of greater subjective comfort. However, such subject show a decrease in arterial oxygen saturation of about the same degree as in exposures without pressure breathing.[4]

DUBOIS: Also, I think they have a decrease in vital capacity after the procedure is over, don't they?

WOOD: Yes.

BJURSTEDT: I agree that you don't change the hydrostatic gradient, but if you are talking in terms of atelectasis or the amount of shunting, one would surmise that some small positive pressure would act to prevent such collapse in the dependent portions of the lungs as could have been created by negative pressure and concomittant suction of blood into the lungs. However, this obviously must await further investigations.

WOOD: There is no evidence at present that this helps any. In fact, there is evidence that it doesn't help.[4]

BJURSTEDT: On the other hand, if you don't use the G-suit during headward acceleration, the arterial desaturation will not, as you know, become as pronounced as with the G-suit inflated. You shift some

blood from the pulmonary to the systemic circulation, and that is exactly what is accomplished when positive pressure is applied.

WOOD: I do not think that you can consider the G suit and the Valsalva together. These are two different things. I think because the G suit makes it worse is no evidence that the Valsalva will make it better.

BJURSTEDT: Perhaps not; it remains to be seen.

FREMONT-SMITH: If I understand it (and I am not at all sure I do), the G suit tends to push blood into the thorax; is that right? If this is correct, then it seems to me it would be possible to use the multiple tourniquet technique of accumulating, in spite of a G suit, blood in the limbs to a limited extent and compensating for this.

As you know, in pulmonary edema the technique which works extremely well is multiple tourniquets on the four limbs, taking off one at a time, and you can sometimes control pulmonary edema very rapidly, as I have seen done under this circumstance. It would be conceivable that you could have a G suit that would give you the pressure and at the same time have additional tourniquet action on the four limbs, and keep an accumulation of several hundred cc. of blood in the limbs. I throw this out as a possibility.

ROTH: What the G suit is trying to do is to prevent the tourniquet effect, to keep the blood out of the limbs in $+G_z$ acceleration.

FREMONT-SMITH: But you are telling me that the G suit is putting more blood in the lung, and this is bad.

DUBOIS: It has come full circle. The first G suit was designed to get blood from the periphery back to the lungs. Now they are suddenly worried about the lungs and have decided it would be better to let it go in the periphery, to prevent these changes within the lung from occurring, even though there might be some decreased cardiac output as the result of that. Here you are in a balance between two limiting factors.

ROTH: How much of it is blood and how much of it is organs being shoved up into the chest?

WOOD: With the G suit, I think it is as much the diaphragm going up as blood going in.

HENDLER: The G suit is certainly there to prevent blackout, which seems to me a lot more serious.

DUBOIS: Yes, but now instead of having a G suit with a man in a sitting position, they have gone to a man in a supine position with no G suit. Not only are they supine, but they are supine with their legs up in the air.

FREMONT-SMITH: The tourniquet might help.

WOOD: We have some direct evidence in that regard on the centrifuge. We were concerned with the possibility that an increased

amount of blood in the lungs might make the effects of acceleration worse as far as arterial venous shunting is concerned. Two types of experiments have been done, one of them in humans. A series of humans were run in the standard Mercury couch position in which the legs are flexed to 100 degrees on the thorax and the knees 100 degrees on the thighs. Then in the same subjects the support was removed from underneath the legs and their legs extended horizontally. The legs-extended position should avoid the accumulation of blood in the chest due to increased venous drainage from the legs. The exposures were repeated in this position and no difference was demonstrated. That is, the same degree of arterial desaturation occurred with the legs flat out as that which occurred in the same subjects in the standard Mercury couch position with the legs up.[4]

Another series of experiments was carried out in a series of eight dogs (who, parenthetically, have about the same degree of arterial venous shunting as does man, probably because they have the same depth of chest) exposed to transverse acceleration in the supine position in three different positions—first horizontal, second with their body tilted to an angle of 15 degrees head-up, and third with the body tilted 15 degrees in the opposite direction, head-down. Although there were some differences in other variables, as far as the arterial venous shunting was concerned no systematic difference was demonstrated between these three positions, one of which should have increased the blood in the chest and another of which should have decreased it.[5]

FREMONT-SMITH: How do you account for this?

WOOD: I do not know. We rather expected to see some differences in these dogs but it was not demonstrated.

Fire Hazard

FENN: I want to go ahead right now with discussion of the problem of fire hazard. Doctor Hendler has to leave and he is one who has had experience with this and we must discuss it while he is here.

This problem of fire hazard is, I suppose, the most important practical consideration in the selection of an atmosphere for use in capsules.

While it isn't our business to decide what atmosphere we should use, we at least ought to have this before us in thinking about it; so, therefore, I would like to ask Doctor Hendler to give us his experience with fire hazard.

HENDLER: In November of 1962, in accordance with a contract with NASA, we conducted a study at our laboratory in which six subjects were exposed to a simulated Project Gemini profile.* Of

*Supported by the National Aeronautics and Space Administration under Defense Purchase Request T-9753-G.

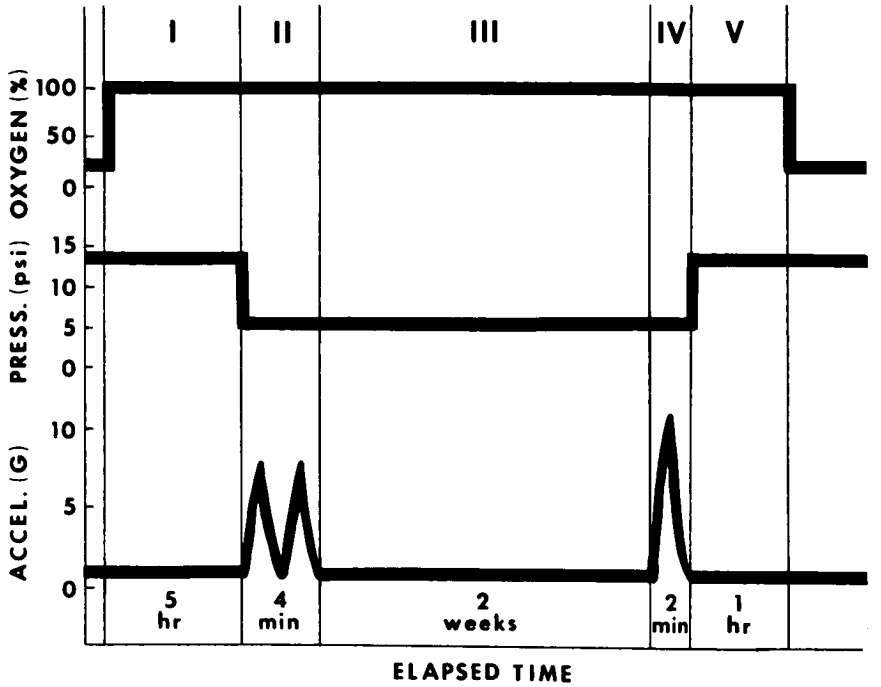


FIG. 6. Diagram of simulated orbital flight conditions. Phases: I—prelaunch; II—launch; III—orbit; IV—re-entry; V—post re-entry. Actual experimental conditions deviated somewhat for each exposure from those indicated in the diagram. (From Dubois *et al.*, 1963.[72])

course, we didn't simulate the weightless state during the orbiting period, but out study was unique in that we did simulate the launching and re-entry acceleration, as well as a two-week exposure to 100 per cent oxygen at 5 psi pressure.

FIGURE 6 shows diagrammatically the sequence of the main parameters involved in our study. During phases I and II, the subjects wore full pressure suits. These were the Mercury-type pressure suits, in contrast to Navy suits. In the latter, a face seal separates the respiratory portion from the remainder of the suit. The suit is ventilated with air, while oxygen is provided for breathing within the face enclosure. The Mercury-type suit forms a single, gas-tight compartment around the body. Oxygen is fed into an opening on the side, is used both for ventilation and breathing, and exits from a port on the helmet.

After donning ECG electrodes, long underwear, and the pressure suit, the subject was preoxygenated during Phase I. Because of the logistics involved, we could handle only one subject each day. To

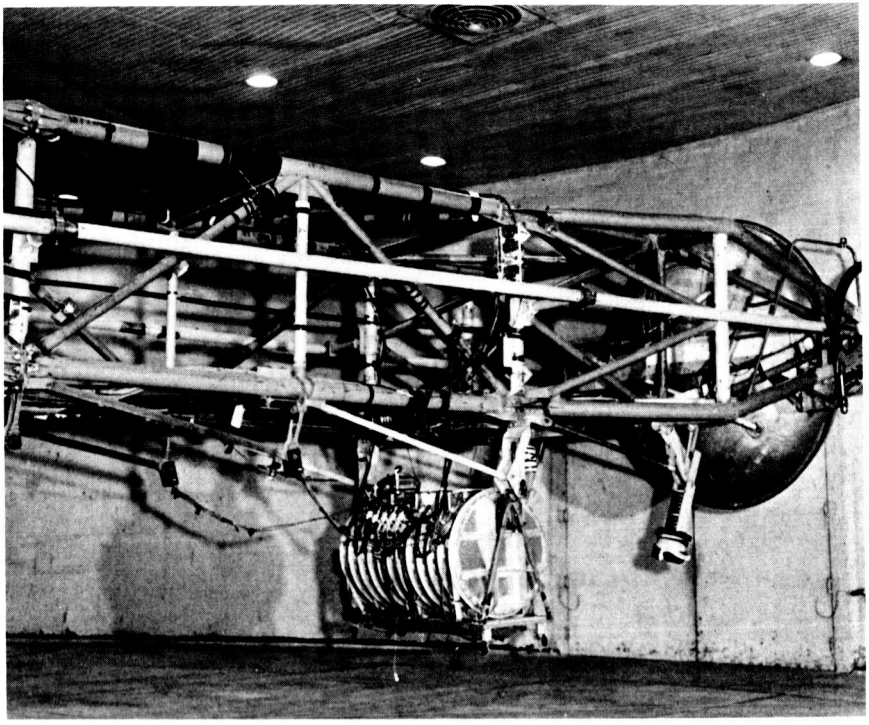


FIG. 7. Portable altitude chamber in which subjects were transported between laboratories and were exposed to centrifuge accelerations. View shows chamber suspended from AMAL centrifuge arm.

preclude scrubbing a day's work, we had a standby subject who underwent the same treatment as the principal subject, up to the beginning of Phase II. In no case was it necessary to replace the selected subject on a given day with his standby.

In order to apply the accelerations shown in Phase I I and IV, we used the Navy centrifuge of the Aviation Medical Acceleration Laboratory located in Johnsville, Pa. To get from our laboratory (ACEL) in Philadelphia, to the centrifuge in Johnsville, and back, the subject was transported in a specially outfitted truck. The distance between these two places was about 60 miles. While the subject was preoxygenating (breathing pure oxygen) in his suit during Phase I, he was taken to Johnsville. He then entered a small, portable altitude chamber (PAC), which had been mounted on the centrifuge arm and which was then evacuated to a pressure of 5 psi (see FIGURE 7). This began Phase II, during which the supine subject was exposed to two acceleration pulses of about 6.8G each. The PAC was then detached

from the centrifuge and returned, with the subject within, to our chamber at ACEL. The subject entered our chamber, removed his suit, and spent 2 weeks in an atmosphere of 100 per cent oxygen at a pressure of 5 psi. These same conditions were maintained when the subject re-entered the PAC, after donning the pressure suit at the end of Phase III, for transfer back to the centrifuge and exposure to the single 11.2G pulse of Phase IV. After recompression to sea level pressure, the subject continued to breathe 100 per cent oxygen while an arterial blood sample was obtained. The schedule was arranged so that each of the six subjects began the test sequence of FIGURE 6 on the morning of the day following his predecessor.

Various procedures were employed before, during, and after the test sequence to gauge the physiological status of the subjects.[46] Suffice it to say here that no permanent adverse effects were detected that could be attributed to the test sequence. Observed visual changes probably should have been discussed under oxygen toxicity, but they constitute an interesting finding coming out of this work. Briefly, it was found during this study, and confirmed by some preliminary, double-blind experiments at sea level and altitude, that high tensions of oxygen in the respired atmosphere produce reversible loss of peripheral scotopic visual sensitivity. We have proposed to NASA that this matter be looked into in a more thorough manner, and we are awaiting their reply.

FIGURE 8 shows a model of the chamber at the Aerospace Crew Equipment Laboratory in which the subjects lived for two weeks. A unique feature of this chamber is the fact that it consists of one gas-tight chamber located within a larger gas-tight chamber. By evacuating the space around the inner chamber to a pressure somewhat below that within the inner chamber itself, leakage from the inner chamber must be outboard. This is an important factor in the maintaining a given gas mixture in the inner chamber containing the subjects. Unfortunately, we were unable to maintain a 100 per cent

FIG. 8. Model of altitude chamber at Aerospace Crew Equipment Laboratory in which subjects spent two weeks to simulate orbital period of Gemini profile.

oxygen atmosphere, since our nitrogen analyzer showed that there was between one and two per cent nitrogen at various times during the run. Although we made extensive tests for leaks, we were unable to locate any particular spot where nitrogen could be entering and contaminating our oxygen supply. We used liquid oxygen as the source of the gaseous oxygen that supplied that atmosphere of the inner chamber.

The inner chamber of FIGURE 8 is entered through a lock and is subdivided into three compartments; a living compartment for food preparation, recreation, bathing, etc; a sleeping compartment containing three bunks; and a work compartment in which the subjects performed tasks and were examined by a flight surgeon. One flight surgeon remained in the chamber during the entire test period, assisting the subjects in donning and taking off their pressure suits, and, with the assistance of another flight surgeon, performing physical examinations. These included making measurements of vital capacity, making arterial punctures, and obtaining chest X-rays. The latter were obtained with the X-ray apparatus located outside the chamber, but shooting through a small aluminum port on the side of the inner chamber.

All of the preceding was by way of introduction to a dramatic and unpleasant end to our study. After three subjects had completed the entire test sequence and were, therefore, out of the chamber, a fire occurred. Three subjects and the flight surgeon still remained in the chamber, however. Apparently one of the subjects in the lower bunk, noting that there was no light coming from the fixture located on the bulkhead near his head, attempted to remedy the situation. When he had opened the aircraft-type light fixture, he reported seeing a small, bluish flame. I'm not too sure of the details of this, because it was difficult to find out later exactly what happened and in exactly what sequence. He notified the others that there was a flame in the fixture and requested something to put it out with. Someone handed him a towel, which had been in the oxygen atmosphere for quite a while, and he attempted to smother the flame, which had apparently grown somewhat in length. At this, the towel burst into flames. The flames, of course, spread rapidly from the towel to the clothing, to the bedding, and practically enveloped the entire area. Fortunately, the people on the outside were well aware of what to do in case of an emergency like this, and the people on the inside acted magnificently, I think, under the circumstances.

There was an attempt made by the flight surgeon to put out the fire on some of the clothing of one of the people; he wrapped an asbestos covering around the man, but this had very little effect. It just seemed that it was almost impossible to control the fire under these circumstances.

They beat a hasty exit through the narrow hatchway into the lock.

RAHN: May I interrupt? You told me once (which I thought was very impressive) about the hands. I think this is a very interesting observation.

HENDLER: Yes. One of the subjects mentioned the fact that something that had melted and was still flaming dropped on the bunk beside him and his natural reaction, of course, to put out the fire was to put his hand over this burning mass. He said when he did this and removed his hand, the flesh of his hand seemed to be flaming. I don't know whether this was because of the material that was burning had adhered to his hand or whether the tissue had become so saturated with oxygen that this, in itself, was burning. It is not too clear, but he started to strike various parts of his body, and of course over those parts he did have clothing so this spread the fire around.

As I say, fortunately, they did get out through the lock, and when they closed the door behind them the chamber was immediately taken up to the highest altitude it could be taken and then recompressed, allowing air to flow in; this put the fire out in the main chamber.

The people themselves were taken out, given cold showers, and then taken to the Philadelphia Naval Hospital located nearby. Most of the burns were superficial, although they covered fairly large areas—up to about 20 per cent of the body surface. In some cases they were second degree burns, and the flight surgeon himself suffered the most. I think he required some skin grafts on his legs.

All of the subjects have since recovered, including the flight surgeon. The possibility of this type of event occuring must certainly be kept in mind when 100 per cent oxygen atmospheres are considered.

There was a formal investigation, of course, of the whole matter, and, as a result of that, various modifications were recommended for our chamber. In fact, we haven't gotten around to making another run in the chamber yet because of the changes that are in the process of being made. These changes will, in effect, remove just about everything capable of initiating a fire from the interior of the inner chamber. The ventilating system in the chamber is also being modified to minimize accumulation of smoke near the exit hatch, if a similar situation should ever arise in the future. Fire under these conditions of high oxygen concentrations with little or no inert gas is an ever-present threat. The Air Force in a previous study involving two people—Bill, do you remember if that fire also occurred under the same conditions at 27,000 ft.?

HELVEY: I believe it was, with the two fellows in pressure suits.

RAHN: That was at 33,000 ft., the same oxygen pressure as in this room.

HELVEY: Didn't they have a previous one at a different level? I don't know what level it was.

ROTH: That was seventeen, I believe.

FREMONT-SMITH: Did they make a decision in your case as to what started the fire? Was it that light bulb, a short circuit in behind the light bulb, or did he take the light bulb out of the socket?

HENDLER: Yes, it was actually removed.

FREMONT-SMITH: And then he saw the flame?

HENDLER: He saw a small, blue flame.

FREMONT-SMITH: Is it understood why there would be a blue flame when you took a socket out under those circumstances?

DUBOIS: The version I heard was that somebody saw that the light socket was empty; there was no bulb in it, and when he put the bulb in, there was arcing between the wires, and that is when the flame occurred—it was when the circuit was made.

FREMONT-SMITH: It wasn't when he had it out, but when he was putting it in ?

DUBOIS: Yes. It wasn't clear whether there had been a bulb in there before or what happened to the original bulb.

HENDLER: I think he also reported hearing a clicking sound which attracted his attention to this socket. I haven't read the official record recently, but there were sort of conflicting statements involved here and it was rather difficult, actually, to determine exactly what happened in exactly what sequence.

I think we can't rely upon the individual to do very much. In other words, I think we should try to supply everything for him that he will need, and if possible, to have it work automatically. Doctor Roth has reviewed all of this literature, and he can perhaps add something to this.

ROTH: After these fires broke out, we were asked by NASA to review the problem of burning in space vehicles;[51] i.e., the zero G, oxygen, inert gas problem. Our first attempt was to contact the Fire Underwriters, who supposedly know about these things. We found that they knew about fires under air conditions and apparently hadn't spent much time thinking about 100 per cent oxygen environments, so we spent three or four months reviewing the physics of burning, the inert gas problem, the problems of zero gravity in flame propagation and the inerting of flame, fire extinguishing and the design of vehicles so as to eliminate as many of the fire hazards as possible.

Most of the material came from the combustion engineers whose point of view is entirely on increasing fires rather than decreasing them, but they had a pretty good handle on the inert gas problem and I was amazed to find what a wealth of literature there was on all aspects of inert gas. I have selected several slides that give some in-

sight into the problem by giving a quantitative sense of how much more dangerous a fire is under these circumstances and how the various inert gases might play a role. If you are going to select an inert gas, which inert gas should you choose to keep these dangers to a minimum?

The fire problem has to be divided into five or six different categories, all of which, unfortunately, have quite different effects in terms of inert gases and oxygen.

One has to think of the ignition process, the quenching process immediately after ignition, the inflammability limits, what concentration of fuel and oxygen will support a flame under various partial pressures of oxygen, the various rates of propagation of flame which the combustion engineers think are most important, the susceptibility of flames to free radical extinguishment and water extinguishment, the conversion of a deflagration or slow-burning process to an explosion or to a detonation where a shock wave is involved. All of these things are involved, and we have a report that will be published within the next month on this entire problem.[51]

As far as ignition goes, these are the things one has to worry about: electrostatic or induction sparks, acute deflagration; the actual detonation of sharp points—if you drop a sharp-pointed instrument in an area where there is a potential gaseous combustible, you can get flames. High sheer rates can give hot spots. Other factors in ignition are heated gases; the adiabatic compression that occurs when oxygen is suddenly let into a valve that has oil in it as a possible contaminant; heating by shock waves; and, finally, hypergolic ignition in which you have two fluids that, when mixed, will give you a flame—this is a rocket propellant problem. I don't want to dwell on any of these. They have been thoroughly studied in other systems.

Here is the fire problem (FIGURE 9) in terms of minimum ignition energy required to initiate a linear propagation of a flame with various percentages of propane from 0 to 50 per cent under various indices of oxygen. The oxygen index is the ratio of oxygen to oxygen plus nitrogen. If you compare air at one atmosphere with pure oxygen at a third of an atmosphere, you have more than an order of magnitude of difference and greater than the minimum spark energy required to ignite the former than to ignite the latter. These families of curves hold true for almost every hydrocarbon system that I have been able to get hold of.

If you compare air at one atmosphere to air at one-half an atmosphere, you will see that the former requires almost an order of magnitude higher energy. I think that this gives you a pretty good feel for either homogeneous gaseous mixtures or mists of liquids, like hydraulic

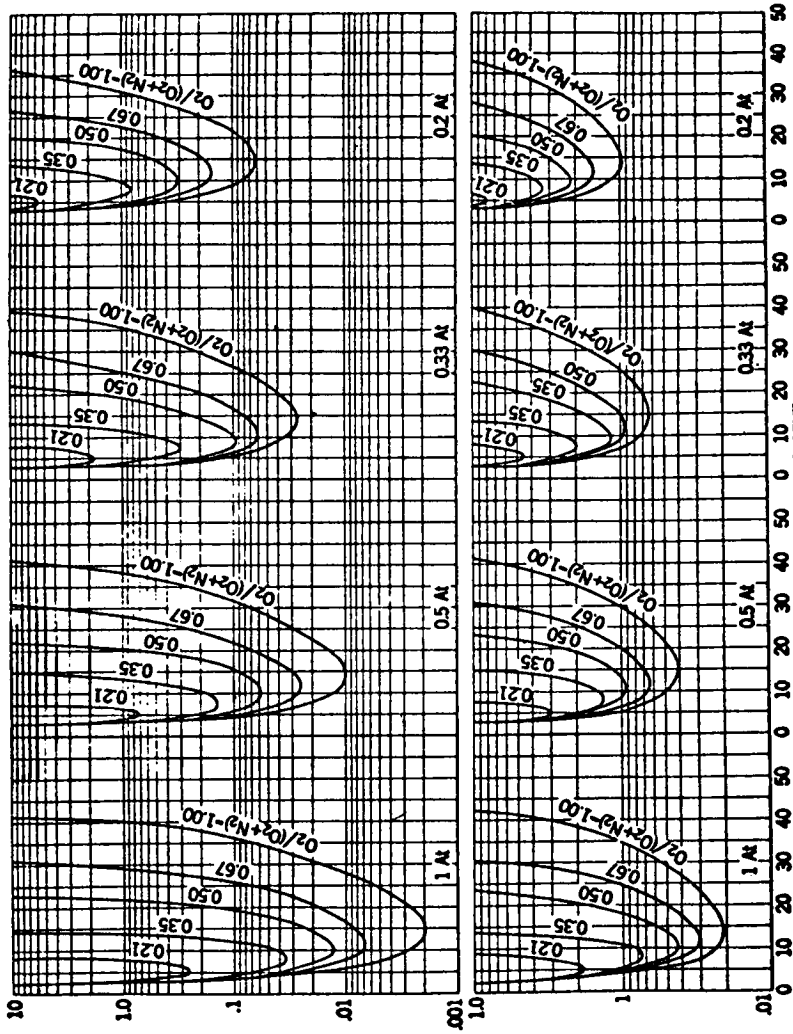


FIG. 9. Minimum spark ignition energies in millijoules of propane, oxygen and nitrogen at one atmosphere pressure and lower, and quenching distances between flanged electrodes for the same mixtures. (After Lewis & von Elbe, 1951.[52])

fluids, ejecting from a disrupted line. These will give you essentially the same sort of ignition curves.

The quenching distance follows essentially the same pattern, quenching distance being the distance between two heat sinks in which a spark is generated in this combustible system. You see the same family of curves holds. Lowering the pressure helps in terms of your minimum ignition energy. I fear that 100 per cent oxygen at one atmosphere would require two orders of magnitude less energy to initiate a combustion sequence than would one atmosphere of air.

There are many, many parameters in the ignition problem and the burning problem. TABLE 2 summarizes the effects of the different inert gases. I have quantitative figures on all of these if you want them, but

TABLE 2
SUMMARY OF EFFECTS OF INERT GASES ON FLAME PROPAGATION*

In reducing burning velocities	
	$CO_2 > N_2 > A > He$
In decreasing composition range for imflammability	
Wide tubes	$CO_2 > N_2 > He > A$
2.2 cm diam	$CO_2 > He > N_2 > A$
1.6 cm diam	$He > CO_2 > N_2 > A$
In increasing minimum spark ignition pressure	
$(H_2 + O_2)$, low pressure	$He > A > N_2 > CO_2$
$(H_2 + O_2)$, high pressure	$CO_2 > N_2 > A$
$(H_2 + N_2O)$, low pressure	$He > CO_2 > N_2 > A$
In increasing minimum spark ignition energy	
$(H_2 + O_2)$, atmos. pressure	$He > CO_2 > N_2 > A$
$(CH_4 + O_2)$, atmos. pressure	$He > N_2 > A$
In increasing quenching distance	
$(H_2 + O_2)$	$CO_2 > He > N_2 > A$
$(CH_4 + O_2)$	$He > N_2 > A$

*After Mellish & Linnett.[53]

I think we will just get a general feel for how the physical parameters modify the actual effects of the inert gasses.

Here you have in a wide tube, CO_2 better than nitrogen, better than helium in decreasing composition range for flammability. Some of the differences in this chart may be of an order of magnitude, and all of these are more or less explainable in terms of burning theory.

This might seem like a hodgepodge, but I point out how difficult it is to say that one gas is better than another in a fire. The spark ignition energies, quenching distances, and spark ignition pressures vary all over the lot.

Argon and nitrogen are poor only in some conditions. In many cases nitrogen seems to be the best of the potential oxygen diluents.

FREMONT-SMITH: Seem to be the best to quench?

ROTH: Right. Most of the studies in inert gases have been done primarily to answer the basic problem of what controls the rate of burning in a system. Jet engine designers and rocket designers are all interested in this particular problem. The big controversy for the past 20 years has been whether diffusion or thermoconduction or heat capacity at the flame front determines the actual rate of propagation. Here is an equation that was put together from a lot of work, mostly by the Russians Semenov, Zeldovitch, and Frank Kamenetsky, who have been instrumental in really defining the theoretical basis of burning.[54]

$$u_f = \frac{RT_o}{P} \sqrt{\frac{2\lambda_f}{X_f C_p} \frac{\int_o^{Tf} \omega \, dT}{T_f - T_o}}$$

where P = pressure, T = absolute temperature, X_f = mole fraction of combustible in the unburned gas, λ_f = thermal conductivity at the flame temperature, $\overline{C_p}$ = molar heat capacity, ω = chemical reaction rates, (o) subscript = initial, (f) = final.

As you see (I don't want to dwell on the equation), the rate of burning here is inversely proportional to the square root of the mole fraction of combustible in the unburned gas and the molar heat capacity and is directly proportional to the square root of thermal conductivity at flame temperature. What you have to do is plug in all factors with the appropriate gases and work it out. This is for a purely homogeneous gaseous system.

When you get into the burning of liquids and solids, things change all over the lot, but these are the model systems we can use.

Here is a study done on the burning velocity in Bunsen-type flames (see FIGURE 10), and these are the types of studies in which you can get the best quantitative feel using various gases. Here is per cent methane with 20 per cent oxygen and 80 per cent of the different inert

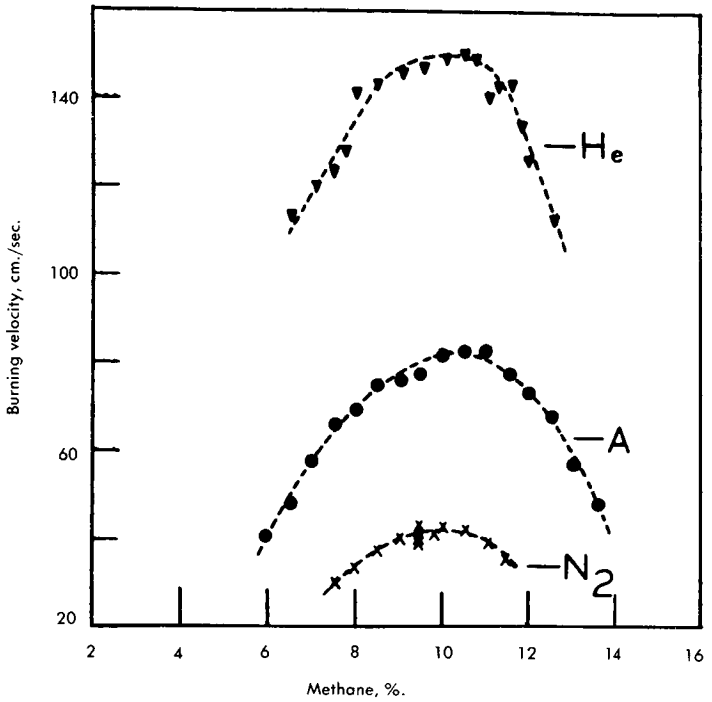


FIG. 10. Burning velocities of methane at atmospheric pressure. (After Clingman & Pease, 1956.[55])

gases, and here you see the helium is the worst, argon next, and nitrogen quite a bit better. This is the pure propagation of flame in a Bunsen burner system, and the actual flammability peak in terms of per cent methane doesn't really vary too much. If you take these burning ratios as Clingman and Brokaw[56] did and insert them into the various equations that might explain burning, it seems that the thermoconductivity and heat capacity factors control these ratios and not the diffusion.

Just to get into solids and give you a feel for the solid problem, the British Fire Research Station at Boreham Wood[57] has done the most sophistocated studies on the burning of fabric solids. They have tried various fire retardants under various concentrations of oxygen (see FIGURE 11). It became obvious in the welding industry, where they had high levels of oxygen and combustibles near fabrics, that they were getting into problems they hadn't expected, and this study was generated by this particular practical problem.

The closed circle represents the fresh fabric. As you increase the oxygen with nitrogen decreasing proportionally, you have a diphasic

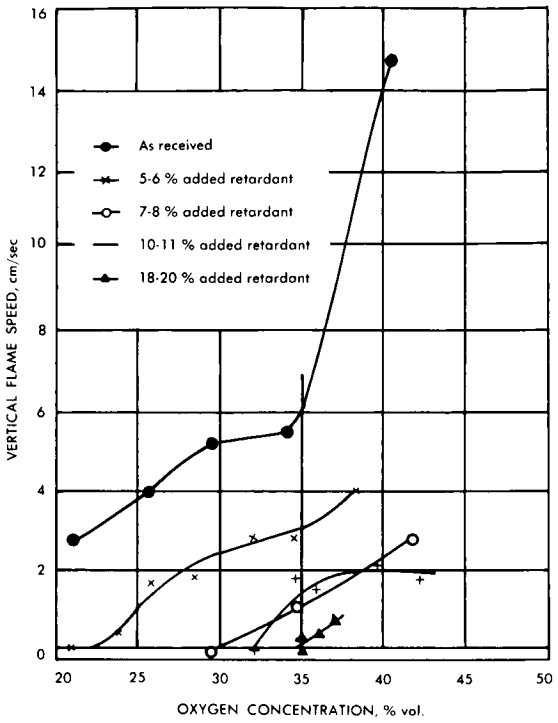


FIG. 11. Effect of oxygen enrichment on flame speed of white drill treated with 70% borax and 30% boric acid. (After Coleman, 1959.[57])

type of situation and once you get around 35 or 40 per cent oxygen you really get a whopping flame that is blue in color, quite intense, with three or four times the burning rate of flame at 21 per cent.

As you increase the per cent retardant, and in this case boric acid or borate mixture was used and proved to be the best one—here even in a case where 18 to 20 per cent of the weight of the fabric was retardant, once you reached 35 per cent oxygen you began increasing flames. Here where only five or six per cent was added, at 30 per cent oxygen, your flame speed was already manyfold greater than the basal condition, so that the whole problem of fire retardants has to be reexamined in view of the elevated oxygen conditions. I heard recently that NASA has granted several contracts for work along this line.

FIGURE 12 includes some data that Klein presented.[58] The data from the studies of Clamann, Simons, and the other fabric studies I could find fit as well. FIGURE 12 compares the ratio of burning rate, at a given test condition to the burning rate in a typical aircraft cabin at 8,000 ft. altitude. In other words, what I want to do is compare the present burning problem we have in jets with the rate of burning of

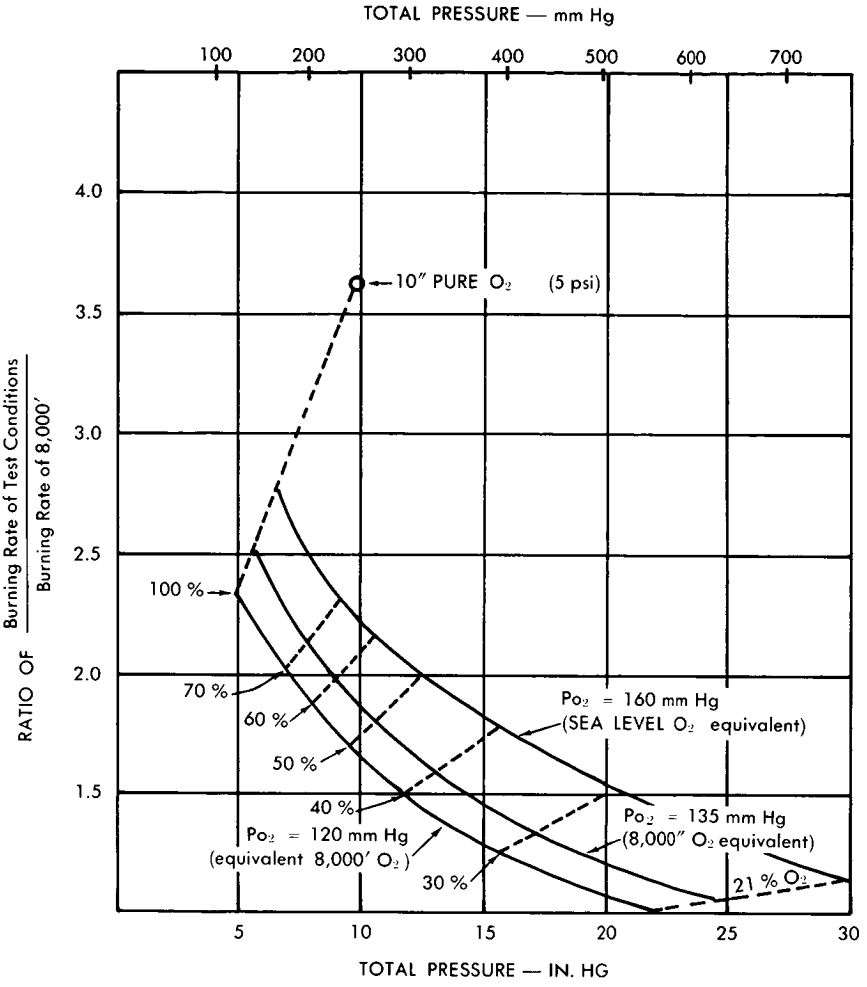


FIG. 12. Effect of atmosphere combustion and pressure on burning of cotton fabric. (After Klein, 1960.[58])

fabrics in other situations. The bottom abscissa is the total pressure in inches of mercury. The top abscissa is the one that Klein used and is in millimeters of mercury. The solid *lines* here represent fixed P_{O_2} equivalents—in other words, you are decreasing your nitrogen as you go up this slope. Also, you are decreasing your inert gas component.

The dotted *lines* here represent fixed levels of oxygen. Now, let's compare the 100 per cent oxygen at 5 psi with an 8,000 ft. cabin situation, and here you see the rate of burning is 3.7 times greater in the former. That is, if you take a fabric and ignite it, it will burn 3.7 times faster in a Mercury capsule-type of environment than it would in a

standard jet cabin, and you go up and down the upper *dotted line* for changing total pressures of 100 per cent oxygen. These points come from fabrics, paper, all sorts of solid textile hydrocarbons of that type.

As TABLE 3 indicates, hydraulic fluids are not as susceptible in liquid form to changes in altitude and oxygen, but there is a noted difference. If you take any one of these particular fuels under various conditions, you see there is not too much of a change. What does cause dramatic change is the misting of fuels. During the war there were many, many explosions in naval gun turrets, for instance, when hydraulic lines burst after shell penetration. These explosions were all on a mist basis. Petroleum companies actually test their hydraulic fluids by determining the minimum concentration of oxygen required to make an explosive mixture in a misted fluid, so that the problem is not too severe in terms of the liquid itself but the destruction of a fluid line does create a problem that parallels very closely the one that showed in FIGURE 9 that represented the propane gas.

TABLE 3
COMPARATIVE IGNITION TEMPERATURES OF AIRCRAFT FLUIDS

Chamber Condition	Ignition Temperature (°F)						
	Fluid A	Fluid B	Fluid C	Fluid D	Fluid E	Fluid F	Fluid G
850′ alt.	910	970	--	895	--	--	--
5,000′ alt.	950	1010	1015	935	955	1095	990
10,000′ alt.	1010	1065	1025	985	975	1115	1050
15,000′ alt.	1100	1100	1045	1040	1000	1130	1090
20,000′ alt.	1200	1120	1090	1090	1025	1145	1125
25,000′ alt.	--	--	--	1140	1045	--	1145
10″ O_2 5 psi.	1060	820	725	575	940	935	505
8″ O_2 4 psi	--	920	975	790	980	975	550
6″ O_2 3 psi	--	1010	1090	980	1005	1040	675
4″ O_2 2 psi	--	1080	1185	1125	1030	1135	1020

A. Hydraulic Fluid - Petroleum Base - MIL-O-5606
B. Aviation Fuel - JP-4
C. Lubricating Oil - MIL-O-7808
D. Hydraulic Fluid - Oronite (MLO 8200) (93.38% Disiloxane, 4.6% Silicone)
E. Hydraulic Fluid - Methyltetrachlorophenyl (G. E. # 81644)
F. Hydraulic Fluid - Disiloxane - Ester Blend - MIL-H-8446A (78.68% Disiloxane, 4.3% Silicone, 15% Di (2-ethylhexyl) sebacate)
G. Naphthenic Mineral Oil-MLO-7117

I have many more slides if anyone wants to look at them, but I won't dwell on this particular point other than to say that zero gravity factor has been brought up as relevant to the extinguishment of the flame. I went through all the equations in which gravity was a factor, and in one of them could one extrapolate to zero. The problem of zero gravity, of course, is twofold: One, in the ignition process, there is a disadvantage at zero gravity because under any ignition source zero gravity decreases the convection of heat away from that source. Thus, the focal temperature, the critical thing in the initial ignition, is increased by zero gravity.

As you get on to the flame propagation problems you run into several factors that are involved. I have discussed these with many of the rocket combustion engineers, and there is still no good answer. Ordinarily, you think of convection as helping the flame by providing new oxygen and new fuel to the mixture, and diffusion as really not playing much of a role. There is also the problem of removal of the products of combustion. Here expansion of the gases by thermal products is a factor that is not gravity dependent. So, you are bucking one against the other.

I reviewed the data on propagation of flame in horizontal directions versus vertical directions, and at most there is a negligible constriction in the flammable range of hydrogen air flames in horizontal propagation. If one compares the theoretical flame propagation parameters in 1g vs 0g, one finds in the latter case, propagation is reduced by a factor of two at the very most. But, I must remind you that these effects are very specific with respect to the system in question: how significant convection is in the total combustible oxygen system, a pool or a mist of burning liquid; whether it is a homogenous or heterogenous condition, a mist or pure gaseous system, these are problems that should be explored. These parameters vary by almost one order of magnitude of the hypothesized gravity effect, and in this report I have gone into detail on each one of these systems, trying to analyze the generalized problem.

We also reviewed the problem of meteorite penetration. When a meteorite penetrates the cabin it actually melts a hole through the wall. All of the recent penetration equations are simply melting equations. You get a mist of liquid metal coming into the cabin and a short-lived flash. Chuck Gell at Ling-Temco-Vought Corporation in Dallas,[59] General Dynamics/Astronautics in San Diego,[60] and the NASA Laboratories at Huntsville, Alabama[61] have done some very nice studies. One hundred per cent oxygen will increase the intensity of the flash, but not more remarkably than one would probably expect from reviewing the pure gas combustion systems.

A minimum penetrating particle passing through three one-

hundredths of an inch aluminum into an air-filled cabin, for instance, will give you a flash equivalent to two GE # 5 flash bulbs, if you calculate the lumens, and 100 per cent oxygen at 5 psi increases the flash only by a factor of two or three. If Gell used glass particles, he could get up to 33,000 ft. per second, which is well within the meteorite velocity range. The particles melt their way through and spew out a spray of molten metal that then gives a flash area in the cabin. A particle that will just penetrate 0.03 inches of aluminum will give a flash area eight inches from the wall so that only a person seated this close to the wall or closer stands a chance of being exposed to serious flash.

We have calculated the cabin blast pressures. These are quite low relative to the pressures required for lung blast damage in humans. A big problem, however, is the blinding of individuals in that these are very intense light flashes. I reviewed data on nuclear blast and flash hazards and found that you could get a blindness that lasted about a minute and a half with a light intensity of this type. There is no retinal burn problem; the flash is somewhat below the retinal burn threshold. This blindness, lasting a minute and a half, as we have indicated, can be modified by the usual procedure of increasing the illumination of the background, as with lighting flashes in aircraft, making sure that in the hazard situation the eyes are as myotic as possible.

FREMONT-SMITH: Is this an after-image blinding?

ROTH: This is a glare-type blinding that you get.

FREMONT-SMITH: Is the person blinded by the persistence of the after-image?

ROTH: Yes, there is a white sheen in front of you.

FREMONT-SMITH: On the way out to Bikini, I did an experiment for Stafford Warren which showed that if you closed one eye, the after-image is only in the eye that is exposed and you can see clearly through the other eye.

ROTH: Yes. Actually, the background is quite important in recovery. You must remember these figures are for very minimum penetrating particle. If you are talking about larger particles, I have equations that scale this whole thing up to different particle masses, so we have a pretty good idea of what to expect.

If you review the meteorite hazard, however, you will find that in the past two years, the hazard has been decreased by a factor of three thousand. I recently communicated with Doctors Whipple* and Hawkins† of the Smithsonian Astrophysical Observatory about this

*Whipple, F. L., 1963, On Meteoroids and Penetration. Paper presented at the Interplanetary Missions Conference, American Astronautical Society.

†Hawkins, G. S., 1963, Personal communication, Harvard Observatory, Cambridge, Massachusetts.

reduction. Their figures have decreased through several mechanisms. One, they finally have a good handle on the luminous efficiency of meteors. As they come in, they flash and the mass-frequency analysis has been done previously on flash data. What investigators did recently was shoot an iron ball out of a rocket and have it re-enter and measure the luminous efficiency of an artificial meteor; this knocked the frequency down by a factor of one thousand. In other words, they were overestimating the intensity of light that a given mass would produce.

The new penetration studies have decreased the penetration hazard by another factor or two or three. I have been in contact with the industrial people working on meteorite bumpers and find you can save weight by dividing the wall into a bumper and wall and separating the two by a space of eight or nine bumper thicknesses.

The current figures for meteorite penetration frequency of a cabin three meters in diameter and wall of 0.03 inches aluminum (Whipple used these numbers in his early calculations), within 500 miles of the Earth's surface, is about once every 23 years.

Actually, there has been a lot of tiny pepperings of glass surfaces from meteorites; these have been found in rockets, but the only serious pitting has been of an Atlas booster body, a huge piece that somehow made it back and landed in Africa. General Dynamics/Astronautics has the piece. It has a surface of a square foot with peppering of classic meteorite-type. You can calculate the depth/width ratio and show that it must be a hypervelocity particle doing it. This may have run into a shower of meteorites. Typically, meteorites come in showers, so that there is always this anisotropy with respect to your meteorites which makes it hard to calculate the hazard. This 23 years is a long-range overall average near the vicinity of the earth, but between Mars and Jupiter where you have bands of these things, the hazard could very well be many orders of magnitude greater.

But this is the meteorite problem, and I don't think the cabin atmosphere plays too great a role in this particular aspect of the blast hazard.

There is a tremendous difference in the conversion of propagation to detonation with oxygen, and this is well-explained by theory. This is a problem that rocket propellant people are also facing—how to prevent a propellant from becoming a detonant, so these are pretty well worked out.

FENN: Why is nitrogen better than helium in quenching?

ROTH: It has a higher heat capacity, which is the major factor.

FENN: And the heat conductivity is greater?

ROTH: Helium is six times more conductive than nitrogen.

FENN: But the greater heat capacity overbalances that six?

ROTH: Yes. If you write out the equations, the free radical equation for a model system such as a hydrogen-oxygen system or a hydrocarbon system, and you insert the density factor at the flame front, the heat capacity factor, the diffusion factor, and everything else you can think of, the results come close to the empirical series of curves for the methane-oxygen system.

What apparently happens is that the generation of free radicals is determined by the local temperature at the flame front, and anything within that flame front that acts as a heat sink reduces the generation of free radicals to a point where the chain reaction is inhibited. Chain reactions, being what they are, once you inhibit the initiating sequence you have a marked effect on the rest of the system; so that relatively minor changes in the heat sink at the flame front have a profound effect on the rate of burning or explosive potential, or anything else you want to consider.

FENN: I noticed helium was better in a small tube and nitrogen in a large tube.

ROTH: Yes. There you are limited by your wall factor. This gets rather complicated in that the wall itself acts as a heat sink and as a free radical trap. Diffusion does play a role but a relatively minor role in those situations where you are not wall-limited, but as soon as you become wall-limited it takes on a different complexion.

FENN: You have someplace to conduct the heat, then, other than the conductivity itself.

ROTH: Yes. For every physical system that is studied there is an entirely different critical gaseous parameter, but the consensus of the people working in the field—and most of them having arrived at their conclusions intuitively never having thought of the problem within a cabin—was that nitrogen would be safer than helium as a diluent, but you would have to specify what sort of fire you are interested in. We have also gone into the probabilities of fires, the extinguishing of fires, etc. Actually most of our fire extinguishers are free radical traps, freons. Your freons, your alkyl halides, trap free radicals and break the chain reactions. They are very easily made into free radicals; the halide radicals come off, and they, in turn, trap the active intermediates in the fire. Oxygen has a tremendous effect on the ability of these compounds to work because it supplies a free radical generator source.

It might be worthwhile to look at an illustration of an idealized system. It is hard really to talk about any one condition, but this is the sort of problem you encounter (FIGURE 13). This is fuel concentration, volume per cent versus an alkyl halide inhibitor concentration. There are no numbers on this. In air you get the inner curve, in pure oxygen this next curve, and with various temperatures of your reactants you

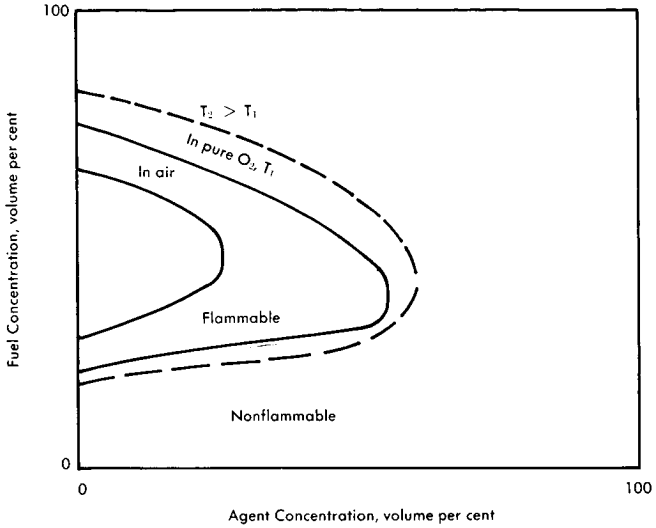


FIG. 13. Flammable limits of a fuel as affected by an extinguishing agent. (After Cary *et al.*, 1961.[62])

get all sorts of families of curves along this line; thus one has to work out these problems for specific situations.

Zero gravity hinders because ordinarily CO_2 and many other agents are dense and they settle on fires. In zero gravity they don't. As a matter of fact, a blast of a fire extinguisher would tend to speed things up because it would add to the convection that ordinarily isn't there in a zero gravity situation. So we have the fire fighting people interested in the whole mechanism of fighting fires. Very sophisticated computer programs have actually been written recently on the whole problem of extinguishing agents in cabins.

One is helped in a cabin by the fact that you can always dump to a vacuum if you have time. I think this was SOP in the Mercury situation, that if you got into trouble with a fire, dump the cabin; but if you are talking about Gemini and situations where you have partial or total street-clothes environments, you don't go about doing this.

All of these agents are toxic in sealed cabins, and we reviewed the toxicity problems. CO_2 itself, which in 1g environments, is a pretty good extinguisher, in a space cabin no longer has the density factor and is probably relatively ineffective. As a matter of fact, in talking with the people at USAF School of Aerospace Medicine about their fire, I learned that the fire started in an electrical system behind an instrument panel. It spread rapidly. It was only about 10 seconds from the time the first glow was seen until the whole panel was in flame.

Playing CO_2 right on this area extinguished the fire, but as soon

as the CO_2 was shut off, flames burst out again, and they finally had to dump the oxygen and get the people out.

We have reviewed the problem of the selection of electrical insulation. This matter came up in the Convair light that apparently was used on the Navy study. At USAF School of Aerospace Medicine they had polyvinyl chloride insulation, which is a relatively poor choice under those particular conditions. Of course, the investigators probably had little time to go over every insulation detail on every single instrument; but, if one were to do it again, probably the best insulation in terms of temperature decomposition, toxicity of products, etc., would probably be an asbestos or a fiberglass insulation with a "Teflon" or silicone filler. We reviewed the problem of the toxicity of all these electrical insulations and these two seemed by far the best. Polyvinyl chloride has a much lower decomposition temperature and produces hydrochloric acid and phosgene as a product.

HELVEY: "Teflon" decomposes to phosgene, doesn't it?

ROTH: No. This has been a big problem. DuPont has been fighting this ever since they came out with "Teflon"-coated frying pans. All sorts of cranks have been on them, pure food fadists, saying that Teflon pans are really dangerous from a toxic point of view.

Actually, "Teflon" is quite stable to about 600°F., which is the point where lead begins melting. At 600°F., the only thing given off are the tetrafluoroethylenes and hexafluoropropylenes. These are the monomers polymerized to form the "Teflon" itself.

When you get up to 750°F., you begin getting some of the isobutylenes, which are toxic, and only when you get to 1200°F., do the composition products actually burn. People have been exposed to very high concentrations of these decomposition materials and come out o.k.

The basic problem with "Teflon" is the fact that people get fume fever from burning "Teflon," the classic metal fume fever from similar exposures. Since animals can't get fume fever, the problem cannot be adequately studied. The current MAC for eight hours' exposure to "Teflon" combustion products is now set at one-hundreth part per million, as it is relatively toxic in the minds of the people setting the level. There are no good data to support these very low MAC levels, so DuPont Company has been fighting this, trying to reduce it by several orders of magnitude.

HELVEY: Do you know off hand what the temperature of a stove burner is? I understand that a cigarette can be as hot as 2000°F. in the center, at time of inhalation.

ROTH: No, no. This is what happened. "Teflon" workers, milling "Teflon," have had the "Teflon" particles fall on their cigarettes. Toxicologists feel that this exposure and exposure to cintering ovens where

"Teflon" is cintered in the fabrication process, are the major sources of the fume fever from the "Teflon." These are usually at temperatures around 600° or above, and it is unfortunate that animals can take products at much higher temperatures and have none of this fume fever syndrome. It acts like the flu; you get shakes and fever and cough.

In comparing this to the next best thing, which is silicone, there doesn't seem to be very much difference. I have data on the temperatures and toxicity of silicones, and they seem to be just about the same. Silicone is a little less toxic in terms of the potential materials given off, but it begins decomposing at a lower temperature.

If you are going to make an insulation and you can avoid any filler, fine, but if you are going to build in a filler the best thing to use would be as little silicone or "Teflon" as possible, with a massive asbestos or fiberglass base.

BJURSTEDT: Do you have any experience with what happens in the chamber above one atmosphere?

ROTH: I have a lot of data on hydraulic fluids above one atmosphere and, interestingly enough, much of it look like this (FIGURE 14).

There are many reasons why you don't get much enhancement and I have gone into this in the report and I won't discuss it now, different fluids act quite differently and it gets awfully involved.

BJURSTEDT: In case you have pure oxygen in the chamber and increase it by more than one atmosphere, what is the most serious thing you could do, in terms of sparking or what?

ROTH: The major problem would probably be in terms of ignition of any homogeneous gaseous system, and then you would go down the line from that. That seems to be the most sensitive in terms of hazard parameters. The homogeneous gaseous systems are modified by 100 per cent oxygen to reduce ignition energies by several orders of magnitude. Propagation parameters and other factors are changed by factors of only 2 to 10 in 100 per cent oxygen.

The big problem, of course, is designing a system that avoids as many combustibles as possible and uses compartmentation. If you have redundant systems, you should keep all of your redundant systems separated by fire walls. The Lockheed Company has set down a very nice set of rules for some of their advanced vehicles, and I have taken these rules and expanded them to include the space environment. I have outlined a suggested computer program for determining the optimum handling of these matters in terms of how much and what extinguishers should be used, how should you detect hazards; how should you choose the various types of flame detectors, the redundancy, the compartmentation problem. You can take each one of these and set up an ideal rocket system.

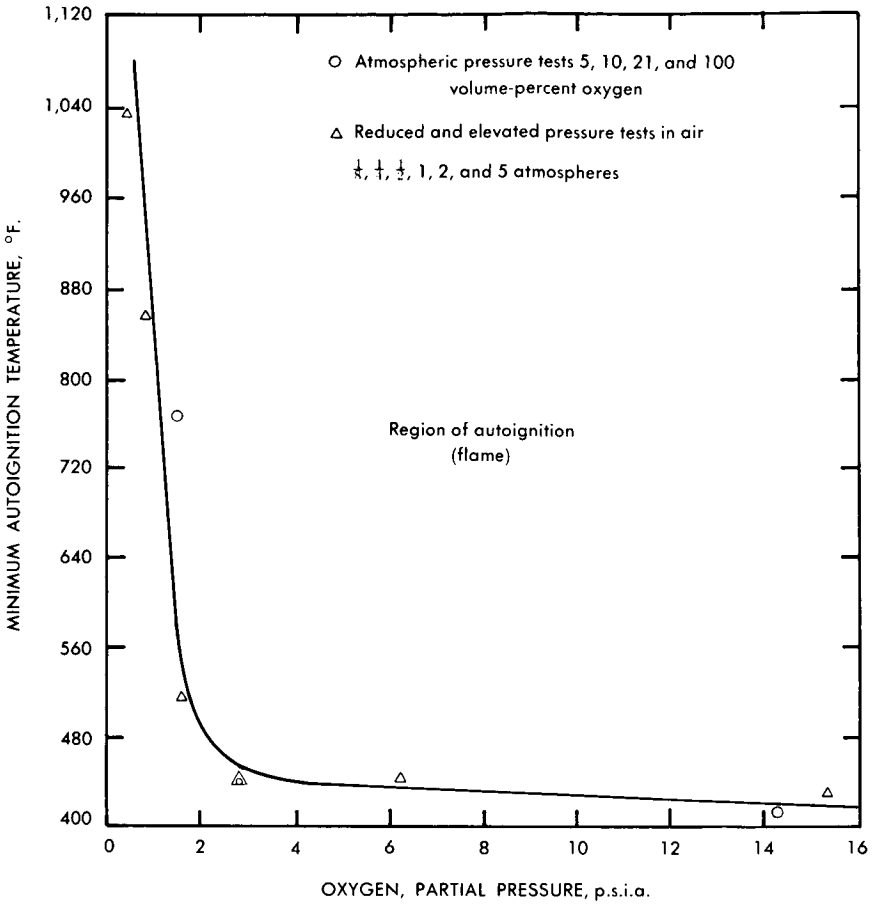


FIG. 14. Effect of oxygen partial pressure on the minimum auto-ignition temperatures (MAIT) of JP-6 fuel-oxygen-nitrogen mixtures at various initial pressures. (After Kuchta *et al.*, 1961.[63])

Of course, Mercury was the problem in fire discipline, and it was amazing that they didn't get into any trouble when you look back and see all sorts of potential trouble they could have gotten into. True, they always had the dumping of the cabin into a vacuum to help them out. Actually, they began getting into trouble on the very last flight when the water in the environment began shorting some of the leads on the AC system, and this is why Cooper actually had to come in on the manual system. They had everything well covered except they didn't put the connectors in back of the black boxes. The water and

high oxygen began corroding things. There was arcing or shorting, and he had finally to come in manually.

If you would analyse the particular sequence of events, he could very well have gotten arcing and burning of the insulation as well. He didn't. Maybe if he had done another round or two, this would have happened. You have to really, in each design stage (and this wasn't done), go through the fire hazard and optimize the system from this point of view. I think if you do that you could possibly get away with a 100 per cent oxygen environment. Now this is fine with a person sitting down, with very little chance to kick things loose. Yet even in the sleep phase, the Mercury situation get pretty ticklish. The astronauts could have hit some of the electrical switches if their arms flailed around.

I think if you are designing a manned vehicle, multi-manned with multi-functions, you have to be very, very careful all the way across the board. The accident potential increases remarkably. I am convinced after reviewing this problem, that the human error is such that we would be best off playing with an environment that has inert gas in it. By virtue of all these uncertain factors, you are just bound to run into an ignition situation that is going to catch you in the end.

HELVEY: Practically speaking, material selection will be looked at pretty hard in reducing fire hazard, but in view of your knowledge, do you think that changing the gas offers a much greater margin of safety in addition to selecting material?

ROTH: Yes, I think you have to do both. I think actually, in terms of fire hazard, an 8000 ft. air cabin would be about the best. Of course, you have to trade this off with other factors. Bruno Balke[64] showed that after decompression, people previously exposed to 14,000 ft. air environments for several days in Colorado could go through as many deep knee bends as physically possible and not come down with the bends. In other words, at 14,000 ft. you reach nitrogen equilibrium where you are in pretty good shape as far as future bends, when you decompress to 5 psi or 3 psi suit pressure.

A 14,000 ft. nitrogen equivalent cabin, I think, would be fine, and, in view of the fire hazard, the family of curves I showed you, the lower the total pressure you get the better off you are. This might very well be a good compromise. From the standpoint of the fire situation, nitrogen looks like the best inert gas. If you look at all the parameters of burning and consider which ones could get you into more trouble than others, I think nitrogen is by far the best. The consensus of the rocket fuel people has pointed to nitrogen in spite of the fact that in some parameters, helium looks better than nitrogen.

FENN: Air at 14,000 ft. is the best?

ROTH: As a trade off on the decompression problem and the fire

problem, this seems to be a good compromise, although you may want to raise the oxygen a bit.

FENN: Thank you very much. It seems to me that this is very impressive study and contribution to our discussion. It is certainly an important factor to put in the balance.

HELVEY: The figures, comparing oxygen and air, are 3.5 times as fast burning in one-third atmosphere oxygen—but Hall in the Navy did a study on burning paper, Doctor Roth, which he has not published, but he said burning was about six times as fast in oxygen as in air.

I just wondered how wide a range there was. You indicate that almost all the studies you surveyed came pretty consistently to 3.5 times burning.

ROTH: Yes. Well, it depends on the thickness of the cloth, the type of cloth, how much of the burning is oxygen-diffusion limited, horizontal vs. vertical burning, etc. So, it gets to be rather complicated, but three to four seemed to be the figure that most come out to.

If you take a very thin, tissue-paper situation, you have different oxygen effects than if you take a heavy, say a heavy suit cloth. It makes quite a difference.

HELVEY: In your study, did you run across work by Bolstadt? He used to be at North American.

ROTH: Yes, as a matter of fact, Bolstadt called me one day before he started the study and asked if he could get a copy of a manuscript we had. All of his studies so far have corroborated most of the materials that we covered.

He went into the burning of plastics and showed that the fire retardant parodox holds, that you can't predict from fire retarding at ground level what is going to happen at 100 per cent oxygen. I have been in contact with him, and he is about to publish much of his data. He presented some at the AIAA.[65] His data have fallen right in line with the predictions we made on the basis of other systems. He is doing this work now at Minneapolis Honeywell. This company has the contract to rebuild the chamber at the USAF School of Aerospace Medicine. We hope to be sitting down with those people within the next few months, and going through every aspect of the system to see if we can minimize the fire hazard all the way across the board.

FENN: This factor of three or four that you speak of is comparing air at one atmosphere with oxygen?

ROTH: No, the three to four was comparing air at 8000 ft. with 100 per cent oxygen at 5 psi.

GRAYBIEL: Hall's study[66] was air at sea level and 100 per cent oxygen, 5 psi, and he has said about six times.

HELVEY: He also had some face suit materials that didn't burn at

all in air, were merely melted, and then burned rather vigorously in oxygen.

ROTH: The variables are amazing. It depends on how you hold your cloth: if it is vertical and you have a flame climbing, or if it is horizontal and you are propagating flame this way. The British[57] have gone into all the variations, the physical systems holding the cloth, the weave, and for their welder's fabrics. They have come up with the same general figures as Klein did for his GI flying suit cloth. The ratio of four or so is relative to the experimental setup.

DUBOIS: One factor to be mentioned is the cooling of instruments. At low barometric pressure, the density of gas is less and so the heat capacity is less; and also under weightless conditions there is less convection so that apparently you need to use fans to cool the electrical equipment. If it overheats and catches fire of course the fans that produced cooling will simply fan the flames. This appears to be an interaction that is hard to get around at low atmospheric pressure of oxygen.

Helium Conductivity

JENKINS: Doctor Hiatt has some extremely interesting data on the fact that the animals seemed to chill when there was 20 per cent oxygen and 80 per cent helium at 14.7 psi. He was able to measure the excess amount of food required by the animal to grow in the helium as compared with in oxygen-nitrogen.

FREMONT-SMITH: Is there any explanation as to why they chilled?

JENKINS: The greater heat loss due to increased thermal conductivity of helium.

FREMONT-SMITH: Conductivity of the helium, not a vasodilatation on the surface of the animal?

ROTH: Yes, most of the animal studies that showed an elevated metabolism with helium could all be extrapolated back to a thermal conductivity problem. Their animals were losing more heat and if they made up for this particular loss in the temperature of the cabin they would avoid the metabolic changes. However, with *Neurospora* and some of the insects and some of the yeasts, this seems to be a change in the activity of the aldolase enzymes and a relatively slower rate of growth. A new laboratory has been set up at the Lijde Company in Tonawanda, New York, for studying the metabolic effects of these inert gases. It is being supported by the Office of Naval Research, and they are reviewing a lot of the work that has gone on with insects and lower animals and trying to get a handle on what upsets the apple cart there.

Linus Pauling has been working on a lovely collapse rate theory,

which he has used to explain the actions of "chemically inert" anesthetics, and in the third part of our review we are going into this particular problem of the possible basis for the metabolic effects of inert gases on various things—cell membranes, mitochondria, all the way up the line, just to see if there is any basis for this.

FREMONT-SMITH: Is this what he calls the freezing effect?

HELVEY: Yes, you get heterocyclic compounds with the tyrosines—any of the cyclic compounds can trap small molecules by Vanderwols. There is no covalent bond, but it traps the molecules and changes the electrical characteristic of the molecule. He is trying to look into the theory of anesthesia on this basis, the old Meyer-Overton rule where lipid solubility seemed to determine anesthetic quality and could be translated in terms of collapse rate theory as well. He is busily at work on this tack now.

Temperature and Humidity

BROWN: Largely out of my curiosity, I am wondering if anyone can explain the rationale that was built into the Mercury system of temperature control. As I understand it, the philosophy was that you keep the suit atmosphere a little on the warm side which makes the man perspire, and then he automatically regulates his temperature by how much he perspires.

SCHWARTZ: I don't know anything about this, but I have the general impression from the few reports I have read, that this was not a very good control system.

BROWN: It didn't work well, for several reasons. Part of it was instrumental. I am sure that other people here perhaps know the details better than I, but the astronauts did come back dehydrated and rather seriously dehydrated in some cases. There was no excuse for this.

ROTH: As for the last flight, I believe that the water retrieval system for the air-conditioning unit was deemed inadequate several weeks before the flight, and a jerry-built system was installed which required the astronaut to suck up the condensate with a multiple syringe. It was a rather complicated and makeshift rig, considering the rest of the vehicle.

Apparently some solid material came out of the condensate and plugged up the syringe nozzle and so he couldn't use the system. He then ran the condensate into the drinking water so that it wouldn't be floating around, and this polluted his major source of drinking water. This is one of the reasons why he didn't drink.

Apparently throughout the whole latter part of the mission sweat was dripping off his face and getting all over the place, and he spent a good deal of time wiping it up. This happened to Cooper. I think it was

a question of having to get a workable system in a very short period of time, which precipitated the whole sequence of events.

I know people interested in desert physiology have pointed out repeatedly that it takes a good deal of time for people in acute stress in a desert situation to make up for their inadequate water intake. Somehow or other being in desert, subjects focus their attention on other things and, physiologically speaking, they are always quite far behind. It actually takes about twenty-four hours after a very severe dehydration exposure before they make up their water loss.

This also may have played a role here, so that the stimulus to drink was reduced by the total situation. Exactly what factor in the situation—whether it is pure anxiety or something else—I don't know, but I think this has been reported by Adolph and others working in this area.

FREMONT-SMITH: There is possibly another factor too. There is a general tendency to sacrifice volume of the body to maintain chemistry. If there was any chemical change, and this might very well be the case in that they had lost some salt in the desert situation, they didn't make up their water loss because they maintained their chemistry better without it.

BROWN: I am afraid that is not the explanation. In the absence of any undue anxiety, a person who is under some heat stress and dehydrating fairly rapidly usually does not drink fast enough to maintain his body weight and it does take time—

FREMONT-SMITH: But he is losing salt under heat stress, too.

BROWN: Yes, but it is not a salt factor, particularly in the acclimatized individual.

HELVEY: As I understand it, they have a control, a temperature control, which has both a gauge or a dial and a light. If I understand it correctly, when the light goes on there is a manual operation where essentially you change a thermostat, and there is a lag time. There was possibly just a simple error in manual control that caused an increased temperature.

They have had, as we know, intermittent trouble with the temperature in the suit on previous flights, but I think the basic temperature control is a water evaporator. I don't think they planned to let the man control himself in terms of perspiration and evaporation.

ROTH: In the early flights, the control dead band was too wide in the temperature control system and this is one of the reasons why they got fluctuations, but apparently the temperature was not too much of a problem in the last flight. It was the condensate water that really gave difficulty. The temperature was controlled very nicely at, I think, around 65 and gave very little trouble, once they had reduced the dead band area.

FENN: But the humidity was too high; they couldn't control it.

ROTH: Yes, it was a question of getting rid of the water from the system.

FENN: You said he tried to suck it up with a syringe? How could he do that?

ROTH: They used a capillary system. One of the problems in the past was the fact that, in the absence of gravity, water tends to stick to the walls of a container especially in the rig that they had—and not come down into a catch basin or some type of chamber from which it could be drawn off. They had a sponge-like system which was filled by capillarity, and they had something to squeeze the water out. Then it was a question of what to do with the condensate water. They wanted to save this for balance studies and system control studies, so the astronaut was supposed to put water into little bags with the syringe system. When this stopped working there apparently was some mechanism whereby, in an emergency, he could run this condensate into the drinking water, so that it wouldn't be floating around and jam up the whole rig. This is what he did.

I don't know whether the contamination of the water was important. I think he did have emergency water supplied, which he was actually using, and I don't think that all this was really much of a factor in his relative dehydration. He claimed that he just wasn't thirsty and didn't want to take the time to drink.[67]

DUBOIS: I wondered how the suit temperature was controlled. Perhaps air temperature, leaving the suit, does not represent the total heat load. Radiant temperature would affect his heat output, or the transfer of heat from the skin to the suit, and evaporative losses would also affect it, So, to obtain a proper temperature controller on the suit one would think you would have to measure radiation, convection, conduction and evaporation, all of these parameters, and I wondered if there were such a sensor built into the suit or if regulation depended merely on air temperature.

ROTH: This was a big problem. In a feedback cycle, the position of the sensor actually determines your deadband. In several of the flights the position of the sensor in the air-conditioning system was varied and it was found that it was indeed a deadband problem. They discovered that when the sensor was in the steam exit duct of the air-conditioning system, there was some problem with the flow and temperature distribution which gave an exceptionally low temperature reading, so that the system overcompensated and the final control point was at a much higher level. By changing the position of the sensor within the air-conditioning unit, they finally got a point where there was minimum cycling and an adequate temperature control.

DUBOIS: Is the sensor a dry bulb thermometer or a wet bulb thermometer, or a radiometer?

ROTH: I think it was just a thermistor. I think they decided on the input section of the second cycle as the optimum spot.

HELVEY: I believe the air comes out saturated. I think you can assume that, unless the temperature in the suit is very low.

FENN: How does it go in? That is important.

ROTH: It is ambient air coming in, and whatever water gets pulled in by capillarity is removed. So, it comes out a little dryer but it would still be relatively moist, I would say.

BROWN: It is not clear from some of the diagrams of the temperature control system, but Stan White, who should know, believes that that the philosophy was to run the astronaut on the warm side so that he would perspire as much as was necessary to keep him in temperature balance.

FENN: But if you can't evaporate the water, it wouldn't do much good to make him perspire.

BROWN: A very interesting point.

HELVEY: We do that all the time in the summer and, within limits, that is a very physiological approach, I should think—not at 120 degrees, perhaps, but if you just got to the margin of perspiration . . .

BROWN: Thermodynamically it is true, provided the man is not expected to evaporate sweat in a saturated environment, but what advantage has this system?

FREMONT-SMITH: Doesn't it make him dehydrate almost automatically?

BROWN: Not if he drinks.

FREMONT-SMITH: Not if he drinks an extra amount.

BROWN: He would probably have to force himself to drink, which he could do if he really believed it were important. The cost of taking water out of the air is not small. The cost of transporting heat, using a coolant and circulating it into a heat sink, is appreciably less, and I can't believe that the decision to use the device that was used on Mercury was not some kind of a compromise based on factors which we don't understand.

HELVEY: I agree we have inadequate data for any of us to answer your question.

REGENERATIVE SYSTEMS

Discussion leader:
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BROWN: I am going to take my assignment seriously and try to say as little as possible so as to encourage interruptions, but I have put down a very minimal list of topics.

If we play Devil's advocate and say we are not going to need regenerative-type systems for maintaining a crew in space for long periods of time, for the next, oh, ten years (perhaps we will have propulsion methods, increased payload capacity, that will make it rather easy simply to store on board all of man's needs, and to store waste products in a harmless fashion) so we end up not with a regenerative system but, basically, with what has been called a storage system.

You can, by making certain reasonable assumptions, predict what this payload capacity would have to be as a function of duration of mission. The figures come out fairly large but not astronomical.

I don't think it is fruitful to argue about how optimistic we should be in predicting technological advances a decade hence. However, I don't believe, on the other hand, that we can expect to carry out missions to various places in the solar system (and I think particularly of Mars) in a matter of a week or two, simply because if you are going some place you will want to stay there and do the job for a while. You may go to the moon and sort of touch base on it and scoop up a sample and come back quickly, but if you are going to invest in what it takes to get a crew to Mars, and explore Mars, this means a relatively long period of time.

Also, unless your most optimistic views are justified, you can't come back just any old time. You will have to wait until the ballistics of the situation are propitious for your returning. Therefore, we had better think in terms of years, and it seems to me, that we are going to need regenerative systems because you simply can't afford the storage capacity to do the job without it. This is not to say what kind of a regenerative system, but it certainly indicates that things will have to be reused extensively. It doesn't mean that the systems will have

to be completely closed in the sense that we ordinarily use this term, either.

Simply for purposes of orientation, I want to discuss the possible systems. There are regenerative systems that have as the only biological component, as far as gas exchange is concerned, the man (we are not considering now the waste disposal problem), and these involve chemical reduction of carbon dioxide with hydrogen generated by electrolysis and the use of oxygen from the electrolysis for man's respiration. Such systems, of course, do not produce food, so they can't become completely closed in the material sense.

Neither does the material balance work out ideally; there will be an accumulation of one or another product depending on how you run such systems. There are possibly non-bioregenerative systems that partly solve the problem, but not completely. Under the bioregenerative systems there are two types that seem competitive, one based on photosynthesis and one based on hydrogen bacteria and electrolysis. The attraction of these is that you can, in principle, balance the gas exchange and the food intake of man and the rest of the system completely; whether or not you can actually achieve complete closure is at this stage an academic point. You can approach a balance of the gas exchange, and whether or not you use as food the algae or bacteria that grow in this system, still you have gained something by taking care of the gas exchange. And if you can use them as food, either partly or completely, then you come much closer to complete closure of the system.

Historically, photosynthesis was a natural and you didn't have to be a botanist or a plant physiologist to appreciate that, at least on paper, you could devise a closed ecological system. The approach that was used was to write the equation and say: We need a photosynthetic component to serve as an oxygen source and a carbon dioxide sink, and the organic product of that process is new cells. These new cells ought to be good to eat. Therefore, automatically, you not only balance the gas exchange but you provide the food.

Quite early, a few plant physiologists, who had worked on photosynthesis and later began to investigate the engineering problems in commercial production of algae for food on earth, became interested in adapting their thinking to space and approached this purely as a matter of managing the closed system of very small dimensions. As far as I am aware, at no time did the ecological fraternity bring much pressure to bear to influence the thinking. I believe Doctor Odum will agree with me here that this was not a subject that the ecologists considered part of their bailiwick, in spite of the fact that the term "closed ecological system" became rather popular.

The question arose later, however, whether this is the right way to go about it. Would it not be better to back off from this problem and take a look at the ecological system that we think we know a lot more about—that is, the biosphere as a whole—and to take a little piece of this biosphere, containing a number of organisms—the particularly important one is man—and to try to build a wall around it so that it will be materially closed but not closed to energy flux.

Looked at this way, I think you come out with very different answers. You can rather easily prove that what you want to do is impossible, that it depends on several assumptions. One of the assumptions is that you can construct, by simply putting components together, a closed system that will automatically control itself and stay in balance.

You can raise the serious question of whether the biosphere itself is in balance. It appears to be, but this perhaps is only because our time scale is so very different from the time scale that the whole earth operates on. If we thought in terms of time units of ten thousand years, we actually may not be in too happy a situation. A small change, let's say, in the carbon dioxide content of the atmosphere could, conceivably, and probably would, if it were an increase change the average temperature of the oceans and make marked meteorological changes that would alter the distribution of flora and fauna on the earth. It might take a remarkably small change to change completely the earth's environment so that it could perhaps be uninhabitable by an organism like man. We can't be sure this isn't the case, and I think our complacency is based on two things: the time scale and our ignorance.

The chemical engineers, of course, or the biochemical engineers, are aware that the bigger the system and the more complex it is, the more stable it is. Also, the more efficiently it is likely to operate. When you scale up any kind of a fermentation reaction, you usually get higher yields, after a while. There are all sorts of automatic controls that you don't really understand that begin to come into play once the system gets very large and complex.

GILBERT: It seems to me that one of the best approaches to developing a minimum closed ecological system for man is to mimic as much as possible the essential factors operating in the natural ecological system here on earth.

Let's consider if the earth's atmosphere is in a steady state. Life exists on a planet when it goes from a reducing atmosphere to one finally composed of nitrogen and carbon dioxide. During this process, dehydrogenation of the planet is occurring. Thus, it should be expected that the earth is losing hydrogen. It appears that the earth is now losing about 10^{8} Emoles of molecular hydrogen per year.[68] The maximum accreted hydrogen[69] is only about one-third of this value.

We do have, therefore, small changes occurring, but the rates at which these changes are progressing are so small that within a short period of time, the earth's atmosphere may be considered to be in a steady state. Perhaps, one should stipulate the time in which one would want an artificial system to be in a steady state.

There is one further point I would like to make. That is, within a very short period of time man has done something to upset some of the geochemical balances of nature. Carbon dioxide has been liberated not only by burning of fossil fuels but also by removing forests, which releases this gas. The carbon dioxide concentration in the atmosphere has increased about ten per cent since the year 1900.

Correlating with this increase is the fact that carbon dioxide does play a role in absorbing infrared radiation and tends to prevent heat from leaving the earth's surface. Indeed, it has been found that the temperature has increased on the surface of the earth for the first part of this century, and it is probably still increasing.

The consequences of this carbon dioxide liberation will probably be found out in the next one hundred years or so. It depends upon how fast the carbon dioxide can be removed by the oceans. Anyway, man is already upsetting a geochemical balance.[70]

BROWN: What we are trying to do is work in the other direction: to make this closed system as simple as we can. The virtue of simplicity is that you can understand all of the regulatory factors that you have to worry about; you can put in the proper manual or automatic controls; and the fewer the components, the better.

Simple versus Complex Systems

Is this a sensible approach? Is it reasonable to think you are going to come out with a workable system by starting with the simplest system you can and working up to something as complicated as a closed system that must keep a crew alive for literally years?

ODUM: I think you stated it very well. However, I think we have just as good a chance of getting a simplified working system the other way, and we propose to try it the other way—in other words, to start with a complex system and to simplify this or reduce its size. I am thinking particularly of Doctor Robert Beyer's microcosms, which he has recently described in a paper in Ecological Monographs.[71] He has obtained stable, self-supporting, moderately complex systems by first adding a large number of components to a closed vessel and then allowing the system itself to select those components that will function under a given light-temperature regime.

RAHN: Can you define this complexity for me, what you mean by complex versus a single culture?

ODUM: A complex system is one with high information content or

feedback possibilities resulting from several rather than a single unit capable of doing a particular job—for example, several kinds of autotrophs not just one. The way Doctor Beyers constructs his microecosystems can be illustrated by the procedure he used to set up a series of hot spring microcosms. He gathered material from a real hot spring and seeded a number of vessels. Then he cross-seeded these vessels many times before he closed each vessel to insure that everything, every kind of bacteria, every kind of plant, every kind of small animal, and all the chemical elements normally present in the hot spring system got to each one of these vessels. In other words, each vessel had a good chance of containing many components that have evolved together over many thousands of years of evolution.

My point is, why not take advantage of the fact that nature has worked on systems for years. We are amateurs. We have just started and are trying to build one with no experience. The interesting thing about Beyers' ecosystems is that after he closes them he finds that he has, indeed, a dozen systems that will turn out to be pretty much the same.

FREMONT-SMITH: A dozen separate systems, or a dozen complexities in a system?

ODUM: No, a dozen separate systems that will come out similar if the external condition of light and temperature are similar.

BONGERS: Actually, you provide a set of conditions with respect to temperature, light and substrate.

ODUM: This is true as far as light and temperature are concerned, but food production is balanced against food consumption and gaseous exchange is balanced in a self-regulatory manner.

BONGERS: And you maintain this throughout?

ODUM: As long as the general environmental condition is maintained, the system is maintained. The interesting thing is that the system goes through a period of succession. In other words, it is not immediately balanced.

RAHN: After he closes it?

ODUM: After he closes it there is an early period in which photosynthesis exceeds respiration resulting in a buildup of organic matter, and this is what we see in open nature. Any succession that we study in nature goes through a stage where autotrophy exceeds heterotrophy, and then it goes to a stage where these become balanced, more or less.

FREMONT-SMITH: Are these stages visible in the hot spring or is the hot spring very stable already?

ODUM: You don't see this succession in hot springs unless you do something to disturb the steady-state such as remove some of the standing crop or transport it to the microcosm vessel; then you see the

succession toward a return to the steady-state. The same would be true in a forest—you don't see succession unless you cut it down and then you watch the forest go through successional stages until something closely resembling the original returns. Succession takes years in a forest but only weeks in a small microcosm.

What we are proposing with Doctor Beyer's help (and a little financial support from NASA) is actually to take these self-evolving systems apart and to determine more exactly how many species have been selected to survive in the closed system. Doctor Beyers, and I hope I am quoting correctly, says that he has not been able to get a stable system with one species of plant. It seems that three of four or more species are needed.

BONGERS: Is it not dangerous to state: "We have four species of algae." What you mean is that you assume that the species are different but adapt to the same set of conditions.

ODUM: That is true.

BONGERS: They might well be the same.

ODUM: Suppose you do have four species of algae—each of which functions best at a different temperature. Then total function (rate of oxygen production) would be less affected by a temperature change since one species would take up where another left off. In fact, Beyers has a little article in *Science*[72] showing that a mixed species system is more homeostatic to temperature than any one of the component species alone. The more diversity in your gene pool the more readily the system adapts to changes.

GRAYBIEL: Has he seeded vessels with single organisms, the way they do bacteria?

ODUM: No, he has not. For the present he has been interested in trying to duplicate systems from nature. This is a different approach from pure culture but, to me, is a very exciting approach.

BROWN: How can we pin down this kind of approach to something that will be useful for present consideration? I understand why these studies are of interest to the ecologist; he wants to know about these communities and what makes them tick. But it obviously is not feasible to just dig up a chunk of nature and put it inside a container and say, "This is my closed system," and then allow man or a population of men to adjust to whatever size is appropriate over many generations. How can we make use of this kind of information, or what sorts of information do you expect to generate that will be immediately applicable to a space mission?

BONGERS: This wouldn't work for the simple reason that the family of consumers in your systems have to be replaced by man, with different requirements.

ODUM: That is true, but man is not actually different in the eco-

logical sense from many organisms that function in the same trophic position of man.

BROWN: Man would be only one of the consumers in such a system.

ODUM: I think it is very obvious that a space system will have to combine natural components with mechanical shortcuts, but I'll still hold out for diversity of mechanism as "backup" in case the major performer fails.

Incidentally it impresses us that imbalance between what we call the "grazing food chain" and the "detritus food chain" is a frequent cause of failure of small systems, both experimental and natural. If living plants are eaten too fast the system becomes unstable as a result of "overgrazing" and lack of biological structure to buffer the physical environment. On the other hand, if too much organic matter accumulates as result of inadequate detritus decomposition, the system may become anaerobic or otherwise stagnated.

Duckweed and algae cultures often seem to go along beautifully for 30 days or so until a big pileup of undecomposed organic matter causes failure. Large systems of nature have many means of adjustment that we don't understand and hence can not as yet engineer into small systems.

BROWN: Certainly the concepts that have prevailed so far have been those of what I prefer to call a completely managed closed system, where you feel that you know at all stages the energy and material budget in some detail, and this, at least on paper, seems possible. In fact, it looks much easier than it is; thus if you believe that this line of thinking misses the boat, I think that the burden of proof is on you to raise questions that ought to worry a person who is this provincial in his viewpoint.

ODUM: One question I raise with algae culturists. At the last AIBS meeting I listened to reports comparing different kinds of algae in the log phase of growth, the inference being that the species with the fastest log phase growth would be the best species for a life support system. But in space travel aren't we more interested in steady-state growth? In other words, we don't want a big "bloom" and then a "bust"; we want moderate but steady performance dependable for a long time. *Chlorella*, a favorite experimental subject, is an early successional organism in nature. It is never a permanent organism at any one time or place. There is no such thing as a *Chlorella* ecosystem in nature. It is always something that comes in early when nutrients are abundant, takes hold and builds up, and then is replaced by other more "climax" species.

BROWN: You can say the same thing about maize. A cornfield doesn't exist in nature. It has to be managed.

ODUM: Yes, but it is managed and supplied with nutrients from *outside* the cornfield ecosystem. In space we will have to manage from the *inside* so man will have to be a *part* of the ecosystem, not just a plantation overseer who has other resources of food and oxygen in case the corn crop fails.

BROWN: And you can harvest the *Chlorella* culture continuously and maintain it essentially in its log phase. This may not be the way to manage it to get the best yield, but I think Doctor Bongers will agree that with a bacterial culture, that is the way to do it to get the best yield. There are reasons why the two situations are different.

RAHN: Doctor Odum, are you trying to say that we have to have a climax culture in order to succeed, or not?

ODUM: No, all I want to do is to recognize that there are these two basic different types of ecological systems—just recognize they are there. If you use an early succession like agriculture, let's take a rice paddy and maybe put that in a space capsule and take it with us. It is a very stable system provided man is in there planting, draining, flooding, planting every year. It is a very beautiful system. It remains stable and in the early stages very productive, with lots of excess food that man could use. This can be done, but it requires that a man be the consumer and regulate the whole thing; whereas, the climax system would operate with less trouble but not as much production, so you can't have both, I think.

You can't have the very productive system making tremendous amounts of oxygen and have a stable one, so I don't know the answer here, which it should be; but I think that this has not been recognized by people who have been working with these laboratory systems—that they do tend to go from a grazing system to a detritus system. We think that nature works this way, and the reason nature goes to the detritus system is that this creates more stability because it creates the organic environment.

Let's put it this way: Looking at it very broadly, all through the evolution of the biosphere, what do we have? We have increased control of the physical environment by the biological environment. You might say that this is the entire purpose of all of this evolution; so when we have these changes you are talking about, the present very diverse biological environment we now have can probably adapt. The whole purpose of evolution or the whole purpose of man is to be able to control the physical environment—and that is the purpose of the forest. A forest controls the temperature—the temperature is not nearly as variable in a forest as it is out in the open area. It controls the chemistry, because organic processes are pretty well controlled. The whole chemistry of the sea, for example, is controlled by orga-

nisms in the long run, and so on.

So, why don't we make use of the control that can be brought about by a diverse system containing lots of organic components?

BROWN: This is a viewpoint, and I recognize the merit it has. At the very least, it calls attention to what the person who is building a managed system is doing if he hasn't thought of it. I am not sure you are being fair to the people who have been working in this area when you say they have ignored these matters. I think at least the ones I have talked to are well aware of this kind of thinking but don't see yet how it can be made use of, until there is some reason to think that a managed system of small dimensions won't work, then they are going to keep plugging.

FREMONT-SMITH: I think they should keep plugging, but I think it is very important for the ecological group to keep plugging, too. The fact that the other group can't see yet the practical use would be no reason whatsoever for discouraging it, because the results that may come of this line of thought are unpredictable, just as the limits of what may come of the first line of thought are unpredictable. Moreover, if we really have a crucial problem to solve, it seems to me of the utmost importance to encourage as many lines of approach as possible.

ODUM: I think that is very good. What I am thinking about is 20 years ahead. As you said, we won't really need these complete ecological systems for 15 or 20 years, since various storage or partly regenerative systems will do for time being. My point is we must begin work now. We have barely started thinking about metabolism in relation to structure at the ecosystem level. Most work in biology has been at the suborganism level, and most of the real knowledge we have is at the molecular level. To transfer our thinking and our work to other levels is going to take time. All I am saying is, let's come at the problem from more than one level.

BROWN: If it is fair to oversimplify, I think that one can say that the ecologist is just beginning in this field. Relatively few ecologists are very knowledgeable about the state of the art. The approach of the managed system proponents is fairly well advanced. There is a background of quite a few years of thinking, and I don't see that it is desirable, let alone possible, to make value judgements here. You don't solve problems by taking a vote on who is right, of course.

We might as well look today, I think, at the state of the art as it is, being aware that an entirely different approach exists. If the ecological approach has something to contribute, even if it just calls you up shortly by pointing out you made a mistake in an assumption, this would be helpful.

ODUM: That is about all we can do at the moment.

Mutation

ROTH: One thing that gives people working in chemical systems nightmares is the spontaneous mutations that occur in bacterial and in yeast systems. It is not a question of whether these mutations are lethal or not but a question of whether or not there are mutations that change feedback set points in control mechanisms.

If you are studying these particular problems, a very minor, or relatively minor, change in a control setting within a culture can radically alter the behavior of the culture. If you are pitting organisms against one another in a competitive environment, and you can do this with multistrained bacteria, it doesn't take long before you have completely overwhelmed the cultural environment by a single mutation in a single cell that modifies its rate of growth or its response to any physical variable.

I just wonder, in these systems proposed, how sensitive are your individual algae and plant components to these mutations which might really upset the apple cart in a single quantum jump and not require waiting for detritus to pile up? Is this a factor the plant people worry about?

ODUM: It seems to me that the multiple or diverse system is safer in this sense. If you had just one bacteria or just one algae and it mutated, then, sure, it takes over; but the system itself will determine what mutations survive and if the system has the control (this is my only point), if the system has biological control, then the mutations, if they are favorable to the system, will be OK. If not, they won't survive.

BROWN: This is, I think, much too simple.

ODUM: It is not like the parasite.

BROWN: Certainly there are automatic mechanisms to produce stability, the more complicated the system becomes, but on this one point of the mutation being deleterious to the end product, let's suppose that the mutant is not capable of carrying out photosynthesis, or whatever reaction we depend on, as well as the wild type. Then, the wild type will continue to dominate. The mutant may not disappear, but at least it will be held to a very low percentage of the population.

However, suppose that the mutant is capable of competing very well and happens to produce some toxic material that doesn't hurt the algae or any other component of the system except man. The whole business would break down.

ODUM: This is cancer. This is the same thing that happens in cancer. What you are talking about is a cancerous development in the system. A certain probability risk may have to be taken, but if cancer develops in the *only* species you have you might wish you had some other species along.

BROWN: I am afraid the diversity of the system is not sufficient to make me feel secure in this regard. If we have four algae and one of them mutates to produce a strain that overgrows all the others, it makes very little difference in the end whether there was one to start with or four or fourteen, I think, if that one is really capable of outgrowing the rest.

GRAYBIEL: Does radiation in space affect mutation rate—would the rate be the same out there?

BROWN: The populations are very large. Therefore you are going to find mutant forms popping up all the time, and I can't believe that the algae will be less well protected than man, so I am not sure that space radiation is going to contribute very much to the rate of mutation occurring naturally.

FREMONT-SMITH: Both will get more radiation, won't they? In spite of protection, they will both be subject to an increased radiation?

BROWN: You predict what the man is going to experience, and I will assume the algae will have essentially the same experience. Certainly, the algae are not very sensitive, they will tolerate much higher radiation fields than does man.

NEUMAN: Don't you think we are talking here about two different things? Jim Odum was talking about the genetic effects on a colony that is undergoing many, many cycles, so that the genetic effect becomes a crucial factor in the colony where it is not in man. As a matter of fact, all the astronauts already have children, and presumably the genetic factor can be ignored; so I think this multiplication factor makes the genetic aspect much more important, although I think we are also talking about dose rates which certainly wouldn't more than double the natural mutational rates.

ODUM: Why not take along a terrestrial system with perennial plants having a life span of a year or two. Then mutations won't make any difference because you are not going to have more than one generation during the trip.

BROWN: I think the answer is very simple there. We started off in this space business launching grapefruit, and we haven't yet started to think big.

ODUM: But man is big.

BROWN: And we are still concerned with efficiency—with the weight penalty for doing it this way versus that way; really the only reason for selecting an algal system or bacterial system is that it seems to be efficient. I would like to run through what seems to be some of the serious problems and indicate why the bacterial system possibly offers advantages. There are some strictly engineering problems that are difficult to solve, but not really exciting to contemplate. For instance, whether or not one can easily separate the gas from a

liquid phase, the stripping and the sparging of the liquid system in the weightless state of course poses problems that are not really biological. There are a number of ways these can be solved. If foaming or fouling becomes a problem, a whole series of solutions are possible. These problems are not unimportant, but they are more or less obvious, and the engineers will solve them in the course of time.

Matching Assimilatory and Respiratory Quotients

Let me point out some of the problems inherent in the nature of the system itself. In photosynthesis, you know that carbon dioxide is taken up and oxygen produced; and in the respiration of man, CO_2 produced and oxygen consumed. The ratio of man's CO_2 production-oxygen consumption (respiratory quotient, R. Q.) is not exactly 1. It only is approximately 1. In the case of photosynthesis, the comparable ratio, the assimilatory quotient with the gases moving in the opposite direction, is again not exactly 1, and, depending on which system one is dealing with, and under what conditions, both of these ratios can be modified a bit. Probably most of you are familiar with the way in which you can move the respiratory quotient by controlling the diet, including the nitrogen content. The same thing is true of a photosynthesizing system, by changing the nature of the nitrogen, one changes the current assimilatory quotient for the growth of these organisms.

Let us suppose that these quotients, the assimilatory and respiratory, do not match; then your system cannot possibly stay in control. One or the other gas is going to increase excessively or decrease toward zero.

BONGERS: I have some objection against considering only oxygen and carbon dioxide for closed ecological systems. Part of the inhaled oxygen ends up in metabolic water and is therefore still available. If the system is closed with respect to gases, food, and water, there is no reason to expect a serious mismatch.

BROWN: I am afraid there is, if you don't use the plant or bacteria for food, if you just use the system to balance gas exchange. There is no guarantee at all that you can match the assimilatory and respiratory quotients.

However, if you do plan to use the bacteria or the algae as a major component of the diet, essentially all of the diet, then you bring into play an automatic regulation that makes it almost certain that you will come very close to a match. Again, it may not be perfect, but it should be very close, and if it isn't perfect it is because of the detritus argument where there is pooling of some of the materials that must be cycled through a waste disposal system.

RAHN: In other words, if you have a particular culture and a

particular man, can you balance them or can you not balance them?

BROWN: You can balance them; by controlling the energy source to the algae in photosynthesis, you can produce an assimilatory quotient exactly the same as the quotient that man exhibits. It is possible, but there is nothing automatic about it. In other words, your diet must be a severely restricted, protein-rich one if you are not going to eat the algae.

SCHWARTZ: This is a purely quantitative balance. It has nothing to do with the qualitative balance, whether the spectrum of the nitrogen you are giving this particular man is what he needs. You have first to tell the bug to produce nutrients right for the man. The total caloric balance may be perfect or the thermodynamic balance may be perfect, but, biologically, it may not be so.

BROWN: Even if the man does not digest all of the algae, and you must incinerate the rest of it or reprocess it by some other route, I think it is still approximately true.

But, it does point up the fact that if you are not going to use the algae as food and you do use a photosynthetic system, you certainly have a problem in producing exactly the right kind of diet.

SCHWARTZ: Agreed.

BROWN: Not that there aren't problems if you are going to eat the algae, of course.

BONGERS: Is it, with respect to trade off, valid to consider algal systems for atmospheric control only?

BROWN: It could be, I think.

BONGERS: Actually the oxygen-rich carbon dioxide is stored in algae and is lost if the algae are not used for food.

BROWN: In the long pull you will trade your stored food for stored algal products.

BONGERS: That is right.

BROWN: That is, if you are not going to eat the algae but must carry food along. Ideally, we would like to be able to close the system as completely as possible, I don't know, and I am sure you don't know either, how complete the closure can be.

The thinking that has gone into the selection of algae over other plants has been simply that they are more efficient. The algae are all photosynthetic machinery, and for a minimum amount of plant protoplasm you ought to be able to do the job of balancing man's needs. Plants other than algae appear to be less efficient.

ODUM: What do you mean by efficient? Can you define "efficient"?

BROWN: Operationally, this is what it amounts to. Suppose we take mission time against weight penalty. Now we can convert power into kilograms and express everything in terms of what it costs in weight. We are assuming in this kind of calculation that the lighter system,

everything else being equal, is the better one to use, and if we have a mission of very short duration in which we store everything for only a few days we can put a point on a diagram and say, "This is what it costs to fly this mission."

If we extend the time, we have to increase the amount of stored material and we will get an ascending curve, not necessarily linear but a rising curve expressing the weight for any particular mission. A diagram describing partial closure of an ecological system would have some slope, presumably less than that for the "carry along" system. Even if the initial weight penalty were higher for the photosynthetic system in which the algae are not eaten, but gas exchange is taken care of, at some time these curves cross over. So for a mission shorter than the cross-over points you would use the storage system; for missions longer than that you would use a partially closed algal system.

If you could completely close the system and didn't need to carry any spare parts, and so on, the slope would be essentially zero. This is the very naive thinking that goes into the predicted calculation.

Very roughly, for missions of less than a month, it is silly to think of anything except a storage system, regenerating only water, if anything. For missions longer than a year or so, it is almost certainly necessary to use regenerative systems, but exactly where the break points are, I don't know. If we knew all we needed to know to make the engineering estimates necessary to establish the slopes of these lines and their height above the abscissa, then we could say for different kinds of missions exactly which system is best. The unfortunate fact is, we can't be sure at this time. We simply don't have the information we need to make estimates accurate within perhaps an order of magnitude, and that isn't quite good enough.

The limitations on the photosynthetic system are those of power, largely, because if you are not going to use natural illumination, you must convert some source of power into electrical energy and this into light energy, and that, in turn, into the energy of chemical bonds by photosynthesis. This, over all, is a rather inefficient process—something less than five per cent efficient.

Hydrogen Fixation

The calculations that one can make for establishing crossover times, and so on, must take this into consideration, and the use of bacteria instead of algae, and of electrolysis as the oxygen-producing mechanism instead of photosynthesis is a way to get around this problem. By producing a system (which I hope Doctor Bongers will talk about shortly) that is inherently more efficient in terms of the power conversion factors, you aren't necessarily solving any of the other problems. The equations balance there, too, but whether or not

the quotients will match precisely remains to be seen, and whether the bacteria turn out to be more palatable or nutritious than the unknown species of algae that we might end up with, again remains to be seen.

So these systems, at the present time are, in principle, competitive, and I think since we have the expert on the one type here, I should encourage an interruption at this point.

BONGERS: FIGURE 15 illustrates schematically a closed ecological system based on the coupling of electrolysis of water and bioregeneration by hydrogen bacteria. In this diagram it is shown that the oxygen required for human respiration is obtained directly from the electrolytic unit. The organisms do not participate—at least not directly—in the regeneration of oxygen, as occurs in the photosynthetic system. The hydrogen evolved by electrolysis and the carbon dioxide that is separated from the atmosphere by a scrubber are assimilated by the hydrogen bacteria.

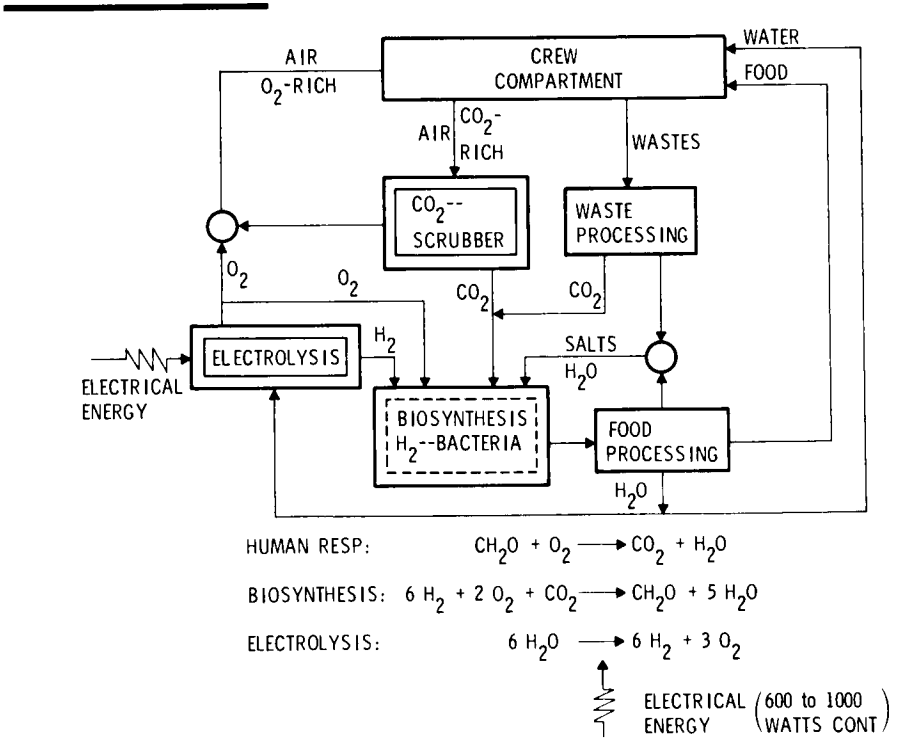

FIG. 15. Block flow diagram of a chemosynthetically balanced closed ecology. Biosynthesis by hydrogen bacteria.

The chemical balance involved in this ecosystem is described by the equations in FIGURE 15. A constant oxygen intake of 22 liters and a respiratory quotient of unity is accepted. Biosynthesis by hydrogen bacteria occurs, on the average, at molar ratio's indicated. The closure of this ecosystem requires electrolysis to the extent of six moles of water per hour and per man.

Depending on the efficiency of power conversion, the energy input to electrolysis is estimated to be in the order of 600 to 1000 watts continuously per man. This power requisite is less by some orders of magnitude than demanded by photosynthetic bioregeneration under artificial illumination.

In order to evaluate further the power and weight demands—two most important aspects of any life-support system—I will present now some information on growth characteristics, efficiency of energy conversion in carbon dioxide assimilation, and population density restrictions. In particular, efficiency and cellular density are of importance with regard to weight and power aspects.

FIGURE 16 illustrates the effect of suspension temperature upon growth rate and the rate of gas uptake. The optimal temperature for growth of *Hydrogenomonas eutropha,* used for these experiments is 35°C. The temperature optimum for gas uptake usually is higher, and might be reached at 45°C. Although the rates at these elevated

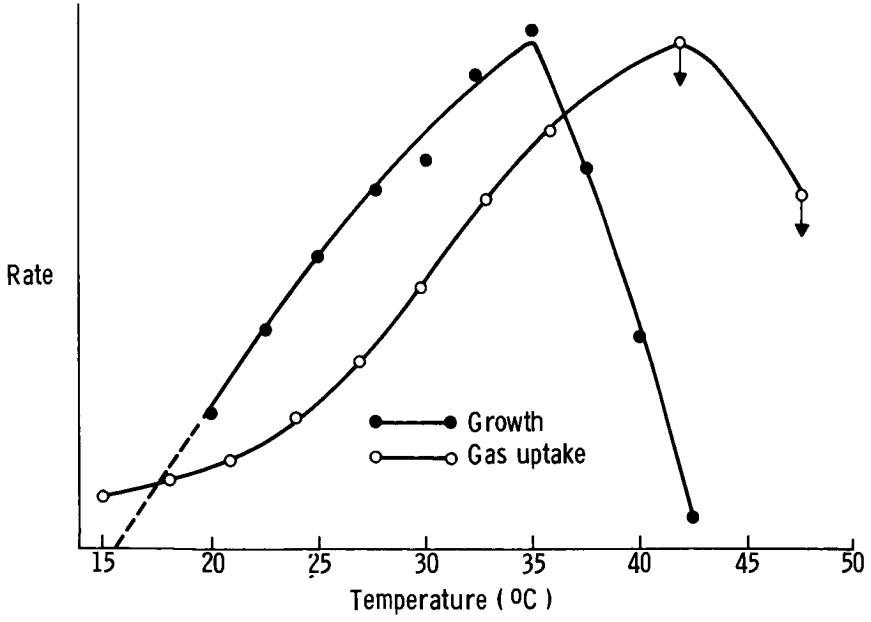

FIG. 16. Relationship between gas uptake and temperature (open circles) and growth (closed circles). *Hydrogenomonas eutropha.* Gas phase: 80% H_2, 10% O_2 10% CO_2.

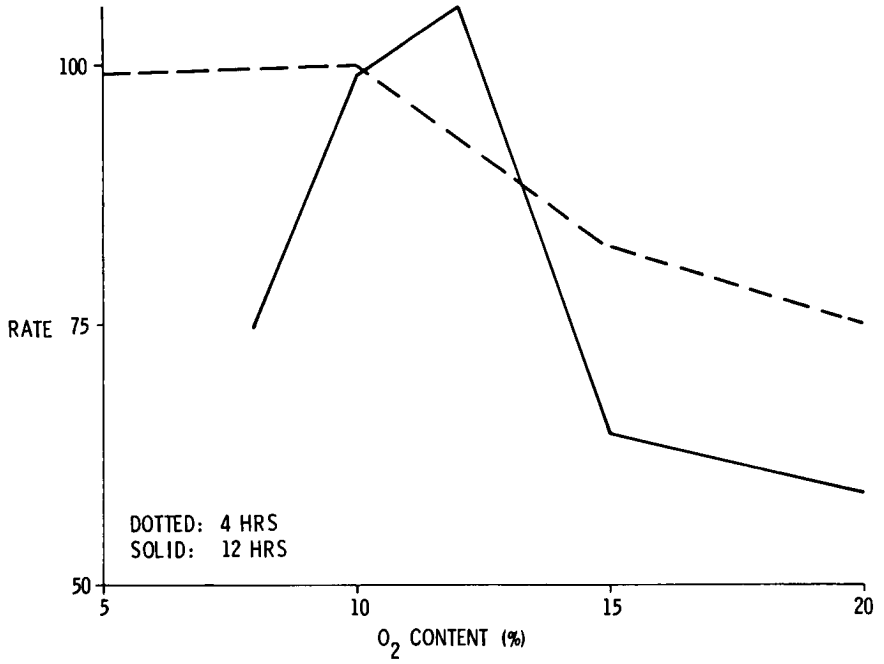

FIG. 17. Effect of oxygen on growth of *Hydrogenomonas eutropha*. Suspension temperature 30 C. Gas phase: 70% H_2, 10% CO_2, O_2 as indicated, N_2 balance.

temperatures are relatively high, they are unstable and fall rapidy after 40 to 60 minutes. For practical purposes the strain examined here functions best at 35°C. No significant effect of temperature upon biological conversion efficiency was observed.

The oxygen concentration in the liquid phase has a profound affect on the growth rate as indicated in FIGURE 17. Oxygen inhibition occurs assuming equilibration between gas and liquid phase if the oxygen content in the gas phase is 15 per cent or more (total pressure 1 atm). A solvated oxygen concentration in the order of 0.10 mM of oxygen is optimal for the organisms tested *(Hydrogenomonas eutropha)*. It is assumed that oxygen inhibition occurs through interference with hydrogenase, the enzyme that mediates the conversion of molecular hydrogen into a biologically acceptable form.

In addition to suppressing the growth rate, overoxygenation leads to a decrease in biological efficiency. This, in turn, would lead to an added energy input requirement. Experimental evidence indicates that the energy requirement might increase by some 30 per cent under such conditions. An accurately controlled oxygen supply is therefore advantageous considering both power and weight requisites.

The suspension volume of hydrogen bacteria, which is demanded to recycle the carbon dioxide output of one man, depends mainly upon the population densities at which these organisms can successfully be cultured. In order to estimate attainable population densities and to study the effect on carbon dioxide uptake by these suspensions, a series of experiments, represented in FIGURE 18, were carried out at varying cell densities. At optimal temperature (35°C.) hourly carbon dioxide consumption rates of two to three liters of carbon dioxide per liter of suspension were observed. Results have indicated that relatively high cell concentrations can be maintained if gas supply is equal to gas demand. No significant effect of high cell concentration on conversion efficiency was observed under the conditions of adequate gas supply. One might therefore conclude that a suspension of 10 to 30 liters of cells can consume 22 liters of carbon dioxide per hour. From a biological point of view, the relatively low volume requirement appears feasible. From a technological standpoint the higher volume requirement of 30 liters seems to be acceptable, as indicated by experimental information on gas transfer in yeast cultures.[73]

Presently, we may assume (disregarding uncertainties with respect to food acceptability and operation under steady-state conditions)

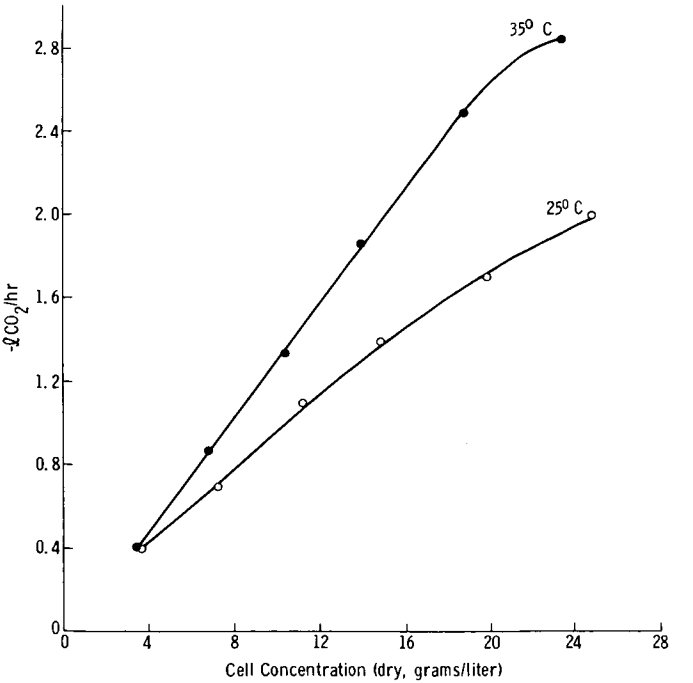

FIG. 18. Carbon dioxide consumption rate vs. cell density. *Hydrogenomonas eutropha*. Gas phase: 80% H_2, 10% O_2, 10% CO_2.

TABLE 4
POWER (WATTS) AND WEIGHT (LB) ESTIMATES FOR THE BASIC SUBSYSTEM INVOLVED IN THE LIFE SUPPORT EQUIPMENT REQUIRED FOR A THEORETICAL 270 MAN-DAY MISSION[74]

PARTIALLY REGENERATIVE		FULLY REGENERATIVE SYSTEMS					
		ALGAL				BACTERIAL	
		SOLAR III*		ART. III			
LB	WATTS	LB	WATTS	LB	WATTS	LB	WATTS
284 446†	1750	784 0	600	1300 0	25,000	285 0	2600
WASTE PROCESSING							
60	600	60	600	60	600	60	600
TOTAL							
790	2350	844	1200	1360	25,600	345	3200

*Gafford & Fulton, 1962[75]
†Food storage

that an ecosystem of 20 to 30 liters volume with a requirement of some 1000 watts of continuous energy input is both biologically and technologically acceptable.

A comparison (see TABLE 4) of this bacterial ecosystem with two algal systems and a partially regenerative system reveals that recycling of carbon dioxide and (pretreated)wastes via bacterial regeneration would involve the lowest weight penalty and be competitive in power demand for certain missions. At the present time, however, the partial regenerative system with food storage has a considerable advantage with regard to availability and reliability.

ODUM: Is it completely unrealistic to use solar energy in a space flight?

BONGERS: No, it isn't.

ODUM: Then, the algae system would not require any power.

BONGERS: If solar illumination is used, power is required for suspension management only. The data relating to the solar illuminated system (TABLE 4) are taken from Gafford.[75] Results obtained indicate that some 50 to 70 liters of algal suspension (per man) are needed on the condition that a sufficient turbulent suspension flow is attained.

This would introduce the so-called light intermittency phenomenon, leading to a more efficient light utilization.

JENKINS: The space engineers say that this isn't practical in a space craft. Also, his[75] figures are for light intensities at the level of earth and not out toward Mars where it drops significantly.

BONGERS: This would increase the surface area required per man. The light intensity of Mars is approximately half the light intensity that strikes the earth. Therefore, twice the illuminated surface area is required.

BROWN: There is no disadvantage in cutting down the intensity because it is much too bright anyhow.

BONGERS: If the illuminated area is calculated on the basis of an intermittent exposure, decrease in light intensity could indeed have an effect.

ROTH: In terms of oxygen sensitivity, many anaerobes are sensitive to oxygen. They can have their sensitivity altered by cobalt ions in the solution. This catalyzes the destruction of peroxides which are supposedly the agent in the oxidation of your enzymes. I wondered whether anyone has tried cobalt in these systems to push the oxygen sensitivity more toward the 20 per cent.

BONGERS: But how far do we change the hydrogenase-oxygen complex in this?

ROTH: Are you denaturing your enzyme?

BONGERS: No, you make it ineffective.

ROTH: You are not denaturing your enzyme, you are just shifting your equilibrium.

BONGERS: That is right. You don't gain much.

GRAYBIEL: Are any of these bacteria edible?

BONGERS: I think that is a nasty question. I don't know.

JENKINS: *Hydrogenomonas* bacteria have been sampled at Ohio State and they have been found to be palatable and rather tasteless. Detailed studies have not yet been carried out on animals nor suitable tests on man.

BONGERS: Hydrogen bacteria belong to the family of Methanomonadaceae. They are characterized by their ability to grow on substrates containing no organic matter and by their ability to use the oxidation of molecular hydrogen as a source of energy for growth. These organisms can be isolated from garden soil and grown in simple media. They are colorless, more or less rod shaped, approximately one micron long and gram negative.

GRAYBIEL: What is the longest period of time you have had your system in operation?

BONGERS: A day. This is a very recent system. This is not as far advanced as the algal system, and is not running continuously yet.

BROWN: Nobody has had any of these systems in operation for any extended period.

ODUM: You didn't have any food storage? As I understood it you had no food storage in the bacterial system?

BONGERS: That is right.

ODUM: If you add that, you are no better off than you are with the other.

BONGERS: The main reason for a closed ecological system is not to have food storage.

ODUM: You are assuming they would eat the bacteria?

BONGERS: That is right.

ROTH: What is the status of the artificial photosynthesizing systems that have been proposed?

BROWN: You mean the cell-free systems using enzymes?

ROTH: Yes, using enzymes or metallo-organic systems.

BROWN: Let me state arbitrarily that it is not worthy of consideration now. Maybe someone will wish to argue with me about this, but it seems extraordinarily unlikely that these are going to be the answer.

Could I raise a word of warning about basing considerations just on these tables of weight and power. My own very strong hunch is that the decision will not be based strictly on weight. The reliability of the system is almost certain to be much more important in the long run. On the three months' basis, within a factor of two or three, the algal, the bacterial, and the partially regenerative nonbiological systems are not very much different. As one goes out to longer and longer times the differences get somewhat greater.

But assuming that we are going to have payload capacity to do pretty much what we have to do, then I think that weight itself is not going to be the sole criterion at all. If it turns out that the bacteria can be eaten with less difficulty, and processing, and so on, than the algae, this in itself may be the deciding factor, or vice versa.

The reliability of the system, the ease of managing it over a long period of time, I personally think are going to be most important.

BONGERS: A final remark is probably in order. The closed ecological system that I have discussed seems feasible with respect to weight and power requisites. Application would require solutions to many more problems.

BROWN: The areas of least knowledge are the two we haven't discussed much: One is the nutrition problem. There is much too little information on the nutritional properties of either the algae or the bacteria. The other is the waste disposal problem, which is a very practical one. As far as the waste utilization is concerned, if we are to approach closure of an ecological system, we have to reutilize as much

of the waste as possible. If you decide that this is wrong, that we won't utilize any of it, then you have a monumental storage problem to solve.

The methods of reutilization involve both the chemical-physical and the microbiological. I think if microbiological methods are used, it will not be possible to convert completely waste materials to components which can be directly fed into an algal system, but the extent to which this can be done remains, at least for me, unknown.

As far as human nutrition is concerned, neither you nor I know what problems will be salient two or three years from now regarding the nutritional aspects of humans eating algae or algal products, or bacteria or bacterial products. At the present time there are no studies being carried out on the nutritional properties of *Hydrogenomonas*. As far as algae are concerned, there have been a few studies on growing and mature animals, and some tests have been carried out in humans. There have been no extensive studies on humans fed algae or algal products as even a major, let alone exclusive, part of the diet. The reason for this is not lack of interest, but rather the unavailability of usable algae.

Intermediates

ODUM: There is one point I might make about decomposition of waste materials. Again, in natural ecosystems, it is never accomplished by microorganisms alone. There is always an intermediate group of organisms which we sometimes call detritus feeders or something of this sort.

In the case of plant material, this may be millipeds; in the case of animals it may be insect larvae or something that greatly accelerate the breakdown and allow the microorganism to complete the job of breaking down the waste in about one-tenth of the time which would be required if you had only the microorganisms; so again I say your system will have to have another unit.

BROWN: This is quite true in so far as the natural systems you may have in mind. However, I am thinking of the managed systems where there is essentially one crop and one consumer, man, so that the waste products that we must deal with are the gaseous, liquid and solid wastes that man produces, and this is very different, really, from the natural systems you are thinking of.

It is very difficult to find organisms which will reduce raw algae to CO_2 and water. For some peculiar reason, algae resist this kind of decomposition. However, if man eats processed algae, presumably, this will be largely digestible. Then we are dealing with fecal material of a very strange composition, probably. We don't yet have good samples of this material to work with.

ODUM: You say that algae are very hard to reduce back. In this, you are referring to *Chlorella*, that type of algae?

BROWN: No, I am referring to a comment made by Halvor Orin Halvorson of Illinois,* who has been looking into organisms which will process natural algal populations and not just *Chlorella*, and he was struck by the difficulty in getting complete reduction of this material. It is quite different from the ordinary kinds of sewage that one deals with.

ODUM: I see. In fish ponds, which are chiefly algal cultures, we find many annelid worms, or insect larvae, or something that eats these dead cells the minute they fall to the bottom. The animal tissue converted from plant tissue decomposes rapidly.

BROWN: Our experience in this area stems very largely from experience in sewage processing where it takes quite a while to build up the proper flora for thoroughly processing a particular kind of material; but once you have it you can usually expect this to go to about 90 per cent completion.

ODUM: I think we miss a bet on sewage disposal by not thinking about having an animal component in there. Again, we leave out, theoretically anyway, the "chopper-uppers."

RAHN: What you want is a middle-man in there.

ODUM: That is right. The reason we feel strongly about this is we had a student who did a thesis demonstrating that a certain shellfish was vital to the ecosystem in speeding up the regeneration of phosphorus.[76] We might ask ourselves, in all fairness, why we have animals in the world, because, theoretically, with plants and bacteria we could have an operational system. One of the roles of animals is to break down the plant material quickly and to get the nutrients returned; man alone may not be quite enough to break this down, unless he chews up his food better than he has been doing.

FREMONT-SMITH: Are there any special components in algae that are known chemically, that are difficult to break down, like cellulose? There isn't any cellulose, is there?

BROWN: Yes, although the algal cell wall is not predominantly cellulose as is the higher plant cell wall. Since no expert is interrupting, I will say that apparently the answer to your question is yes, but I don't understand why it is so.

ODUM: You can select algae, as you well know. *Chlorella* has a tremendous range. We can breed strains that have high protein, and we can breed strains of high fat and so on; so you should be able to select a strain which decomposes.

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*Personal communication.

FREMONT-SMITH: What are the components that are difficult to decompose?

SCHWARTZ: The cell wall, the polysaccharides, the polygalactans, the mannans, and that kind of thing. Unfortunately, man does not have cellulases of any very varsatile quality as compared with the ruminant, who one way or another manages to devise ways* of digesting cellulose.

ODUM: Put an organism in that has cellulase.

FREMONT-SMITH: This is the middle-man you are talking about.

ODUM: Yes. It is very striking that if you put napthalene or PDB on top of the litter in a forest, you inhibit the small animals which chop up dead leaves, without interfering with the microorganisms themselves. Yet the rate of decomposition of the leaf litter is greatly reduced, because microorganisms can not "get at" the detritus until "chewed up" by the animals; these "middle-men," these animal decomposers, must come between the plant residues and the microorganisms.

FREMONT-SMITH: The chain is broken?

ODUM: Yes. At least, there are so many complexities to decomposition that you need a chain.

FENN: My own practical suggestion for a middle-man is a snail.

CALLOWAY: But it has a shell and would accumulate minerals.

ODUM: How about the slug? You know, a slug is a snail without a shell. The *Mollusca* have this cellulase enzyme; they have a crystalline cone, a special device which is associated with this enzyme system.

CALLOWAY: The rate of growth is quite slow.

RAHN: How about the protozoa that live in the intestines of termites?

ODUM: This is what I think we should do in agriculture, as I mentioned before: I think we should cultivate organisms that can turn cellulase into sugar and use the sugar to increase our own food supplies.

BONGERS: What about efficiency if you include another cycle? As far as I can see, it means a decrease in your efficiency by a factor of four or five, and an increase in your power requirement by a similar factor. This is already high.

BROWN: It depends on where you introduce your middle-man. If you introduce him to process the plant food, then surely this is the result; but if you assume that the plant food will not be completely digested by man (and certainly if it is eaten directly it won't be), then a middle-man can come in during the waste processing cycle. Then your objection doesn't hold.

**Ed note:* Breakdown of cellulose in the rumen is accomplished by the resident bacteria and protozoa.

ODUM: Also, the metabolism of these extra components is very small. That is what I am basing my suggestion on: that the actual increase in respiration or use of oxygen by the organisms is very small in terms of the effect they have in quickening or hurrying the decomposition phase. At least, if we use soil as a model, you can take out the soil animals and you remove only one one-hundredth of the total soil respiration. The rest of it is microbial but that one one-hundredth has a large effect in terms of mechanical breakdown.

BROWN: But if you introduce another organism as a middle-man in processing the plant material before man consumes it, then the effect is not small. Doctor Bongers mentions a factor of five.

ODUM: A factor of five what? I don't understand.

BROWN: It takes five times as many calories to feed a man if you turn the plant material into animal material before the man eats it. This factor of five is a rough approximation.

SCHWARZ: I wonder whether this will always hold true if you pick the right organism. I think that is true of our present managed economy.

BROWN: You mean the cost of the middle-man, or the need for a middle-man?

SCHWARZ: I am talking about the efficiency of the middle-man. I guess the chicken is the most efficient converter, isn't it, from vegetable—or is it fish?

SONDHAUS: Fish.

ODUM: The reason I challenged you on the word "efficiency" a moment ago is that too often the efficiency ratio is not a dimensionless ratio. A pound of chicken produced by 10 pounds of chickenfeed is not the same as one calorie of chicken produced by 10 calories of food intake. One needs to be careful about these ratios and be very sure the components are in the same energy unit.

BONGERS: When I am referring to efficiency, I am really thinking about electrical power.

ODUM: Well, a 10 per cent jump in food chain is what we assume is a reasonable figure. In other words, you have one hundred calories of corn, you can get 10 calories of pig, or 20, maybe.

BROWN: That is conservative; it is probably less than 10, even as low as seven to five in some cases.

SCHWARZ: Do these figures hold in all cases? If you work through microorganism chains, I think it is a little better.

ODUM: The laws of thermodynamics are the same, but maybe there is some difference.

BROWN: Thermodynamically, the efficiency loss could be very close to zero, could approximate zero. It won't really, but in principal you could say it should.

FREMONT-SMITH: There is one point Doctor Odum made which I think needs to be stated again, and that is, the word "middle-man" came in, but it seems to me that "middle-man" is the wrong term. You have two cycles. You are talking about a second cycle rather than an intervention in the primary cycles. Isn't that true? I think this makes all the difference in the question of efficiency.

ODUM: I am talking about getting the detritus quickly done. This is the bottleneck I mentioned and most natural systems have trouble with this—getting the organic matter quickly decomposed so as to release the minerals for growth.

FREMONT-SMITH: But this is not the main cycle; really it is a side cycle off the main cycle.

ODUM: It could be. If man eats the algae, then there is not very much left to be decomposed. If he doesn't eat it, then you have a bigger job.

FREMONT-SMITH: But in the first case, where man eats it and there is only a little bit left, your efficiency would not be very much reduced, whereas, in the other case, as I understand it, you put the animal (the middle-man) in the main chain and then it will make a big reduction in efficiency. Is that correct?

ODUM: I think so.

DUBOIS: In the case of algae, we are told by Doctor Frank J. Hendel,* North American Aviation Co., that to get enough algae to make enough oxygen, the reproduction rate of algae was such that the algae would oversupply food, so that you get a pound a day more algae than you can eat. I wondered if this were current thinking and, if so, what you do with the extra 40 per cent.

ODUM: That is why you need a detritus eater. You need some kind of organism that will take care of it.

BROWN: I am afraid the 40 per cent discrepancy comes from the way you calculate. Let's simplify this by saying that the assimilatory and respiratory quotients are both unity—at least they match. It is simply a matter of the law of conservation of matter that you cannot produce more food than the man would eat in order to balance the gas exchange, but since the quotients are not exactly the same you can take the extreme respiratory quotient and the extreme assimilatory quotient, and the mismatch can be as great as 0.4. I think this is the origin of the calculation, as I understand it.

ODUM: This is assuming 100 per cent digestibility.

BROWN: I think it would be independent of that. That would be another calculation.

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*Interim report of proceedings of Working Group on Gaseous Environment Man in Space Committee, Space Science Board, March 13, 1962.

HELVEY: If you have a middle-man, as Doctor Odum has suggested, can you safely generalize whether additional components will affect the reliability of a biological system? and, secondarily, what do you consider the reliability of most of these biological systems, relative to chemical or physical systems?

BROWN: I don't see how one can generalize on that point. On the assumption that we are dealing with managed systems, we will produce essentially a single crop. I don't know what species will be the species of choice.

But, assuming that you can produce the best of all possible crops with a single species, I think, in terms of processing the waste, you are faced with essentially the same problem: You will have to produce the best of all possible mixed flora, certainly not a single species, to process the particular waste that will be produced and this, too, will have to be managed. My own hunch is that waste processing will not be sufficiently close to 100 per cent to enable you to avoid a short circuit.

If man produces some wastes which are decomposed by incineration or microbiological processes that produce carbon dioxide, this in a sense is a waste of energy of the whole system. But it is a necessary waste, and my hunch is that we will use both microbiological and chemical-physical methods to accomplish the waste reprocessing operation. I can't defend this, though.

SCHWARZ: It is a fair assessment of the present state of our knowledge, I think.

Edibility of Algae

HELVEY: Could a man stomach as much algae as is produced, in terms of a balanced diet?

BROWN: There is no evidence yet that ordinary dried algae can be eaten as the sole component of the diet. There have been few attempts, and in one case the result was rather disastrous, and the substitution was not complete by any means.

It is a little difficult to say whether the result was due to the algae or to the other things that went along with the algae. The material used was not pure *Chorella* even though it was supposed to be. It contained other algae species. It also contained yeast, and I am sure bacteria.

CALLOWAY: In my experience, about the largest amount that can be fed to animals for extended periods of time is 60 per cent of the dry solids of the diet. We have fed nearly 100 per cent algae diets and some animals lived, but there was cannibalism. Presumably, mouse is a good dietary supplement to algae.

BROWN: Young animals or mature animals?

CALLOWAY: These were mature animals. Growing animals are not especially good for assessment of this system.

BROWN: Not everybody thinks so, because many experiments are carried out on growing animals. I think this is quite inappropriate.

SCHWARTZ: This is a basic misconception, in my opinion, but it is only an opinion.

CALLOWAY: It depends upon what you want to know. If you want to determine a specific factor—perhaps biological value of the protein—then you will select a test system designed to describe that factor precisely. But, if you want to know whether algae will support mature men, then you can use a mature animal, although preferably not a furred one.

In man, the most extensive study reported is the one to which you referred earlier, I think. A mixed Japanese culture was used and it was autoclaved because they were afraid of bacterial contamination.[77] I don't know of anyone who has fed algae grown in pure culture.

Using the contaminated cultures, levels up to 200 and 500 grams a day were given but gastrointestinal distress was reported. These responses could have been partially subjective. I don't think the evidence can be counted applicable to other algal preparations.

FREMONT-SMITH: How long were they able to take that amount?

CALLOWAY: The men started with small doses, 10 grams a day for the first week. Algae content was progressively increased up to 500 grams, with a day or two of regular diet between increments. Only two men tolerated the 500 gram dose for two days.

BROWN: Doctor Jenkins, can you tell us what NASA is doing about providing material for these experiments—that is, finding some clean algae that can be used so that the results will be unequivocal? I know you don't have any program, but how hard are you trying to get some?

JENKINS: NASA has two groups that are growing bacteria-free algae that are mitobiotic: Doctor Robert Krauss at the University of Maryland and Doctor Calvin Ward at the Air Force laboratory, School of Aerospace Medicine.

BROWN: What quantities are going to be accumulated by these two contracts?

JENKINS: Not large quantities. These are studies for proving that you can grow continuous cultures of algae that are not contaminated by bacteria or fungi.

ROTH: Do algae have viruses?

BROWN: If you can find one, a lot of people would be excited about it. You can, of course, grow uncontaminated algae in pure culture, but when you want tons of algae—which is probably what you will need before you are through—this is a rather heroic venture compared with

the small Erlenmeyer flask scale that we are operating on now. There is no reason why it can't be done, but it just isn't being done, so far as I know.

FREMONT-SMITH: It is not so easy to exclude viruses. You can prove that you haven't found any viruses in a culture of algae or something else, but that is a long way from proving there is no virus there. There are quite a number of surprises along these lines which have taken place, and I should think should be anticipated.

BROWN: It is possible that a virus that will attack man can be carried through the algae without showing up as a disease of the algae—*possible*, I said.

FREMONT-SMITH: Yes, and all you can do is report the absence of any virus by the methods that we use to try to find the virus, but there are other possibilities. For example, it is possible to get viruses out of certain bacteria using ultrasonic energy, where you would never guess that they were there otherwise, as in the transduction experiments.

ROTH: A question was raised before about the fact that you get more food than you have photosynthetic capacity. Has anyone attempted to select strains where you get a dissociation of photosynthesis and cell production, or is there a drug analagous to, say, thyroxin, where you get dissociation of oxidation and phosphorylation that would allow you to increase photosynthetic capacity without increasing your general metabolic or biosythetic capacity?

BROWN: Photosynthesis is biosynthesis and if you measure photosynthesis as the production of oxygen or as the consumption of CO_2, or as the transformation of light energy into chemical energy, then you are going to produce food. There is no way around this.

ODUM: But you can have a higher respiration rate in the whole culture and use up some of that oxygen so you get around it that way. All you need is a climax culture that has a large respiration rate and will use up its own food.

BROWN: Then you are making the plant itself do what you hoped the man would do. There has been the suggestion that one should select algae for low respiration rates so that they will carry out photosynthesis and produce a lot of food but won't respire the food they produce. This is, as far as I know, only a suggestion. The same thing is true on the bacterial side, and probably with bacteria will be more serious.

I don't think this is a major factor because the amount of loss of material by what amounts empirically to the reverse reaction (respiration) is relatively small and is swamped by many other considerations.

ODUM: I still think you go about these problems in a hard way. In other words, we take man, who is used to 20 per cent oxygen, and

put him in 100 per cent; and here we are making man an algal feeder and he has never been adapted to, nor had any reason to be, an algal feeder.

I can find no published work on duckweed as possible plant for spacecraft, although I heard a report on such work at the last AIBS meeting. Jenkins or Reynolds of NASA can undoubtedly supply a reference to a report or paper in press. I know some people have done work on some of the small-size higher plants which are more palatable, such as the *Wolfias*, the *Lemnas*, duckweed, and so on. They are small floating aquatic plants, higher plants, and, therefore, a little closer to what we are used to eating—but they are small. May I ask what is the status of that research in terms of nutrients?

BROWN: I have only second-hand experience with this. The duckweed has apparently about the same potential, roughly, in terms of photosynthetic efficiency as does *Chlorella*, and is said to be more palatable than *Chlorella*. I don't think *Chlorella* is unpalatable, and I don't think anybody has lived for a long time just on duckweed any more than he has on *Chlorella*.

CALLOWAY: The Air Force has nutrition studies of duckweed programmed.

FENN: Do they have as high a percentage of protein as *Chlorella?*

ODUM: Strains can be selected for protein—anything you want. Just like other plants, you can breed anything you want.

BROWN: High protein is not a desirable feature.

FENN: I wondered if it was undesirable.

ODUM: If you get up to 12 per cent, that is not very high.

ROTH: What about the problem of carbon monoxide that Syrrel Wilkes[78] once brought up, as a by-product of incomplete or pathological photosynthesis? Is this something that one concerns oneself with these days?

BROWN: To get rid of carbon monoxide in the cabin atmosphere is relatively easy, technically, so that we don't think this is going to be a serious problem. The rate of production is low and if you simply oxidize it to CO_2 catalytically, you take care of the problem, whatever its magnitude.

NEUMAN: I want to go back to human nutrition, if I may. It seems to me, from the standpoint of logic, that we have been talking about complex ecological systems and simple ecological systems. Of course, as a biochemist, a system that is simple appeals to me, at least as an approach. But, if the simple system isn't adequate for human nutrition, it is cooked.

CALLOWAY: Not at all.

NEUMAN: Without supplement.

CALLOWAY:But there can be supplements.

NEUMAN: If the supplements are minor in weight, all right, but this is a terribly crucial point, it seems to me—just as important as feeding the thing and testing efficiency and measuring energy requirements. If you can't eat the algae or whatever, they won't work.

BROWN: Of course, if they make you sick you can't eat them, but if they are simply low in the sulfur-containing amino acids then you can supply these as a supplement and make do.

HELVEY: Does anyone think we are going to feed algae cookies and vitamin pills for periods of months or years? This is a very serious question.

Submarine crews are known for the best food in the Navy. I was just looking the other day at the variety the Army is providing for troops in a foxhole, which we expect a man to live on for, we hope, no more than a week. I just wondered what people who have more experience than I feel about this. What is the likelihood of feeding crews this way for long periods of time, even if they are able to eat such things as algae as a primary source of food?

CALLOWAY: It depends entirely on the mission. I think it is fallacious to compare the pioneers in space with the man in the foxhole or the submarine crew. The pioneer is more to be compared with people like Peary and Hillary, who are dedicated to a mission. It wouldn't be a lot worse to live on algae cookies than penguin and whale blubber. That is a different category.

But when you talk about putting men for a year on a space station where they are assigned a mission for which they did not volunteer but were selected just as for any other military duty, you are in another area entirely. They will not tolerate, I think, what your pioneer will.

Chemically Defined Diets

SCHWARZ: The basic question starts, I suppose, with, what is the minimal nutritional requirement for the man in the capsule?

CALLOWAY: What are the minimal requirements before you get him in the capsule?

SCHWARZ: OK, then you have some special problems once you get him in.

CALLOWAY: Minor compared to the big one of what he requires normally. I think we could predict reasonably well what a population of one hundred thousand people could eat and stay healthy. The problem is to decide the requirements for one individual of that population.

SCHWARZ: While there is a great deal of nutritional information, and some of it amazingly ingenious for the state of the art of measurement at the time it was done, we still haven't taken advantage of all of the sophistication that is now available to us to determine what the minimum nutritional requirements, of man may be.

ODUM: This may well determine your minimum system.

BROWN: Could you expand on that, what do you mean, specifically?

SCHWARZ: This isn't just a question of calories. It is a question of balance, and of what goes into the calories, and I think the first thing you need is a tool to establish such standards. This is what NASA is in the process of trying to do now with completely defined liquid diets.

I think you need such a tool as a first order of business in order to decide what you have to do with any microbial harvest to suit it to the nutritional needs of man.

BROWN: Would you explain the rationale of these liquid diet experiments? Is this simply a feasibility demonstration, or is there much more to it than that? Why bother to feed man a completely defined diet?

SCHWARZ: I think it is only partially a feasibility test. I think it is a tool around which one designs the whole approach to the nutrition of man in space or anywhere else.

DUBOIS: Could I ask about this completely defined diet? Has man ever been kept on a chemically defined diet over a long period of time and been found to stay healthy and in balance, or is there always some unknown, crude, factor which has been included in the diet?

BROWN: So far as I know there is only one human study in which the diet has been completely defined, and this has been extended for some weeks—the California prison experiment?

DUBOIS: In the past, many people were fed diets in which there was wheat germ or some other crude factor. When you buy vitamins in the drug store Vitamin B is often included, but it is not known whether this is essential in the human diet. What is the answer to some of these questions.

SCHWARZ: The answer is that insofar as better than normal standards of purity are concerned, the present test diet is completely defined. Insofar as ultra pure chemistry, is concerned, it is obvious that there are trace minerals kicking around, which we haven't tackled, but which may very well be necessary. After all, Klaus Schwarz[79] discovered that one part in four hundred million of selenium is essential as an antinecrotic factor for liver, or certainly it is in some instances. Surely in the sulfur compounds included in this diet there is probably this amount of selenium. You just don't get it out. But in terms of chemical definition, every component of the diet is highly purified and substantially known.

DUBOIS: I am lost. By "this diet" you mean the diet fed to the prisoners?

SCHWARZ: That is right.

DUBOIS: Is that one prisoner or several prisoners?

SCHWARZ: Originally, there were twenty-four, but not all of them

completed the study for reasons unrelated to the direct goals of the program.

DUBOIS: How did you know what to put in this synthetic diet? Did you put vitamin E in, for instance?

SCHWARZ: Maybe this is the time to give the background on this program. The diet is a development of the completely defined diets developed by Greenstein, *et al*,[80 89] during the fifties, at the National Cancer Institute. It was their conception that a completely defined input, which had the capacity of being varied one factor at a time, would be an enormously useful tool in studying growth of all kinds, including cancer. For them it was a basic biochemical tool.

Their first experimental animal was the rat, which has its own nutritional requirements, and these rats were not gnotobiotic. It was an inbred strain, the Sprague-Dawley strain, which presumably had a varied intestinal flora which unquestionably played a role. They were able to carry a number of experimental sets through generations of life with complete success from weaning through mating, gestation and very successful live births.

So the basic practicality of developing a completely defined diet on which a mammal could be propagated with something like the same control one gets in a microbiological population was essentially achieved.

Perhaps I should give a general overview of what is in this diet, for those of you who are not familiar with the literature. The nitrogen portion is supplied entirely by highly purified L-amino acids, both the essentials and nonessentials.

The first amino acid profile was more or less patterned after the amino acid profile of casein and took into account the excellent work of Rose and others. There also is a calcium and phosphate source in the form of calcium hexose diphosphate, which in addition to serving as a soluble organic calcium and phosphorus source, also serves as a general chelator and "solubleizer" of this diet.

Then, there are water-soluble vitamins and trace minerals in the form of reagent grade salts. The only source of fat in the diet is ethyl linoleate and it is fed at the level of two grams per man per day.

Fat soluble vitamins are dissolved in the linoleate. The balance of the diet is glucose. Other carbohydrate sources have been used such as dextrins, sucrose, etc. In experimental animals the carbohydrate source can make a difference.*

Ed note:* Results have been published of the experiment in progress at the time of this conference, in which a chemically-defined diet was fed to prisoners for four months; see Winitz, M., J. Graff, N. Gallagher, A. Narkin & D. A. Seedman. 1965. Nature **205: 741-743. Differential carbohydrate effects were reported separately; see Winitz, M., J. Graff & D. A. Seedman. 1964. Arch. Biochem. Biophys. **108:** 576.

In this diet, all of the components are soluble. There are some problems in getting the fat portion to distribute uniformly or to disperse completely in the water soluble portion. In the Greenstein work, "Tween" 80 was used as a disbursing agent. This has been cut down in the human experiments because the amount of "Tween" employed in that earlier work would have been well over the FDA limitations and it was obvious from a few early unpublished human experiments that this caused some trouble.

At present, I believe, the fat portion, including the fat soluble vitamins, is being added to the diet at the time it is offered, or it is offered separately, and this doesn't seem to have had any effect on its acceptability.

One can make a concentration of this mixture, which is as high as 70 per cent solids, but the most common concentration in animal experiments has been 50 per cent. The diet is a clear, somewhat viscous, very pale yellow solution with a caloric value of about two thousand calories per litre.

Its palatability, as it is now prepared for the California experiments, is acceptable. There have been no complaints on that score. I understand that flavoring is being added. The flavors used are such things as raspberry, lemon, and so forth, which are not completely defined. However, they are very small amounts. I am not sure that this is necessary. I think there are other ways of controlling palatability by varying the nonessential amino acid components. We are going to work on that.

There remains some question as to what concentration will be acceptable. Initially, the diet was offered without a limit and I understand some participants have an intake in the range of three to four thousand calories, which seems high for the amount of physical activity they're engaged in.

This diet has several virtues which I think are more or less unique. In the first place, it can be sterilized by filtration with, so far as anybody has been able to discover, no change in its total nutritional value. This can be rather important if it becomes necessary completely to control the microbiological population of any system.

Secondly, it produced negligible residue. As I understand it, the average so far is in the order of thirteen grams per day. Since the intake is something between six hundred and seven hundred fifty grams of solids a day, efficiency of utilization is pretty high.

The human trial, which NASA is supporting at the California Medical Facility, at Vacaville, was originally designed as a ninety-day pilot study to see whether one could manage such a human feeding experiment successfully; what the problems would be in administering the diet to man. There has been great enthusiasm for the early results.

The goal is to conduct experiments in which more sophisticated nutritional information can be obtained. We now feel it is feasible to feed such a diet to man for a reasonable length of time. One of the theories that we hope will be tested is the notion that individual amino acid requirements may be predicted by the fasting serum free-amino-acid spectrum of an individual. So far this is an idea, which has not been confirmed.

We think it is a fair assumption that every individual to some extent must have slightly different optimum requirement in the spectrum of amino acids offered; perhaps also in the ratio of glucose to total nitrogen, and some other things. The question is, how can you find out what this is for any individual without doing a one factor, empirical range-finding experiment, which might take a very long time? It has been suggested that the free amino acid ratios of the fasting plasma of an individual might give some information on this. I am not sure I am convinced, but it is an intriguing idea.

BROWN: Is it true that these prisoner-subjects are actually maintaining or gaining weight?

SCHWARZ: They are all maintaining weight. Initially they lost some weight but they are all going well now and they are all in positive nitrogen balance.

BROWN: And this is also probably the most expensive food ever eaten by man over a long period of time, is that not right?

SCHWARZ: At the moment it is. But I don't think this is a particularly frightening factor. The purity standards set for this initial work reflect the standards established by Greenstein and his associates for a research tool. This makes the diets more expensive than I believe they will need to be when we've come to understand better the significance of various variables.

As a tool for precise nutritional research, the diet is as good as it should be, but no better. There are dividends here that go beyond finding what we are going to feed astronauts.

I think none of us who is associated with this program has the notion that what we have now is the archetype or even a prototype We do feel that the defined diet is a very potent tool to focus on what it is that we have to provide in either a totally or a partially closed ecology, to sustain man for a long time in exotic environments.

Our particular role* in this is purification of the ingredients, a study of the stability of this diet under various conditions; and the possibilities of offering it in various physical forms, and organoleptic qualities. It is perfectly possible to make a wide variety of food forms from this dietary formula.

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*Under NASA contract NASW-517 with Schwarz BioResearch, Inc., Orangeburg, New York.

GRAYBIEL: What is the cost of the diet per day?

SCHWARZ: The purified solid components, complete, run romething in the neighborhood of $30 a kilo.

BROWN: It is a little more than "Metrecal."

GRAYBIEL: You said there is a need for more calories than ordinary. What happens to them?

SCHWARZ: I have no explanation. All I know is that they are taking a substantial amount. It seems to me that for the kind of activity that these men are engaged in, 3700 calories a day is a lot.

BROWN: Wouldn't someone like to expand on how this tool is going to be exploited?

FREMONT-SMITH: Might it not give an introduction to the more difficult problems of the absolute needs of a growing child? Doesn't this open the door—not that it would provide an answer, but wouldn't it give a new approach to it?

CALLOWAY: May I say a couple of things about the tool? To answer your question, Doctor DuBois, the vitamin and amino acid levels do not represent minima for man, nor did they for the experimental animals. Most of these were set at levels known to be above the requirement for the species under study. This diet was used in Doctor Greenstein's laboratory for rats and mice, and has been fed to some human subjects who were cancer patients.[90]

The diet includes materials that may or may not be required but once you establish (and Doctor Schwartz' point was quite good) that man can get along on this diet, then presumably you could withdraw from it or add to it.

There are other things to consider. The diet has a high osmotic load and, in concentrated form, it is quite lethal to poultry.[91] If you have a man in rocky water balance, presumably the diet could induce a dumping syndrome. So you can't treat it as the be-all and end-all without some consideration of what else is going on in the system at the same time.

Another factor that may limit the extension of findings to practical feeding situations is that the diet might not support the usual bacterial population. Intestinal flora are not without influence on the nutrition of the host animal.

Also, it takes more calories to maintain a man with this kind of diet than with more slowly absorbed forms. There are many differences, I think. That doesn't take away from its experimental value but when you talk about human feeding, you have to differentiate between the experimental and the practical.

SCHWARZ: I would accept everything that you have said. We have begun to look into the question of water balance in some of our experimental animals. This is extremely interesting. For instance, there

are tremendous individual variations which we don't pretend to understand yet. I think it is pretty obvious that water balance in the astronaut is a highly important factor.

I might also say that, the prisoners, at present, are taking water ad lib, but it is all measured, and they are trying to get a water balance on them too.

I suppose before we are through we will concern ourselves with feeding the diet at various concentrations. This, as far as we can see, doesn't present any serious problem in terms of the closed capsule because water is not going to be a limiting factor.

I think the question of intestinal flora is important too. It is true that you are certainly not adding any bacteria—there is no bacterial input here because the diet is sterile. It doesn't mean that one couldn't devise means of stabilizing bacterial intestinal flora if this turns out to be valuable. Certainly if one looks at the size of the caecum (the caecum may be six times the size of a normal caecum) and the caloric requirement of gnotobiotic animals one is impressed by the fact that although they eat a great deal more they are obviously suffering from lack of the symbiotic action of microflora.

Maybe one could intelligently introduce intestinal symbiosis in some way, but the literature offers very little on this subject.

BROWN: Maybe something can be said about the effect of high oxygen tension on the gut flora.

HELVEY: We did look at that. Doctor Galt, a microbiologist, took skin filth and fecal samples of all of our subjects.[3] The fecal samples showed no remarkable changes. The spectrum was essentially unchanged, although the six subjects in the chamber together developed a common pool of flora. There did appear to be some possible change in the morphology of the skin bacteria, but nothing significant in the throat. Also, in the intestine, some previously undescribed anaerobes may have been present. I should add that Doctor Galt is, I would say, one of the foremost recognized authorities, if not *the* authority on anaerobes; she might spot something previously undescribed, that many other investigators might miss. In summary, we would say that the fecal flora was essentially unchanged by the oxygen environment for the two weeks except, as I say, for a more common spectrum among the six subjects.

ROTH: Vaguely, I remember a fact about rodents; that they depend much more heavily on the GI flora for their general nutritional status than do carnivores and humans. I just wonder, in terms of your projection from the animal studies, how much of a role the fecal flora would really play in determining individual differences, and whether, if you were really strapped, you could feed a broad spectrum antibiotic, start from scratch, and get a more uniform dietary requirement.

SCHWARZ: This is certainly one of the things we are going to try to do. People have various views on how practical this is. Are you talking about humans or animals?

ROTH: Either one; take a primate or a dog or something and do the same type of experiment with him rather than with an animal that you know is heavily loaded with bacterial flora that constitute variables in nutritional studies.

SCHWARZ: No doubt it would be highly desirable to come as close as you could to wiping out the intestinal flora and then reimplanting a new population based on whatever data you have as to what the normal population was, and see what stabilized. This, we have in mind to do.

GRAVITY AND ACCELERATION

Discussion leader:
HILDING BJURSTEDT
Laboratory of Aviation and Naval Medicine
Physiology Department, Faculty of Medicine
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FENN: When you start with oxygen, you can begin by defining what oxygen is and going through all the physical chemistry of it and introducing the subject on a basic level. However, with gravity, we don't need to do this, because we don't know what gravitational force is and we don't have any 0 G. We just balance it out with an acceleration and say that there is nothing there. Whether we define it or not, it is a very fruitful and interesting subject, and we are grateful to Doctor Bjurstedt for coming all the way from Stockholm to introduce the subject.

BJURSTEDT: A moment ago I was asked whether we were going into impact acceleration today. I propose, though, that we concentrate our discussions on problems of prolonged acceleration, and perhaps we can then see if there will be time left for dealing with problems of impact acceleration stress.

One way of dealing with our topic is to list on one hand the types of G environment we are going to talk about. For this purpose I propose that we discuss the effects of: *(1)* various G time patterns of the nearly rectangular shape, which have often been used in centrifuge studies: *(2)* G profiles used in the launch and reentry phases, or proposed for these phases in the Apollo or other space missions; and *(3)* the effects of body position in relation to the direction of G force. If the duration of the G force is sufficiently long, we will have to deal with several more or less generalized effects on the body. This leads to a number of problems, which I have tentatively listed as follows (without even trying to make this list complete). I think the discussion will soon show whether it has to be changed or supplemented. For example, we might consider: *(1)* primary effects on the systemic circulation, *(2)* primary effects on the pulmonary circulation and gas exchange, *(3)* adaptive cardiovascular responses, *(4)* functional dis-

turbances secondary to insufficient adaptation, *(5)* need for protection, *(6)* means of protection.

FREMONT-SMITH: When you say prolonged acceleration, do you mean a prolonged new level of rate, or do you mean a continuing acceleration—an accelerating acceleration?

Pulmonary Effects of High G Forces

BJURSTEDT: I mean both. However, it might simplify some of the discussions if we start with the nearly rectangular G time pattern, which has been used for many years in centrifuge work to study various cardiovascular effects of G. After going through some of the effects of varying the height of the G plateau and its duration, we could go on to more complex shapes of the G profile.

I should perhaps add that "by prolonged acceleration" I mean G forces of very long duration, lasting longer than 15 to 20 seconds. This is in contrast to the acceleration patterns that were encountered in combat aircraft during World War II, at which time most of our knowledge was restricted to the effects of relatively short-term exposures, lasting less than 30 seconds, and with the G force acting in the head-to-foot direction. However, with the advent of jet propulsion, pilots were exposed to G profiles of much longer duration, and as a result new problems were introduced. Previously, blackout and loss of consciousness had been the two most important effects from the practical point of view. With the new, long-duration exposures, we had to consider whether some harm might be done to other physiological functions, especially in the CNS, if the level of acceleration was kept below the so-called blackout threshold. Acceleration physiologists therefore began looking for effects that might not show up until the G stress had lasted for several minutes.

In the search for physiological changes with longer "time constants" than those responsible for blackout or loss of consciousness, work was begun in many laboratories, around 1955 I believe, to study the effects of subblackout G levels on respiration and pulmonary functions. In this country, perhaps most of the experimental work pertinent to this problem area has been concerned with the effects of transverse acceleration (G force acting perpendicular to the long axis of the body), while in our own centrifuge experiments interest has centered on the effects of G forces acting in the head-to-foot direction.[92 94] Previously, any effects of G stress on pulmonary functions had been thought to be of only minor practical importance, possibly because of their relatively sluggish responses. By contrast, it could now be argued that prolonged acceleration might lead to progressive deterioration of the supply of O_2 to the blood and the elimination of CO_2, secondary to such disturbances in the pulmonary circulation as may be

caused by the increased effective weight of the blood. Gross disturbances in the perfusion of the lungs could be expected because of the low pressure head in the pulmonary circuit, the distensibility of the lung vessels, and because of the absence of counterpressure on the outside of these vessels.

It soon became clear that the pulmonary circulation was, indeed, very susceptible to G stress, and this could be demonstrated in different ways. One way of doing this was to study the pulmonary gas exchange. Another way was to use X-ray cinematography or other X-ray evidence to study the nature of local disturbances. Many such investigations have been made during the last few years, but the problems are yet far from being solved. Indeed, there is every reason to believe that the susceptibility of the pulmonary circulation to such stress is the limiting factor to man's tolerance to acceleration.

When comparing the pulmonary effects of positive and forward acceleration (G force acting in the head-to-foot and chest-to-back directions, respectively), our problems differ somewhat. For instance, if we look at the gas exchange, it seems that the oxygenation of the arterial blood, which is just one index of the disturbances occurring in the lungs, may be affected in both situations, but perhaps more easily in the case of headward acceleration. As an example, I might mention that our own results—which refer to headward acceleration—show that the arterial oxygen tension may assume such low values, around 40 mm. Hg, or lower, that the degree of hypoxemia might in itself be sufficient to endanger the functions of the CNS.

In connection with our space projects, it seems that less emphasis is put on the arterial desaturation in itself than on its cause, those pulmonary disturbances that consist of regional atelectasis or lung collapse. Perhaps one might say that the potential hazards here are twofold. On one hand, we have a situation that, in some respects, simulates the hypoxemia resulting from inhalation of gas mixtures with a lowered partial pressure of O_2; on the other hand we have the pathological changes in the lungs. I hope that somebody can say something pertaining to the relative hazards of arterial O_2 desaturation as opposed to its underlying cause, the pathology of the injurious effects of high G stress on the lung tissue. From what Doctor Wood tells me, it seems that the arterial O_2 saturation does not decrease to such low levels during forward acceleration as it does under positive acceleration.

WOOD: Yes, that is true.

BJURSTEDT: What I am aiming at is that it seems that we are worried about two different things. While the problems pertaining to pulmonary pathology seem to be more pressing in connection with space missions, the more generalized effect of arterial desaturation

might be a more important problem for conventional flight, that is, in fighter aircraft. Is this viewpoint justifiable, if we are talking in terms of failure of a mission?

RAHN: In other words, in one case the pilot is more expendable than in the other case? Is this a crude way of saying it, or not?

WOOD: No, I think Doctor Bjurstedt means that during positive acceleration the pilot may develop symptoms due to anoxia, while in transverse acceleration there is some danger that he might suffer actual structural damage to the lungs. The degree of hypoxia in transverse acceleration is usually not so severe.

BJURSTEDT: Both effects may result from conventional flight and from the stresses involved in space flight, but it is a question of their relative hazards—one may require more immediate concern than the other from the safety point of view and, at least in this respect, the two types of acceleration stress may pose different physiological problems.

SCHMIDT: Shouldn't you say something about the symptoms associated with high transverse G: the pain, the cough, the incapacitation, the inability to carry out a mission?

WOOD: FIGURE 19 shows the average and range of values for arterial oxygen saturation in a series of four subjects exposed to

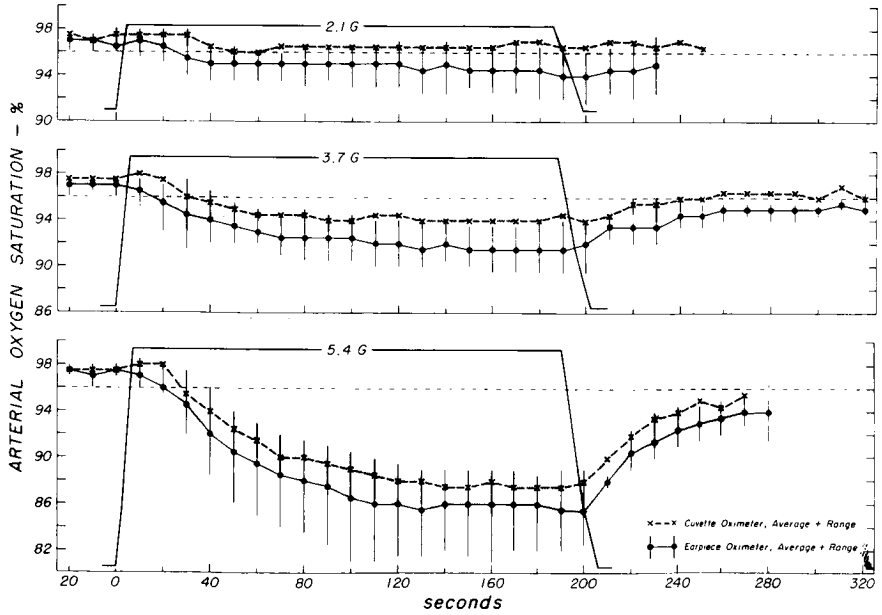


FIG. 19. Average and range of changes in arterial oxygen saturation of four healthy men, recorded by cuvette and ear oximeters during three minutes at 2.1 to 5.4 G, breathing air.

transverse acceleration in the supine position (acceleration in this direction in relation to the body is termed forward, eyeballs-in or $+G_x$ acceleration) for periods of about three minutes. Such exposures particularly at a plateau level of 5.4 G are perhaps similar physiologically to the exposure experienced by an astronaut during the launch and reentry phases of space flight. Oxygen saturation values are plotted on the ordinate and time on the abscissa. Two sets of values for blood oxygen saturation are included, one determined by ear oximetry (the black line) and the other (the dashed line) determined by cuvette oximetry. This latter determination is made directly on arterial blood being withdrawn continuously throughout the periods of exposure by means of an indwelling catheter in the radial artery.

The values of about 98 per cent saturation during the control period at 1 G are normal. About 20 seconds after the onset of the exposure to 5.4 G, a progressive decrease in arterial oxygen saturation begins, evident both in the values determined at the ear and in those determined directly on arterial blood. A level in the low 80's is reached toward the end of the three-minute exposure to acceleration followed by a slow recovery when the exposure is terminated.

RAHN: Is a saturation of 85 per cent considered a considerable handicap for general performance?

WOOD: I do not believe that this level of arterial oxygen saturation for this period of time would cause a serious handicap. I believe a pilot can perform reasonably well with an arterial oxygen saturation of 85 per cent. However, I definitely would not recommend such a circumstance if it could be avoided. I believe he would be capable of maneuvering his craft and carrying out various tasks, particularly if these were being done in a set routine or in response to verbal instructions.

HENDLER: Isn't this the saturation that is used operationally, that occurs at 43,000 feet under pressure breathing? I think they get down to about an 85 per cent level under those circumstances.

ROTH: I remember a report by Barr, where on occasion it got down to below 80 per cent on centrifugation.[93]

HENDLER: What is the expiratory rate during this period? I assume it is much decreased.

WOOD: No, the external ventilation is actually increased. This is not a ventilatory phenomenon. At these levels of acceleration, the rate and depth of the respiration are increased during the exposure.[55]

FREMONT-SMITH: Hyperventilation occurs, which means that there is also arterial constriction in the brain. Thus, there is not only a diminished arterial oxygen saturation, but also a diminished rate of delivery of unsaturated blood to the brain, since there is hyperventilation.

WOOD: Hyperventilation does not necessarily produce hypocapnea, because they have an arteriovenous shunt in the lung.

BJURSTEDT: It depends on how one defines hyperventilation. External ventilation, that is, the respiratory minute volume, is increased, but the effective ventilation during increased G stress is not in excess of the need for O_2 supply and CO_2 removal.

FREMONT-SMITH: Do we know whether they blow off CO_2?

BJURSTEDT: The CO_2 level of the arterial blood remains remarkably constant during transverse acceleration. Also, in the case of positive acceleration, the arterial CO_2 stays nearly constant, despite the fact that over a two-minute period at, for example, 5 G, we may have an approximately threefold increase in the respiratory minute volume. That means that the efficiency of the pulmonary gas exchange is much reduced with regard to the blowing off of CO_2.

Returning for a moment to the effects of forward acceleration on the oxygenation of the blood in the lungs, we have so far been discussing the changes of the oxygen saturation in the arterial blood. The corresponding fall of the arterial oxygen tension would be quite marked, but perhaps not alarmingly low. However, in the case of positive acceleration, the calculated O_2 tension may fall to very low levels, so that at 5 or 6 G, with an exposure time of less than one minute, levels below 40 mm Hg may be obtained. Thus "acceleration hypoxemia" is much more severe with the force acting in the head-to-foot than in the back-to-chest direction, for a given level of G.

WOOD: This is what would be expected on a hydrostatic basis in the upright as compared to the transverse position, since the cephalad-caudad dimension of the lung is considerably greater than the ventral-dorsal dimension.

BJURSTEDT: The subjective pulmonary symptoms which result from exposure to headward acceleration were first described by the British.[95] They found that a combination of increased G, the use of a G suit, and the administration of 100 per cent oxygen caused coughing paroxysms and chest pain. These symptoms were attributed to local atelectasis or collapse of the lung, which had been observed in x-ray studies.

This was checked afterwards, and it was quite evident that there was atelectasis in the lungs. Whether this caused the coughing, I don't know. Of course, there are other possibilities for these symptoms.

ROTH: What about the back-to-front direction? Is there any difference in saturation relative to the vector of the G gradients? What sort of an unsaturation profile would be obtained or would be expected if it were taken in the other transverse direction, 180 degrees from that described above?

BJURSTEDT: I think that has been described in a report from NASA Ames Research Center.[96]

WOOD: There is some information on this from the University of Southern California and Ames group, which indicates that when the reactive force is back-to-chest ("eyeballs-out") the desaturation is not as severe.[97]

MARGARIA: I know that with eyeballs-out acceleration compared with the "eyeballs-in," the desaturation is not so high. I suppose this is due simply to the fact that with the eyeball-out acceleration, the heart is held by the chest wall in approximately the normal position; in the eyeball-in acceleration, the mass of the heart is pushed backward, effecting a compression of the lungs, which may possibly lead to atelectasis.

I think the O_2 desaturation of the blood is due to the atelectasis, and the short circuiting of the blood in the lungs.

SCHMIDT: There is some possibility that two factors are involved, isn't there? We were talking at breakfast this morning about the possibility of arteriovenous shunts in the ventilated parts of the lungs in addition to perfusion of unventilated alveoli.

BJURSTEDT: This is an interesting question, because it could be argued that if the free flow of blood is restricted regionally by collapse of nonventilated portions of the lung, other channels may be forced wide open in functioning parts of the lung. Diversion of flow through such channels would make them act as a shunt, no matter whether one prefers to call it anatomical or physiological, in parallel with the shunt caused by perfusion of nonventilated alveoli.

FENN: You mean that the normal vessels simply grow larger, so that more blood goes through the open ones?

BJURSTEDT: That is correct.

FREMONT-SMITH: In the eyeballs-in situation, where the heart is pushed backwards, would there not also be some compression of the atrium, of the left atrium, and the inferior and superior vena cava and, therefore, some diminished inflow into the heart?

MARGARIA: That may be, but in this case the removal of the acceleration would be promptly followed by a return to normoxemic conditions. The slowness of the return to normal, I suspect, is due to the atelectasis that has to be removed, and this is a rather slow process.

DUBOIS: It seems to me that the physiological alterations depending on whether the G is from back-to-front or front-to-back have been explored inadequately. The report, which is probably the one that you mentioned, and is also one that I read, indicated that there was preservation of function by having the person accelerated in the prone position rather than supine. He could function better, think better,

breathe better. There weren't any measurements on circulation but presumably that was better, too. This has not been pursued as far as it should be. The only thing wrong with the man was that tears formed on the front of his cornea and he could not see very well.

WOOD: I agree with Doctor DuBois that the effects of acceleration in the prone position have not been adequately explored. Possibly one of the reasons that the prone position may be preferable is not so much the weight of the heart on the lungs but the fact that in the eyeballs-out situation the atria are at a relatively lower level in relation to the rest of the pulmonary vasculature than in other body positions. In the prone position, the heart would rest on the dorsal surface of the sternum near the level of the dependent portions of the lungs, so that the venous pressure would not have to build up so high in order to return blood to the left atrium from these dependent portions of the lung. In the supine (eyeballs-in) position, in contrast to the prone position the heart comes back against the vertebral column and there is a considerable vertical distance from the level of the atria to the dorsal dependent portions of the lungs. Pulmonary venous pressure must, therefore, build up higher in these regions in order to return blood to the left atria. In fact, it appears probable that both the venous and the arterial pressures may build up higher in dorsal (paravertebral) regions of the lung in the supine position than is the case in the ventral lung regions when in the prone position.

This has not been adequately explored. One of the next series of experiments in our laboratory is designed to compare the effects of prone and supine—that is, eyeballs-in and eyeballs-out acceleration in dogs who will be supported in individually fitted casts somewhat like the individually molded couches used by the astronauts.

ROTH: There is one factor that hasn't been mentioned, I don't know how important it is. If the anatomical structures are being thrown forward or backward or distorted, then the lung roots or the bronchi would, I suppose, be bent to allow the movement. How much of this is a factor? Does the lung root come in the midline or is it forward or aft of the midline? If it were aft, then in the backward to forward direction, ($-G_x$) there would be a greater tendency toward bending before the compressing effects of the lung in front of the bronchus would stop the forward bend. So you could really have a constriction there. Is this a factor?

WOOD: It is possible.

SCHMIDT: If that were the whole story, artificial inflation should remove the atelectasis promptly after the G force is removed, shouldn't it? This is not what happens. Forcible inflation produces an immediate improvement in arterial oxygen saturation, but this is tem-

porary and the saturation comes right down again, to resume the same slow recovery rate as before.

BJURSTEDT: That is right.

ROTH: It is more severe in the front-to-back vector ($+G_x$). In both cases, there is atelectasis, but in one case during the episode the ventilatory function may be also more restricted, as well as hampered by shunting.

WOOD: I believe it would be worthwhile to show a few pictures of hydrostatic models of the lung so that we can talk from that viewpoint. FIGURE 20 shows roentgenographic changes in the lung fields of a healthy subject, produced by an exposure to 5.5 G on a human centrifuge. The left panel is the control (pre-exposure) roentgenogram. The arterial and venous catheters visible in the subjects's chest were used for measuring cardiac output and vascular pressures. The panel on the right was taken about a minute and a half after an exposure to 5.5 G for a period of two-and-one-third minutes.

FREMONT-SMITH: In what position?

WOOD: In the Mercury capsule position; that is, eyeball-in acceleration. The subject was supported in a net seat in a position very similar to that used by the astronauts.

GRAYBIEL: How far away was the tube?

WOOD: The X-ray tube was about three feet in front of the subject and the plate right back of his chest.

SCHMIDT: Was there a G suit?

WOOD: No G suit was used. The subject's thighs and legs were flexed 100° and his back supported at a 12° angle from the horizontal, a position simulating as closely as possible the Mercury capsule position.

The things of interest to be seen in the roentenogram are: *(1)* the obvious elevation of the diaphragm. Both figures were taken at maximum inhalation; the subject was instructed to inhale and hold his breath while the X-ray was taken. And *(2)* the increases in radioopacity at the bases of the lungs, which our clinical radiologists say are indicative of the presence of atelectasis and perhaps some pulmonary edema in the dorsal regions of the lung. It was these changes, along with the finding of arterial saturation, that prompted us to attempt to find the explanation of these phenomena by experiments on dogs.

FREMONT-SMITH: Why was the diaphragm up? Why was he unable to inflate? Was it because of the pressure on the abdomen, the G pushing the abdominal cavity up into the chest?

WOOD: No, the subject was at 1 G during both roentgenograms. The right panel was taken after the subject was back at 1 G, about a minute after the exposure. Supposedly his diaphragm is up because of

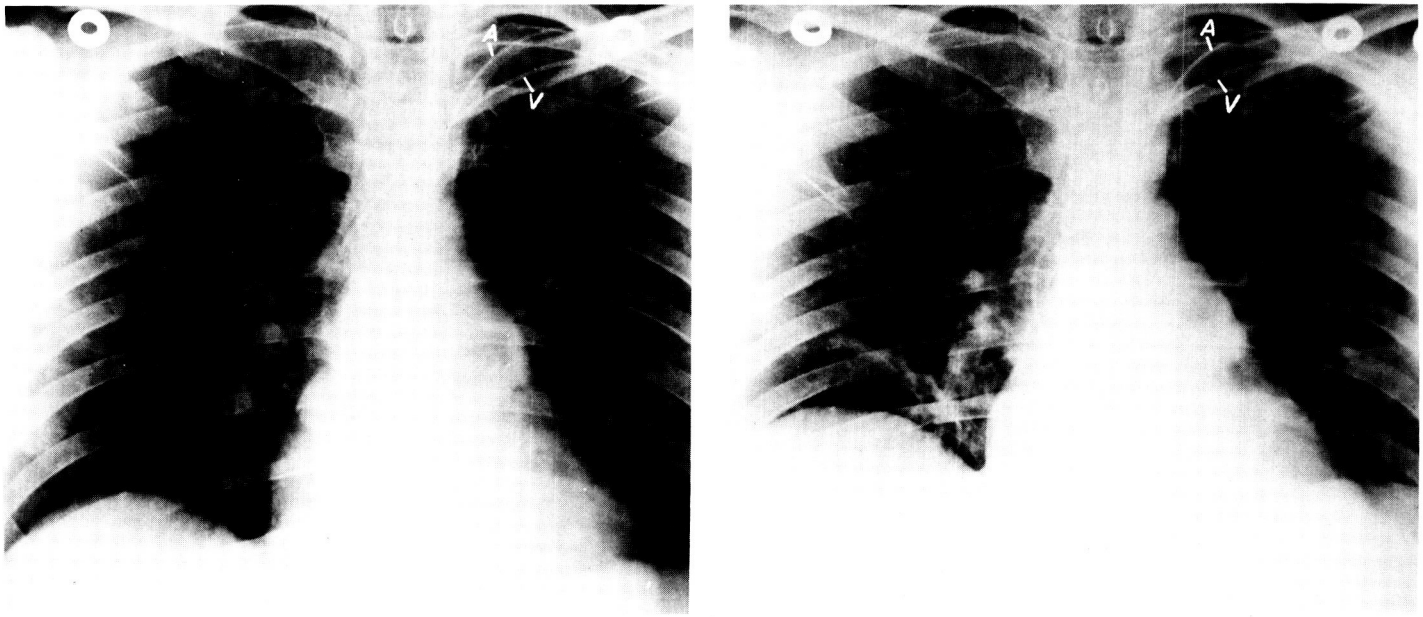


FIG. 20. (*a, left*) Normal thoracic roentgenogram of a healthy 38-year-old man just before acceleration. (*b, right*) Same subject five minutes after termination of acceleration to 5.5 G for $2\frac{1}{3}$ minutes while breathing 99.6 per cent oxygen. Note the focal areas of increased density indicative af atelectasis bilaterally, with associated diaphragmatic elevation. "A" denotes aortic catheter, "V" denotes venous catheter in right atrium.

a decrease in lung volume and possibly a reflex inhibition of inspiration of unknown etiology.

FENN: He is not still holding his breath?

WOOD: No, he is at maximum inspiration in both pictures.

SCHMIDT: Isn't the inspiration apt to be less deep after exposure than before?

WOOD: I am sure it is. The subject was simply told to take a deep breath and hold it. It is true that after such an experience the subjects have a tendency to cough, due to a sensation of irritation in the deep pulmonary airways. Because of this it becomes a little more difficult to take a deep inspiration, since this will very often bring on a paroxysm of coughing. All we can say is that the subject was instructed to make a maximal inspiratory effort and hold it while the roentgenogram was taken.

This type of picture is very similar to those the English investigators obtained with positive acceleration in pilots before and after high G maneuvers, particularly when they breathed oxygen and used the G suit.

FREMONT-SMITH: You didn't measure vital capacity in this case?

WOOD: In this case, no.

HENDLER: What was the magnitude and duration of exposure?

WOOD: 5.5 G for two-and-one-third minutes.

FREMONT-SMITH: And that was breathing air?

WOOD: The subject was breathing 99.6 per cent oxygen. In fact, these changes are usually demonstrated only when the subjects breath oxygen.

DUBOIS: There is, however, a characteristic drop in vital capacity under those conditions, demonstrated by Al Hyde. It is about 50 per cent drop postrun, as I remember.

WOOD: This is true. FIGURE 21 is a schematic hydrostatic model of the pulmonary circulation. The three panels from right to left represent the situation at 0, 1, and 5 G, respectively. The ordinant is expressed in terms of pressure in centimeters of water. The mean pressures in pulmonary arteries and veins at midchest level are assumed to remain constant at 20 and 10 cm. of water, respectively, during exposure to 0, 1, and 5 G. Since the specific gravity of blood is about one and the dorsal-ventral dimension of the lung is about 20 cm., it can be calculated that at 1 G, venous pressure at the ventral surface of the lung, if the subject is lying on his back, would be zero: while on the dorsal surface of the lung it would be 20. These same hydrostatic pressure difference would be expected on the pulmonary artery side.

At 0 G, since there is no hydrostatic gravitational effect, hydrostatic pressures would be equal in all areas of the lung. At 5 G,

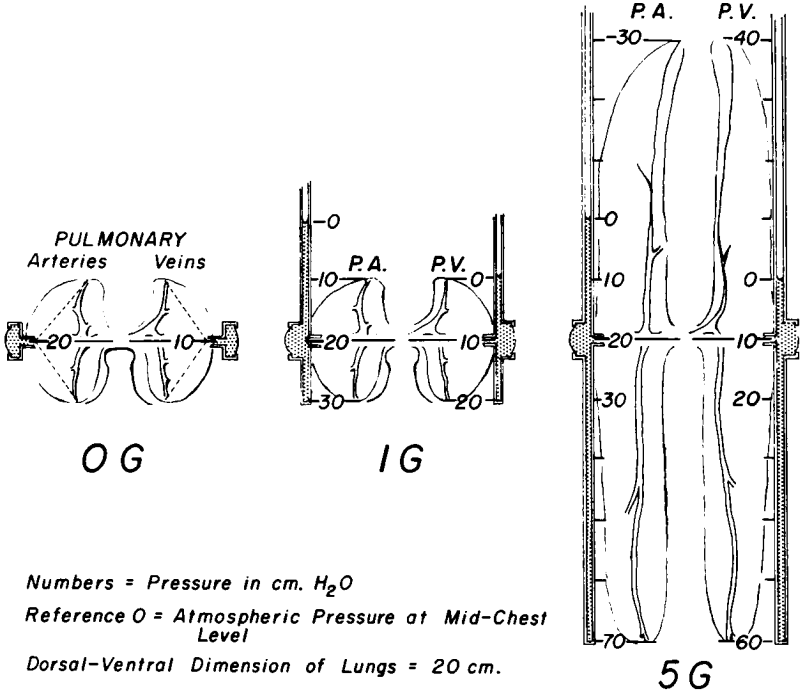


FIG. 21. Diagram of hydrostatic effects of forward (+G_x) acceleration on pulmonary circulation. Mean pressures in pulmonary arteries and veins at midchest level are assumed to remain constant at 20 and 10 cm. H_2O, respectively, during exposure to 0, 1 and 5 G. Since measurements in dogs and in humans indicate that these pressures actually increase at this level during exposures to forward acceleration, the amount by which pulmonary capillary pressure exceeds the pulmonary edema value in the dorsal regions of lungs during an exposure to 5 G would be greater than the value suggested in the diagram.

however, since the weight of the blood would be increased five times, one would expect that if vascular pressure levels actually stayed the same at midchest level, that venous pressure at the dorsal surface of the lung would be increased to 60 cm. of water and the pulmonary artery pressure to 70. In the dorsal regions of the lung, therefore, capillary pressure would be far in excess of the colloidal osmotic pressure of the blood, predisposing to pulmonary edema. In the ventral regions of the lungs, however, pulmonary arterial pressure would be insufficient to lift the blood up to the ventral surface of the lung, and if the vessels actually stayed open one would expect negative pressures of -30 and -40 cm. of water, respectively, at the ventral sufaces of the lung.

We have measured left artrial and right artrial pressure. In humans, right atrial pressure increases about 5 cm. of water per G of

acceleration, so that at 5 G it is not uncommon to record right atrial pressures in normal healthy humans of 30 to 40 cm. of water. Left atrial pressures have not been measured in humans under these conditions.

In dogs, with about the same anterior-posterior chest dimensions as the human, the increases in right atrial and left atrial pressures of about 1 to 2 cm. of water per G are less than in humans. Therefore, at 5 G the mean pressures at midchest level would not be 10 or 20, but would be considerably higher than this level. Vascular pressures in dorsal regions, therefore, would be expected to be more positive and those in ventral regions less negative than indicated in the model. This model represents the situation with exposure to acceleration with the reactive force in the ventral-to-dorsal direction; i.e., eyeballs-in acceleration.

BJURSTEDT: How would you explain a negative pressure in the pulmonary vessel? It won't be negative, will it?

WOOD: Yes, it would be negative if the vessel stayed open.

BJURSTEDT: If they stayed open?

WOOD: Yes, if the vessels stayed open.

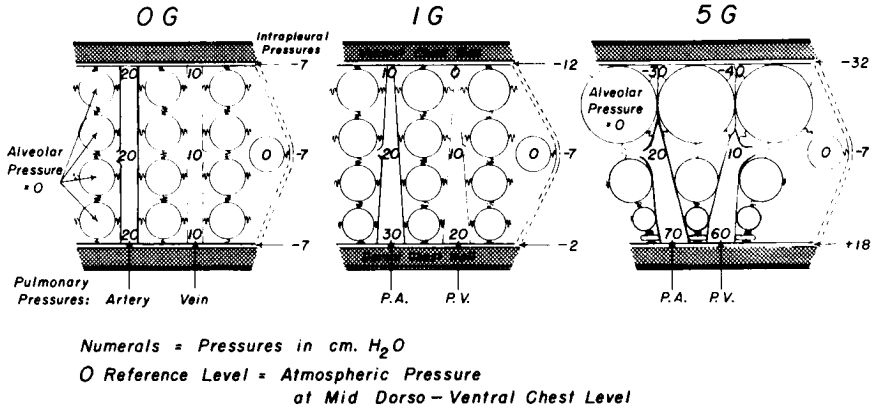


FIG. 22. Diagram of effects of forward (+G$_z$) acceleration on intrathoracic pressures (dorsal-ventral dimension of lung = 20 cm.). Numerals indicate pressures as cm. H_2O and zero reference level = atmospheric pressure at midthoracic coronal plane. In absence of obstruction of the airways, pressure in alveoli (represented as open circles) would be approximately equal to ambient atmospheric pressure and would be the same in all alveoli, independent of level of acceleration or position of alveoli in the thorax. Mean pulmonary arterial, pulmonary venous, and intrapleural pressures at midchest level are assumed to remain constant at 20, 10 and -7 cm. H_2O, respectively, during exposure to 0, 1 and 5 G. Intrapleural pressures shown at ventral and dorsal surfaces of the lungs at 1 and 5 G were calculated by assuming that the thoracic contents react to the change in weight caused by acceleration in a manner similar to that of a fluid with a specific gravity of 0.5. These estimated pressure values are closely similar to pressures actually recorded at these sites in dogs exposed to 1 and 5 G in the supine horizontal position.

BJURSTEDT: But they don't.

WOOD: The next diagram (FIGURE 22) is a model that brings in the concept of the anatomical structure of the lung itself. The middle panel again represents the situation at 1 G. The lung is illustrated as a series of balloons, representing the alveoli separated by springs, which are meant to represent the inherent elastic recoil of the lung. The intrapleural pressures at the dorsal and ventral surfaces and midpoint of the lungs are given at the left of each panel. The ventral chest wall is represented at the top of each panel. The ventral-dorsal dimension is 20 cm.

The thin-walled columns represent the venous circulation; the thick-walled columns, the arterial circulation; and the circles, the alveoli. If the glottis is open, so that the alveoli are in free communication with the ambient air, the alveolar pressure would be essentially zero all over the lung. The same vascular pressures are represented in this diagram as in the previous Figure.

The average intrapleural pressure is negative, and, according to our measurements in dogs, about −7 cm. of water at midchest level. If one assumes that the thoracic contents have weight, then it should immediately be expected that, if they acted at all like a hydrostatic system, the intrapleural pressure would be more negative anteriorly and more positive posteriorly, since the weight of the lungs and blood therein must be supported majorly by resting on the dependent chest wall. For this diagram it was assumed that the thoracic contents have a specific gravity of about 0.5 and pleural pressures calculated on the basis of the vertical distance separating the midchest from the dorsal and ventral lung surfaces. The calculated intrapleural pressure dorsally is about −2cm. of water. This is less negative than it is at midchest level, while ventrally it would be more negative—about −12 cm. of water.

As a matter of fact, measurements of pleural pressures ventrally and dorsally in dogs give approximately these values. If this pressure difference is true, one would expect that the alveoli would be a little more expanded ventrally than they are dorsally. This is represented in the middle (1 G) diagram by the fact that the ventral ballons are drawn a little larger than the dorsally positioned balloons; i.e., the alveoli. When this physical system is exposed to an acceleration of 5G, the weight of the thoracic contents increases five times. If the specific gravity of the thoracic contents is 0.5 and it acts like a hydrostatic system, it would be expected that pleural pressure at the dependent (dorsal) lung surface would increase to positive values of about 18 cm. of water and ventral pleural pressure would become more negative decreasing to about −32 cm. of water. If this occurred, the alveoli would be overexpanded in the ventral regions of the lung and since

they are inherently elastic, as soon as the pressure attained a positive value on the dorsal surface of the lung the alveoli in this region would collapse.

Measurements of dorsal and ventral pleural pressure in dogs during exposures to 5 to 6 G in the eyeballs-in direction are compatible with the values predicted by this model.

RAHN: Doctor Wood, is there any way that you could possibly fix a lung during 5 G so that you can, just by histological section, obtain evidence for this? I think this is very interesting and important.

WOOD: We have not done this, but I can show a section of a lung obtained at necropsy examination of a dog after a series of exposures to accelerations of 2 to 6 G in the eyeballs-in direction (FIGURE 23). The last exposure in the experiment was at 6 G for a period of a minute, but the dog had a series of exposures over a period of several hours varying from 2 to 6 G, during which measurements of intravascular and pleural pressures and changes in oxygen saturation were made.

The dorsal surface of the lung is on your left. The congestion and absence of aerated alveoli in the dorsal portion of the lung are evident as are the over-expanded alveoli and the absence of blood ventrally. The small section at the lower right side of the Figure is a coronal transverse section of a ventral lung margin. At close range, individual alveoli are visible to the unaided eye.

Gross inspection of the lungs of dogs after undergoing such a series of exposures to eyeballs-in acceleration reveals an interesting appearance. If the lungs are kept expanded as the thorax is opened, a sort of foamy appearance is evident along the ventral margins of the ventral lobes. In fact, one can practically see the individual alveoli with the naked eye in these areas of the lungs after they have gone through this type of exposure to acceleration.

DUBOIS: Can I interject that, in answer to Doctor Rahn, there have been attempts to find out how the lungs were changed while during G. One was made by Captain Charles Gell* at the Naval Medical Acceleration Research Lab in Johnsville. He ran a series of guinea pigs during G in which he froze the animal while under gravitational stress, using liquid air of some sort. Of course, the guinea pig came out tear drop-shaped, and there would be a description of sections of those lungs in Captain Gell's thesis, I believe, or perhaps Doctor Schmidt would have them.

*Gell, Charles F. 1956. Pt. I. Theoretical and experimental study of freezing rates in viable animals and physical models. Pt. II. Morphological displacement of organs and tissues of rats exposed to increments of acceleration stress and time with physiological significance. Pt. III. The effect of acceleration stress on the potassium and sodium concentration in the rat brain. (Doctor of Medical Science Thesis, University of Pennsylvania).

The second experiment involved X-rays taken during acceleration. These were taken by Doctor Gauer in Germany around 1942 on a monkey and on a cat. The film shows them in sitting and supine positions, the X-ray change can be followed. He injected dye into the pulmonary circulation so that the vessels can be seen and how they spread down during the gravitational force up to about 5 G.*

BJURSTEDT: Has anybody ever demonstrated a definite level of blood in the lungs during high G? Is there a flat surface of separation between the blood and gas phases?

WOOD: The motion pictures that Gauer made show this, I believe.

DUBOIS: I looked at them very carefully and made enlarged frames from them. You can see the dye passing out into the major vessels and returning to the major veins, but you can't see where it goes in the periphery, which is characteristic of dye in general.

SCHMIDT: One of our young men, Doctor Sandler, did this experiment on dogs on the Johnsville centrifuge last summer. Unfortunately he hasn't yet finished writing up his results, but I have seen them and can tell you a little about them. Sandler made X-ray movies of the chest while injecting a radio-opaque substance in anesthetized dogs at 1 G and during exposure to 5, 10, and 15 transverse G on the centrifuge. These pictures show the expected differences between the forward and backward parts of the lungs, the former being much paler than the latter. But there are distinct streaks in the supposedly ischemic parts, which are toward the center of rotation of the centri-

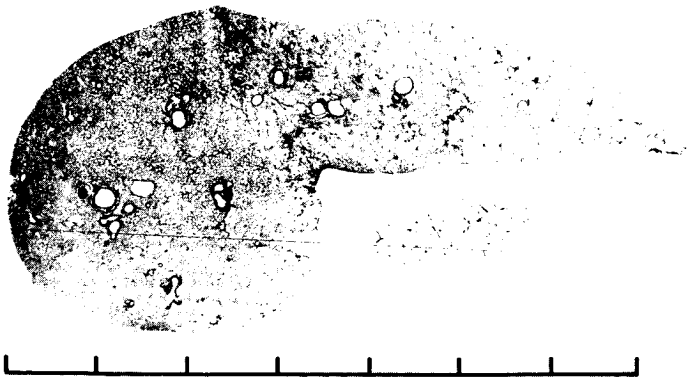


FIG. 23. Histologic section of lung of a dog killed after several exposures, $\frac{1}{4}$ to 3 minutes in duration, to forward accelerations of 2, 4 and 6 G. Total accumulated exposures to 2, 4 and 6 G for this dog were 5, 5 and 20 minutes, respectively. Large-scale divisions are centimeters. Ventral surface of the lung is on right. Smaller oval section is a coronal section of ventral portion of an apical lobe.

*A copy of this film is at the Aviation Medical Acceleration Laboratory, Johnsville, Pa.

fuge. These streaks are clearly visible to the naked eye. Therefore, a few channels of major size must have been carrying blood when the finer vesels were empty. This is my reason for suggesting that we may be dealing with the same mechanism that permits the recovery of glass or plastic spheres from the pulmonary vein after they were injectd into the pulmonary artery.[98] The mechanisms involved in closing and opening these shunts are quite obscure.

ODUM: How big are these glass beads?

SCHMIDT: The largest that went through were 420 micra in diameter. For most experiments beads of 125 micra were used. These passed without any difficulty.

DUBOIS: The third line of approach is to calculate how the lung tissue would be distributed if it consisted of masses and springs, and we tried that out in our laboratory with a computer program. So long as you choose a linear stress-strain characteristic for the springs, you can solve the equations and derive a distribution of mass, but it is unrealistic because lung tissues do not have a linear length tension characteristic. It is S-shaped and this makes the solution much more difficult to calculate, so we do not have the solution to that.

WOOD: That is a very good approach.

ROTH: Could you solve your blood distribution problem by putting a nonvolatile O^{15} compound in the blood and a series of coincidence counters down the chester and as the blood moves down, show the distribution of blood as it actually is within the chest? Is this something that people can do?

RAHN: This is now very successfully being done using either radioactive O_2 or xenon.[99]

WOOD: In this regard, in a project supported by NASA, we are in the process of installing a roentgen image intensifier tube on the centrifuge coupled with video tape recording assembly, so that roentgen images of the heart and lungs can be recorded continuously on video magnetic tape before, during, and after exposures to acceleration in association with, if desirable, single or multiple injections of a roentgen contrast medium.

An electronic device called a video densitometer has been developed that makes possible dynamic quantitative analysis of these video tape recordings. Changes in the radiolucency of any desired area of the roentgen silhouette can be recorded from replays of the video tape. The video tape can be replayed at will so that densitometric recordings can be made from as many areas in the silhouettes of the lungs, heart, or great vessels as desired. We hope by this means to get some evidence as to what happens to perfusion of different regions of the lung during exposures to acceleration and to correlate these

changes with the variations in pressure and blood oxygen saturation that occur.

FENN: I think you will find a great difference in the electrical conductivity across the lung, the dorsal and ventral areas, that should be easy to follow.

WOOD: I am sure you would. We have not made this type of measurement. I might insert here, parenthetically, a description of an incident that occurred in our laboratory, which was the stimulus that started us working quite intensively on this aspect of transvere acceleration. This occurred during the series of experiments we did on healthy subjects measuring the decrease in arterial oxygen saturation during eyeballs-in acceleration. We were interested in means of preventing this arterial desaturation and hence studies the effects of breathing oxygen, positive pressure breathing, and hyperventilation. One of these healthy subjects, when hyperventilating at 5G in an effort to prevent the decrease in oxygen saturation, suddenly developed a very severe pain in his chest. The centrifuge was stopped immediately and as the observer rapidly approached the subject he could hear what sounded like air swishing in his chest with each heart beat. This sensation could be felt by placing ones hand on the left ventral chest wall. The subject apparently had developed mediastinal emphysema. He was hospitalized and, fortunately, was all right the next day. It was, however, a frightening experience and, actually, one which, should it occur in an astronaut during launch or reentry phases of space flight, could have serious consequences, since the pain was very intense and the subject, consequently, almost completely incapacitated.

This incident occurred while hyperventilating with a maximum effort, and the cause is undoubtedly the very high negative pressures that occur in the superior regions of the thorax in the inspiratory phase of the respiratory cycle during exposures to acceleration.

HELVEY: What G load and position was that?

WOOD: He was in the typical Mercury couch position at 5 G for a minute and a half. FIGURE 24 shows the very strongly negative pressures recorded at the ventral surface of the lung of one dog during an exposure to 6 G. for a period of one minute. Esophageal, dorsal pleural, and ventral pleural pressures are plotted on the ordinant as cm. of water. The solid dots are end-expiratory pressures and the open circles minimum inspiratory pressures. At 1G these pressures are all negative, as would be expected, the ventral pleural pressure being more negative than the dorsal pleural pressure. During the exposure to 6 G, as predicted by the model, the ventral pleural pressure became more negative, while the dorsal pleural pressure, as well as the esopha-

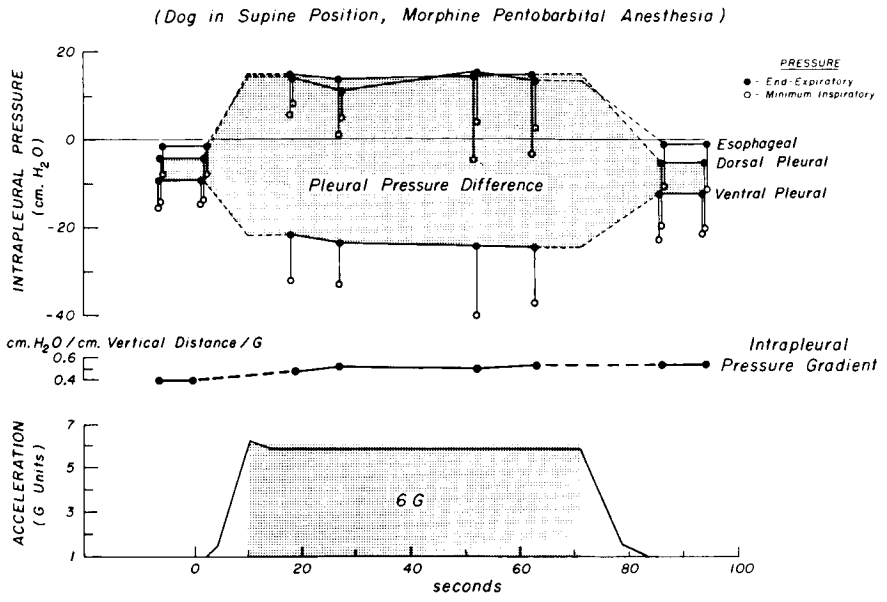


FIG. 24. Variations in intrapleural pressures with changes in weight produced by forward acceleration. See text for discussion.

geal pressure, increased and actually attained positive values of nearly 20 cm. of water as compared to a negative pressure of about −20 cm. of water recorded simultaneously from the potential ventral pleural space. During inspiration in this anesthetized dog, ventral pleural pressures decreased to even more negative values of −30 to −40 cm. of water. With greater inspiratory efforts we have observed ventral pleural pressures as low as −80 and −100 cm. of water. Since a pressure differential of 40 cm. of water across the alveoli approaches the level at which rupture of tissure in the lungs may occur, it appears highly probably that these high negative pressures may occur in the superior regions of the thorax of man during exposure to acceleration and were the cause of the mediastinal emphysema experienced by this healthy young male subject.

The points on this nearly horizontal line are the values of the ventral-to-dorsal pleural pressure gradient expressed as cm. of water per cm. of vertical distance separating the ventral and dorsal recording sites per G. If the differences in ventral and dorsal pleural pressures are the result of a simple hydrostatic weight effect, one would expect the gradient values expressed in this manner to fall on a horizontal line, since the weight of the thoracic contents is directly proportional to the level of acceleration. That this line is actually nearly horizontal, independent of the level of acceleration, constitutes

evidence of considerable strength that these pleural pressure differences are indeed due to a straight hydrostatic weight effect.

BJURSTEDT: How did you maintain respiration in your anesthetized dogs against the pull of gravitational force?

WOOD: They were breathing spontaneously.

BJURSTEDT: What is the rate of ventilation?

WOOD: Similar to the findings in humans, these dogs usually increase their pulmonary ventilation by an increase in both rate and depth of respiration during exposure, although this varies somewhat from dog to dog. Sometimes a brief period of apnea occurs at the beginning of exposure, followed by an increase in depth and a progressive increase in rate during the exposure. These dogs were under morphine and pentobarbital anesthesia.

ROTH: What about the symptom of substernal distress that are reported after exposure to acceleration in 100 per cent oxygen? The pain persists for a while. This is the mechanism of substernal distress in a supposed atelectatic situation?

BJURSTEDT: I don't think anybody knows. It could be due to congestion of pulmonary vasculature or to mechanical effects on the bronchi or to effects on the coronary circulation.

Cardiovascular Effects of High G Forces

WOOD: I have a comment on this. I believe the first time this substernal distress was noted was about 1944 during World War II, when we were requested by the Air Force to study the effect in healthy men of eyeballs-in accelerations of 10 G when in the seated position. All subjects when exposed to 10 G for a one-minute period experienced severe retrosternal discomfort described as an unusual deep worrisome pain. We were unable to determine what caused this pain. Wright Field again studied this just a few years ago and found that if the subject's thorax was tilted forward, this chest pain could be avoided, while it occurred almost uniformly if their subjects were exposed to eyeballs-in acceleration while flat on their backs.

FREMONT-SMITH: Was there radiation at all of the pain to the arm or shoulder?

WOOD: No.

SCHMIDT: I understand that one of the reasons for thinking that coronary impairment isn't involved is that the pain doesn't radiate.

WOOD: It does not radiate and can be avoided by a relatively minor change in position which has not been shown to be associated with changes in the circulation of practically important magnitude. The pain is possible due to tension on the supporting cardiac and/or hepatic ligaments and diaphragm associated with the manyfold increase in weight of these organs during acceleration.

FREMONT-SMITH: One thing I haven't heard mentioned, but may have been in all your considerations, is the inferior vena cava, which is a column of blood. It would be influenced very materially in different positions in G, in terms of return of the blood to the heart in which it would tend to push it forward into the heart or withhold it from the heart, and there is a considerable amount of blood in the inferior vena cava and renal veins, all the way down into the legs. I just mention it to be sure it is not left out.

WOOD: I can make a comment in that regard. In relation to the effects of transversed acceleration on the systemic circulation, that is, the arterial circulation, it appears that these effects, at least as indicated by changes in blood pressures and blood flow, are not particularly dramatic. We have measured cardiac output in healthy subjects exposed to acceleration in the typical Mercury couch position for periods of 10 minutes and their cardiac output in well maintained. Actually their cardiac output was higher during exposures to 4 to 5 G than at 1 G. Their arterial blood pressure at heart level was increased and they showed an increase in heart rate.[100]

FREMONT-SMITH: This is gravity toward the head?

WOOD: Yes.

FREMONT-SMITH: Suppose he is in the vertical position?

WOOD: In positive acceleration, with the reactive force from head to foot, i.e., eyeballs-down? We have made determinations of cardiac output in this position, also,[101] and the cardiac output is—

FREMONT-SMITH: Temporarily closed?

WOOD: Temporarily, probably. A defect in the studies by the dye solution method that was utilized was that each determination of cardiac output required about a half minute. These determinations could be repeated at intervals of about two minutes during 10-minute periods of exposure to acceleration. The cardiac output is decreased some but not very much during these exposures. I would guess, however, if we could have made the measurements during the first 10 seconds when there is an immediate failure of the circulation to the head and then recovery, that larger transient changes in cardiac output would have been detected, but this type of measurement has not been made.

FREMONT-SMITH: And this might be the inferior vena cava.

WOOD: I think probably there is a decrease in venous return.

FREMONT-SMITH: Which would be there.

SCHMIDT: Isn't the stroke volume reduced more than is indicated by what you say, Doctor Wood? There was a considerable acceleration of the pulse.

WOOD: The heart rate is increased and the stroke volume is de-

creased. In spite of the increase in heart rate during acceleration, there is some decrease in cardiac output.

SCHMIDT: It seems to me that the slow recovery of arterial oxygen saturation on return to 1 G deserves particular attention.

BJURSTEDT: So far, we have had evidence of pulmonary disturbances under G stress up to 5 G. For the Apollo mission, they will go much higher than that, and perhaps Doctor Schmidt could say a few words about what sort of G profiles have been proposed or tentatively discussed so far.

Launching and Re-entry G Exposures

SCHMIDT: As far as I know, there has not even been a decision on the Apollo flight pattern. Perhaps one reason for delay is a desire to see the outcome of preliminary observations now being made on volunteer Marine pilots exposed to a number of alternative G patterns on the Johnsville centrifuge.

It is generally realized, I suppose, that in the Apollo flights we will be dealing with much higher G forces than those the Mercury astronauts endured so successfully. The velocity of the Apollo vehicle to escape from the earth's gravitational field will be about 24,000 miles per hour, while that required to put the Mercury vehicle in a declining orbit was about 17,000 miles per hour. The escape tower of the Mercury capsule is to be omitted from Apollo, and if there is an abort during the early phases of the Apollo flight, the astronauts may be exposed to abrupt decelerations of the order of 15 G. There is to be no provision for retrorockets to slow down Apollo when it reenters the earth's atmosphere and the velocity on reentry will be the same as it was on escape. These G stresses constitute one of the main problems that await solution on the Johnsville centrifuge.

The flight patterns being tested include a rise to 5 G in about two minutes (normal launch); aborts involving 4, 5, 10, and 15 G; normal entry at a little less than 7 G for about one minute; and faulty profiles providing surges of 10, 12, and 14 G sustained for 80, 100, and 120 seconds.

FENN: Why don't they have retrorockets, is it a weight problem?

SCHMIDT: I suppose so, but I don't really know. I only know that they expect to come back without any means of slowing down except the terminal parachute.

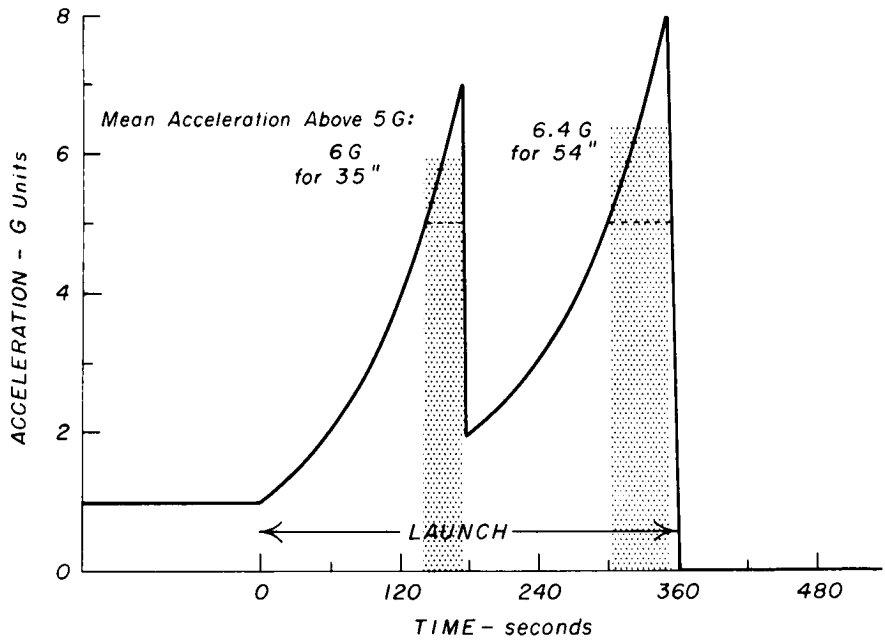
In talking to the people who have ridden these profiles, I find that the ones they heartily dislike are those involving prolonged 5 G after an initial surge to 10 G or more. These surges of high transverse G lead to a good deal of pain, coughing, and distress, which are likely to persist through the 5 G phase. There also is a high degree of

fatigue, and recovery is very slow. Pilots who have ridden this profile once, say they don't want to do it again. I think we are dealing here with the slow recovery of arterial oxygen saturation that we were talking about some time ago.

That is about all I can tell you. I tried to get an illustration showing these profiles but was unable to. Furthermore, the whole business is on a very tentative basis. One can say with some confidence, however, that the G stress the Apollo astronauts will have to endure on reentry is going to be higher than anything their predecessors have been called upon to face. This fact aggravates all the problems we have been discussing.

HENDLER: The G profile that we got from NASA for our tests, in which we exposed six people to the complete profile, consisted of two peaks of 6.8 for the launching phase, each one lasting two minutes.

WOOD: FIGURE 25 shows the acceleration profile of John Glenn's flight. In this figure the cross-hatched area is the time during each of the peaks that the man is over 5 G. During the first peak the ac-



Copied from Figure 9-5, Results of the First United States Manned Orbital Space Flight February 20, 1962

FIG. 25. An approximation of acceleration profile experienced by John Glenn during launch phase of his orbital flight. Stippled areas indicate period during which acceleration exceeded 5 G. Mean accelerations of 6 G and 6.4 G for these two periods of 35 and 54 seconds, respectively, would be expected to cause a significant decrement in pulmonary function.

celeration exceeded 5 G for 35 seconds and averaged 6 G for this period; during the second peak, the mean acceleration was 6.5 G for 55 seconds. The total number of G seconds that the astronaut is exposed to during reentry is, of course, the same as when he is launched, except that during reentry the profile is in a single higher amplitude peak, which physiologically is probably worse. The total number of G seconds to attain escape velocity is at least a third more because escape velocity is about 24,500 miles per hour as compared to approximately 18,000 for orbital velocity. Therefore, the G seconds of acceleration required are about a third more both in launch and in reentry from outer space flight.

RAHN: Is there not some way to modify the engineering design so that the astronaut wouldn't have to experience such high G stress?

HELVEY: I think there is more variation possible in reentry than in launch. For example, in Dinosaur, the engineers were considering such things as bouncing in and out a few times, slowing down in increments with a more controllable vehicle. This is more possible on reentry.

BJURSTEDT: Your question is important, because there is evidence that the pulmonary effects we have been talking about are not caused by G forces that are lower than 3.5. At least, we have not observed any change in the oxygen saturation below 3.5.

WOOD: We have demonstrated systematic changes with transverse accelerations of 4 G but not at 2 G. FIGURE 26 illustrates this point.

BJURSTEDT: So, of course, it would be advantageous from the physiological point of view if we could, instead, use a small G force of a very long duration yielding the same total G time.

DUBOIS: From the engineering viewpoint, I understand if you have a prolonged acceleration through atmospheric pressure, it gives longer time for the heat pulse to leak back into the capsule and, therefore, to heat up the inside.

BROWN: We are not aware of all of the engineering factors that go into this decision, but we needn't be. The hardware man has to make the decision; but if there is something wrong with this profile from a physiological standpoint, then I am quite sure the physiologists will veto the decision. What is important is that communication be good enough so that something seriously wrong is identified in time to bring this change in at the right time.

BJURSTEDT: This raises the question, of course, how dangerous are the defects on the pulmonary circulation and gas exchange? If the astronauts riding the Apollo mission do not experience any serious disturbances that may mean failure of the mission, then perhaps we are discussing this unnecessarily in detail. I am sure the hardware

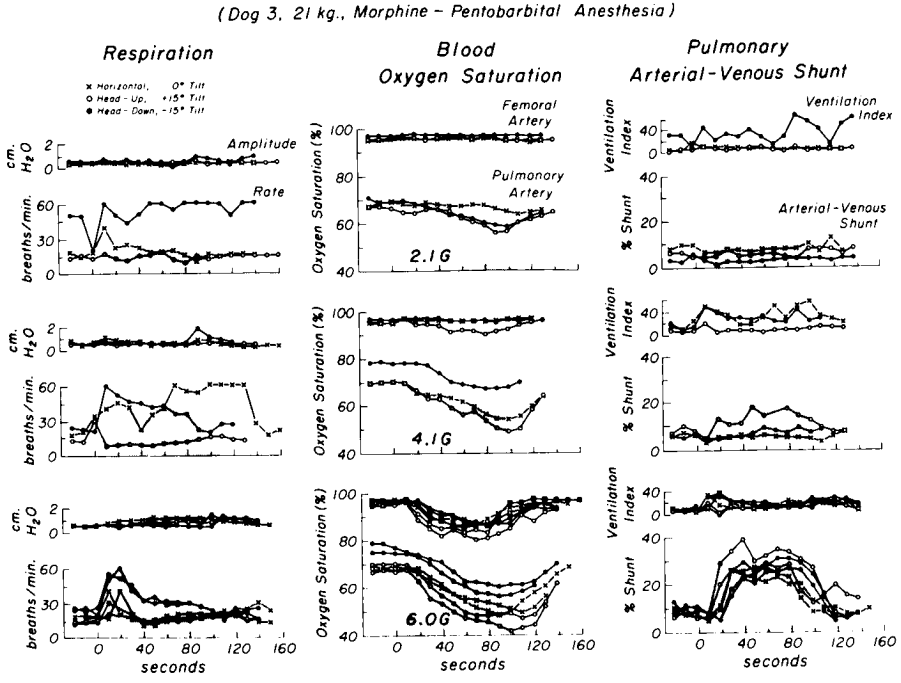


FIG. 26. Effect of degree of forward tilt on rate and depth of respiration, oxygen saturation of arterial and mixed venous blood and estimated pulmonary arterial-venous shunt during forward (+ G_z) acceleration. Note that significant degree of pulmonary arterial-venous shunting was not detected during exposures to eyeballs-in accelerations of 2.1 G (*top panels*) as compared to a minor degree at 4.1 G (*middle panels*) and the severe degree which occurred during every exposure to 6 G (*bottom panels*) and was of approximately the same magnitude within the range of body tilts (plus to minus 15 degrees) studied. The values for ventilation indexes plotted in the *right panels* are the products of the respiratory amplitudes and rates plotted in the *left panels*.

people are especially interested to know which disturbances are sufficiently dangerous to involve risks for abortion of a mission.

ROTH: I think it is important that they get boundary conditions. In other words, they should be given a boundary or an envelope within which they can putter around with the design. I think they are always asking for envelopes rather than concrete limits.

HENDLER: I think experience has shown, though, that they come up with hardware items long in advance of the answers that the physiologists and others can give them. Consequently, the physiologists are always working under these constraints to the general approach.

FREMONT-SMITH: Isn't this a more or less inevitable part of the sequence of events; that is, that the physiologist is only faced with a constraint when the hardware people say, "we can do it this way,"

so that there tends to be a lag period. I think we perhaps are beginning to catch up on this and the most important thing you spoke about was communication: If we could get physiological thinking into the hardware thinking at the earliest stages of the new developments, now that we have begun to learn more than we knew when we started, that would be important.

BJURSTEDT: The reason for placing our astronaut in the lying position, with the G force acting chest-to-back, was because physiologists had found at a very early stage, in fact, long before any space missions had been contemplated, that tolerance to acceleration is highest when the force is acting perpendicular to the long axis of the body.

FREMONT-SMITH: We are going to have the same trouble with the psychologists when we begin to talk about having several people and long flights. Again, we are going to have the hardware people setting up conditions in which no consideration, or little consideration, has been given or could be given to the human factors involved. Then we are going to have to find out what is very possible, what is tolerable, and what is an effective human relationship on a long trip.

I think this same lag problem is likely to arise in the next stages of space flight.

BROWN: Doctor Fremont-Smith, you asked what you intended as a rhetorical question: "Isn't this inevitable," you said, "that the engineer will come up with design and then ask the biologists whether or not man will fit?"

The proper answer is, no, it is not inevitable. This is the pattern that was followed in the development of Mercury because Mercury was not a device to orbit a man. It was a development of a vehicle that happened to contain a man and all the emphasis was in this direction. It wasn't inevitable; it was just the way it happened, and it needn't happen this way in the future.

FREMONT-SMITH: This is just exactly what I was hoping, that if it were inevitable in the beginning—and you tell me it wasn't then—then it is certainly less and less inevitable as we move forward and it ought not to happen.

HENDLER: I think the inevitability goes back much further because this has been the history of aircraft. If you look into it, you will see that they have come up with aircraft and then tried to fit the man into it.

FREMONT-SMITH: I think you are right. This was my point. In the beginning, it goes this way.

HELVEY: I think we can say it is a definite tendency but not inevitable, and I agree with Doctor Brown that we have to overcome a certain amount of inertia to modify this. Communication at the right

spot, at the right time, is very important, and I think we have to acknowledge another thing: that in NASA, generally, the management is an engineering group and we all are subject to our own backgrounds and orientations.

FREMONT-SMITH: Equally in DOD.

GRAYBIEL: Engineers have deadlines where they commit things very early in terms of lag time, and if we are going to talk with them, it has to be before they have done these things at these particular moments.

BROWN: This isn't really difficult as long as you have the right people talking at the right level.

FREMONT-SMITH: And at the right time.

BROWN: Yes. If the engineer feels that the physiologist's role is only to give him data that he can use in design, then he comes up against a problem and he asks a question and gets an answer. The biologist is only sitting around waiting to be asked, in this kind of a scheme, and obviously this isn't the way to run the whole operation. The biologist ought to be contributing all along the line, whether he is asked or not, and in this way some of the problems that can be identified in time to do something about it, will be.

FREMONT-SMITH: This may require quite a little reorientation at the managerial, administrative level, to get the biologist, the human physiologist, into this early planning.

BROWN: I think it takes a surprisingly small amount of reorientation.

FREMONT-SMITH: A surprisingly small amount and not difficult to do it?

BROWN: Yes, I think so.

FREMONT-SMITH: Fine. I am all for it, but I think we need some lines of direction as to how to accelerate through that slight pulse of difficulty.

FENN: Haven't the physiologists really been ahead of the engineers on space? I remember when Armstrong established the Space Medicine Department at Randolph Field, he said, "When the engineers get ready to build a ship, we are going to be ready for them." I think he started it before they started building ships.

ROTH: I don't think they have kept up. This is one of the problems they didn't anticipate. How far ahead can you anticipate?

FENN: But he did in the beginning.

ROTH: Is the lag narrowing down? This is the problem.

Oxygen versus Air during Various G Stresses

BJURSTEDT: If we are still on this question of, how dangerous might the 15 G be for such a short period, perhaps this time is not enough to create any major disturbances in the lungs? I wouldn't be

able to say offhand. This is why I prefer first to discuss this matter using the rectangular G time pattern. With the G levels tested so far, the time course of the decrease in arterial oxygen saturation is quite characteristic, in that we generally reach the maximal desaturation with one minute or so, with the last part of the oxygen saturation curve staying low for the rest of the run. On returning to normal gravity the "off" transient of the oxygen saturation curve will be slower, so that we will not get back to a reasonable level of oxygenation until after a very long time. Oxygen saturation reaches a minimum within one minute and then stays more or less constant. This may be a subject of some importance.

This is in contrast to what happens to the systemic circulation on applying a similar G time pattern. The arterial pressure is affected almost immediately, but soon shows some compensatory adjustment towards its normal level. This happens in about five seconds, which means that there is some rapid compensatory adjustment in the systemic circulation.

WOOD: This is positive, i.e., eyeballs-down acceleration?

BJURSTEDT: Yes, this refers to headward acceleration. However there is no such compensatory adjustment with regard to the oxygen desaturation, and this is true both for forward and headward acceleration.

FREMONT-SMITH: Doesn't this mean that the oxygen unsaturation would be worse if it weren't for the compensation at the blood pressure level?

BJURSTEDT: No, I am just comparing the pulmonary circulation and the systemic circulation. There is some adjustment in the systemic, but obviously, in the pulmonary circulation there is no adjustment to this stress. Therefore you get to a plateau, and this plateau is at least constant over a long period of time, and there is no compensatory rise.

This is not explained, but I think it might be due to several factors. Perhaps part the vasculature in the dependent portions of the lung is forced open, and vasomotor reactivity of these vessels is not sufficient to displace the accumulated blood to other parts of the pulmonary vascolature. In other words, the flow of blood seems to stay restricted to nonaerated areas with no secondary redistribution to ventilated regions. There is no recovery during the stress.

WOOD: In fact, if anything, they tend to get slowly a little bit worse.

ROTH: Is there any reason why you expect recovery? Would there be any compensatory mechanism that would allow it?

BJURSTEDT: According to the concept of homeostasis, one would

expect some compensation to occur, but, if so, it is very small and we cannot detect it.

HENDLER: You get recovery in the systemic circulation from positive G application.

BJURSTEDT: To some extent, yes.

DUBOIS: Doctor Wood's data (FIGURE 26) seem to show a fall in oxygen saturation which is from initial value of 97 per cent at zero time at the first minute or sixty seconds on to about 88 per cent or 90 per cent. Then in the second minute it has gone down still further to somewhat less than that, so it is a fall that continues over the second minute slightly.

BJURSTEDT: From the illustrations that Doctor Wood has shown it is evident that, on stopping the centrifuge, the arterial oxygen saturation returns toward its initial level, but its recovery rate is somewhat retarded. We have the same experience in the case of headward acceleration. Breathing air, it usually takes at least two or three minutes for the oxygen saturation curve to return to its normal level, and sometimes much longer than that. This is after a single exposure with the rectangular shape of the G time curve. If such a run (headward acceleration) is repeated several times, the picture gets increasingly worse. The arterial oxygen saturation may then drop much faster after starting the centrifuge, so that the response becomes similar to that resulting from rather fast decompression to altitude at normal gravity. The final level of desaturation is reached within approximately fifteen seconds. If the exposure is repeated five or six times, progressively lower levels of oxygen saturation are obtained, and also the rate of desaturation shows a progressive increase with repeated exposures. Have you got anything on that in the case of forward acceleration, Doctor Wood?

WOOD: Somewhat to our surprise, particularly in the dog experiments, we did not find evidence of progressive deterioration. The experimental procedure extended over periods of four or five hours during which the animals underwent repeated one-to three-minute exposures to eyeballs-in acceleration of 2, 4, and 6 G at different angles of body tilt. The condition of these anesthetized dogs remained quite constant and did not exhibit progressive deterioration in arterial oxygen saturation or cardiac output.

BJURSTEDT: Does that mean that you shifted the body axis relative to the G force?

WOOD: Yes, we studied the animals in the horizontal position and when tilted 15° head-up, 15° head-down, and then at the end of the series studied them horizontally.

BJURSTEDT: On one and the same dog?

WOOD: Yes.

BJURSTEDT: That might explain why you didn't get any progressive deterioration.

WOOD: But the protocol was one-minute exposures to 2 G, 4 G, 6 G, with a repetition of the 6 G run before and after each series of exposures. The degree of arterial desaturation during these repeated 6-G exposures did not vary systematically during the course of the experiment and was not significantly different when the degree of body tilt was changed over the $\pm 15°$ range (FIGURE 26).

BJURSTEDT: When one looks at the Apollo G profile, one would suspect that, of one continuously measures the oxygen saturation in this case, one might get a very large drop, and then this would stay down all the time.

SCHMIDT: That is what happened. There were oximeters on these fellows.

HENDLER: Could you observe this deterioration only in the negative?

BJURSTEDT: We have only investigated the effects of headward acceleration. What we tried to do in the recovery phase (I think it has been tried in other laboratories) was to inflate the lungs—to ask the subject to make a series of quick and deep inspirations. Since we used continuous recording of the arterial saturation, we could see an increase of the saturation level with every inspiration, but also that these increments were only temporary. It was only after several minutes that we observed a spontaneous recovery to prerun level.

SCHMIDT: Was there any difference if they were breathing oxygen?

BJURSTEDT: We have only done that in our experiments on headward acceleration, and we didn't get much of a desaturation then. Doctor Wood has investigated the effects of breathing oxygen also during forward acceleration and obtained only slight desaturation.

WOOD: Of course, remember that it takes a very large shunt to produce that kind of desaturation when breathing 100 per cent oxygen.

BJURSTEDT: Have you calculated the shunts that you get?

WOOD: Yes, here are some data both during breathing air and breathing oxygen, showing calculated pulmonary arterial-venous shunt values (FIGURE 27). These data are from three dogs. The open symbols are values when breathing oxygen and the solid symbols, values when breathing air during exposures to 5.9 G for about two minutes. The actual oxygen saturation values in systemic arterial blood and in mixed venous blood, that is, pulmonary artery blood, are shown in the *left panels* and the pulmonary arterial-venous shunt values on the *right,* based on the multiple assumptions that have to be

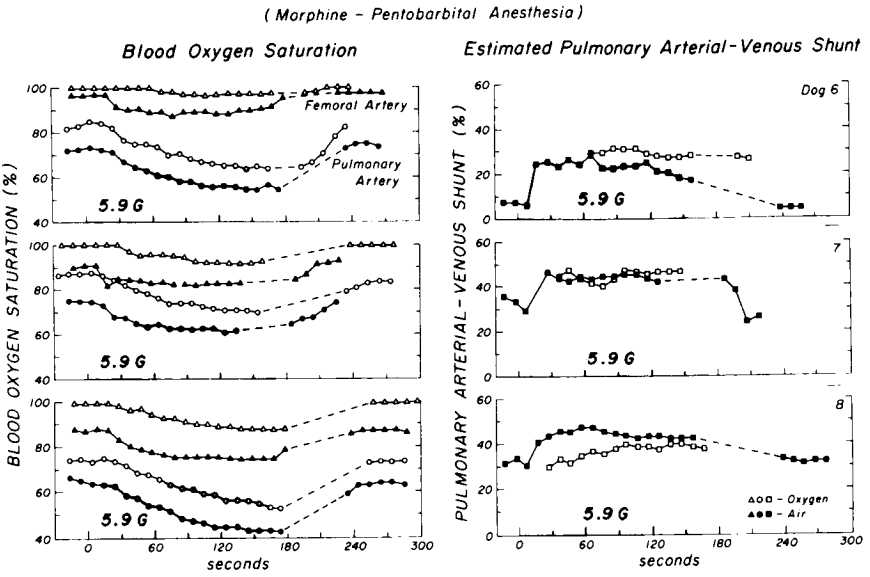


FIG. 27. Changes in oxygen saturation of mixed arterial and venous blood and estimated pulmonary arterial-venous shunt in three dogs during exposures to forward ($+G_x$) acceleration when breathing air or 99.6 per cent oxygen. Note that estimated degree of pulmonary shunting was approximately the same during breathing of air and 99.6 per cent oxygen.

made in calculating such shunts. In this dog (*top panels*) the shunt increased to about 20 and 30 per cent shortly after the onset of the exposure and remained there until the exposure was terminated.

When the dogs were breathing oxygen, shunt values could not be calculated until arterial desaturation occurred. This is because photoelectric determination of blood oxygen saturation does not measure how much physically dissolved oxygen there is in the blood. This cannot be stimated by oximetry until the saturation of the blood is significantly less than 100 per cent. The calculated shunts during the exposures were approximately the same when breathing air and oxygen. The magnitude of the shunt decreases slowly after the exposure and at about one and one-half minutes after the exposure it was back down to the control value. The time for full recovery when breathing oxygen cannot be determined from these data. The two *lower panels* are data from two other dogs. These dogs had a fair amount of pulmonary shunting at 1 G. As pointed out by Rahn and others, when anesthetized dogs are kept on their backs at 1 G, a certain number will develop significant pulmonary arterial venous shunts. When these two dogs were exposed to 6 G for periods of five

minutes, the shunt increased to about the same value when breathing air as when breathing oxygen.

BJURSTEDT: This question of recovery from oxygen saturation, and the question of residual atelectasis and collapse of the lung may be important for practical reasons. The problem is, we have to decide whether 100 per cent oxygen would be a disadvantage or whether it would make no difference as far as the effects of acceleration are concerned.

WOOD: I would like to amend that somewhat. It is true the data just shown did not demonstrate a difference in relation to calculated shunts in dogs when breathing air and oxygen. However, in the human subjects we studied on the centrifuge, in whom thoracic roentgenograms were taken one to two minutes after exposures, we never demonstrated clear-cut roentgenographic evidence of atelectasis when the subjects were breathing air; but frequently found such evidence when the subjects were breathing 99.6 per cent oxygen at an atmospheric pressure of about 740 mm. Hg.[4]

DUBOIS: Can I introduce two arguments? The first is that when you use the word "atelectasis," part of it may be "pulmonary edema" at the base of the lungs, because there is leakage of fluid caused by exceeding the osmotic pressure of the plasma proteins, you will be left with some edema in the alveoli. This would interfere with recovery.

The second idea is that we have been discussing 100 per cent oxygen and its effect on the blood saturation during the acceleration period. But I wonder if we should not go back to "partial pressure," because 100 per cent oxygen at sea level may overcome the desaturation by virtue of the dissolved oxygen in the plasma, therefore you would have to have a 40 per cent shunt before you even began to detect desaturation of the hemoglobin, whereas 100 per cent oxygen at one-third of an atmosphere, which is the proposed atmosphere for Gemini, would result in a partial pressure that would not cause much dissolved oxygen in the plasma, and therefore, would presumably not prevent the desaturation to a large extent so far as the dissolved oxygen is concerned.

However, there is a factor of distribution of gas in the lungs, and when you are breathing 100 per cent oxygen at any barometric pressure, that oxygen will be evenly distributed throughout the lungs, no matter how poorly ventilated some parts may be. It improves the ventilation distribution inequalities.

But I think we have to analyze these factors. For instance, you could trade a third of an atmosphere of oxygen, 100 per cent oxygen, against a 50-50 oxygen-nitrogen mixture at half an atmosphere and try to see how these two would compare in terms of both the per cent

saturation and in terms of the tendency toward collapse at the base of the lungs.

BJURSTEDT: My guess would be that we are going up to 15 G, no matter whether we like it or not, and it would probably help us to find out whether the gaseous environment should be changed or not. Perhaps the pros and cons of any proposed gaseous environment become more apparent by studying the responses to such high G levels.

SCHWARTZ: I wonder whether there is any reason why the respiratory conditions, the atmosphere, has to be the same during the experiencing of these high G's, as it does during the rest of the flight. It doesn't seem to me that you have to tie the whole long-term operating machinery to the needs of this crisis situation. I suppose you have to find out how much you can modify it.

BJURSTEDT: It depends on how dangerous it is, and we don't know that.

SCHWARTZ: Yes, but it seems obvious that once you do know this, it is possible to design a system that fits the time scale of your crisis situation.

RAHN: This has been considered by Doctor DuBois' group* all last year, but then there is another problem that arises. In other words, let's say it might be suggested that during takeoff you breath an oxygen-nitrogen mixture; this is fine, it might give you a little less atelectasis. On the other hand, immediately, Doctor Hendler will say, "What about the problem of bends?" Here is a man who is no longer desaturated, and here is now a man with nitrogen; he is very much more susceptible to bends, should a cabin leak occur. And so it is a matter of deciding, shall we have a man get the bends or is it more practical to have an astronaut get a pulmonary atelectasis during takeoff? These are very difficult questions to solve.

HENDLER: Another very important factor is the realities concerned. Just switching to a two-gas system evidently involves so many other complications. I think this was brought up before—that this is one of the prime reasons that the engineers, anyhow, are pushing for a one-gas system.

RAHN: Doctor Schwartz' proposal, to me, doesn't sound so difficult engineeringwise. You would only have this mixture during takeoff.

SCHMIDT: I don't think the problem is so much on takeoff as on reentry.

ROTH: It takes a finite amount of time to load on nitrogen to a degree where it is dangerous. In other words, you could have the fellow preoxygenate to reduce his slowly exchanging nitrogen to a minimum, and then during the acute takeoff phase, give him nitrogen. Then,

*Ed note: Study Group on Gaseous Environments for Spacecraft, Man in Space Committee, NASA Space Science Board.

you dump nitrogen to the outside. When he gets back onto oxygen again, in terms of the bends problem, his fat is still unsaturated with respect to nitrogen. So, it is a transient affair. You might be able to skin the cat that way.

DUBOIS: To decide how much of a problem there is on reentry, we ought to know how low the saturation comes.

BJURSTEDT: The experiment that Doctor Hendler described in which a man had actually been exposed to the Mercury G profile and kept at an environment of 100 per cent oxygen for some time, produced some results that surprised me a lot, since very little change in the oxygen saturation was observed. The immediate question I would like to raise is: wouldn't it be important to measure continuously the oxygen saturation or tension during the phase of acceleration?

HENDLER: Yes, it certainly is true that our measurements were made within a half-hour or an hour after the man came off the centrifuge, after the simulated reentry phase. He was breathing 100 per cent oxygen at sea level pressure at that time from a mask. The delay and increased oxygen pressure are attenuating factors that may have reversed any atelectasis occurring during application of acceleration on the centrifuge.

DUBOIS: These have been measured on other runs as acute experiments. The problem with the two-week experiment was the mechanics of keeping him two weeks and then transporting him in a small capsule. I think that the tendency was to rely on the data obtained during acute experiments in which the main objective was to measure those things that you have indicated, and there are data in the literature on those particular points.

WOOD: I have not seen those data, Arthur. What happens at 5 psi, 100 per cent oxygen with this profile?

SCHMIDT: We have just done that on Marine pilots exposed to various transverse G patterns on the centrifuge, and have found that sustained exposure to 10 G brings the ear oximeter readings down as low as 70 per cent saturation in 80 to 120 seconds. The longest period of 10 G transverse that was tolerated was 120 seconds. The exposure was terminated because of a mixture of discomfort (or pain) and mental confusion. These were subjects breathing 100 per cent oxygen at 5 psi. In those breathing air the oximeter began to fall a little sooner and it reached about 65 per cent saturation in 80 to 100 seconds.

The most important difference was in the rate of recovery of arterial saturation when air was breathed after the centrifuge stopped. Those who had been breathing oxygen showed a considerably slower recovery than those who had been on air throughout.

FREMONT-SMITH: During this slow recovery, has the vital capacity been measured?

SCHMIDT: Not in these subjects, no.

FREMONT-SMITH: This might give one a lead; if during the slow recovery there was reduced vital capacity, this would support either edema or atelectasis, or both.

SCHMIDT: Here is an illustration taken from a report[102] of a study made by the British on RAF pilots exposed to positive accelerations up to 7 G in Hawker Hunter fighter aircraft (FIGURE 28). The vertical coordinate shows percentage decrease in vital capacity. The symbols are *AM* = air mix (less than 40 per cent oxygen). *S* = anit-G suit. G = positive acceleration from pulling the plane up at high speed. O_2 = 100 per cent oxygen inhaled throughout. It is obvious that there was a greater decrease in vital capacity in the pilots who breathed pure oxygen than in those who breathed a mixture of air and oxygen. The greatest decrease was seen in those who used both pressurized suits and oxygen.

These observations were made after the pilots had landed and left the aircraft. They were asked to avoid taking a deep breath, if possible, and were rolled from the plane to the laboratory on a wheel chair. In the laboratory chest X-rays were first made and then vital capacity was measured. The X-rays showed changes typical of atelectasis at the bases of the lungs.

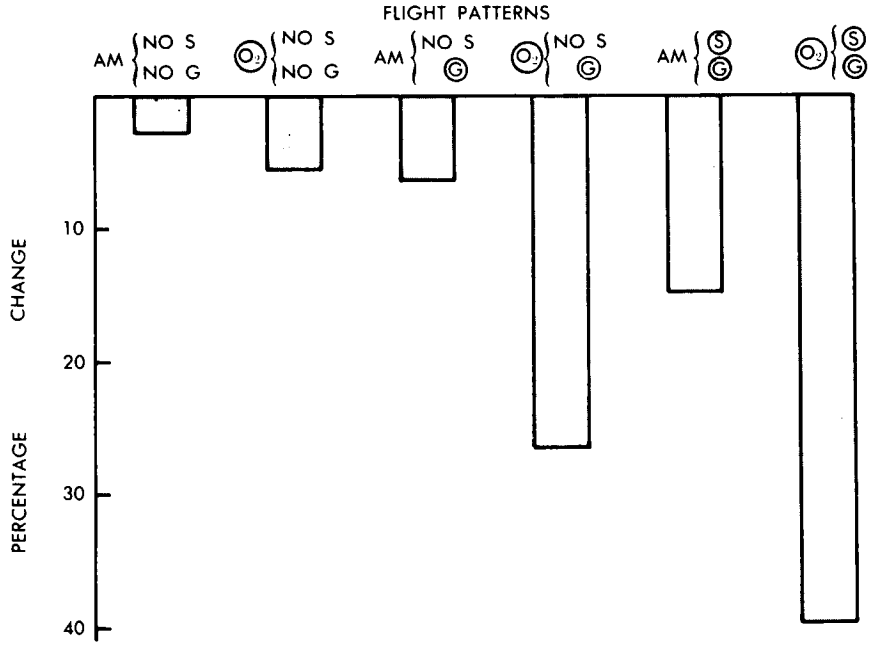


FIG. 28. Post-flight percentage change in vital capacity. Mean value for six subjects (see text for details). From Green & Burgess, 1962.[102]

This Figure indicates a decrease in vital capacity of more than 25 per cent from acceleration plus oxygen, of 40 per cent from acceleration plus oxygen plus antigravity suit. The effect of the suit is attributed to squeezing of abdominal contents upward.

BJURSTEDT: Did you say that the arterial oxygen saturation had dropped to 65 per cent in your centrifuge experiments?

SCHMIDT: Yes, in subjects exposed to 10 transverse G for 80 or more seconds while breathing air. In those breathing 100 per cent oxygen at 5 psi, the corresponding saturation was about 70 per cent.

ROTH: A one-minute—four-minute sequence?

SCHMIDT: No, a 10-G ramp sustained until the medical observers terminated it. The dominant consideration was either intolerable discomfort (pain, cough) or disorientation.

BJURSTEDT: In that case, the degree of hypoxemia is certainly sufficient to cause gross disturbances in CNS functions.

SCHMIDT: It certainly is something to think about, and some of the engineers have begun to worry. I understand that the North American people (who are making the Apollo vehicle) are talking about a reexamination of the decision to use 100 per cent oxygen at 5 psi.

DUBOIS: The problem, as I understand it, is that the man has to think during this period. He has to control the attitude of his craft, to stay in the optimal attitude so that he doesn't maintain more G or less G than a certain flight path would yield as optimal. He has to stay within pretty narrow limits by controlling the attitude of the craft. You are depending on a man who has a 65 per cent saturation, essentially, to fly a space craft. It isn't that he can't survive the episode. It is that he may not perform as well as he should. Isn't that why one would worry about this?

SCHMIDT: Yes, and the slower recovery on 100 per cent oxygen indicates that the presence of nitrogen in the lungs is an important factor in the rate at which he is going to recover his capacity.

DUBOIS: Did you say there were data on that point of slower recovery?

SCHMIDT: The observations I am talking about were made in conjunction with NASA people and are not yet written up. The work was finished only two weeks ago at Johnsville. The conclusions rest entirely on ear oximeter readings, which may not be entirely dependable. Nevertheless, the general trend was consistent enough to provide a caution signal and to call for further investigation. The same young Johnsville staff members who participated in these studies are getting ready for another series of observations as soon as they can get on the centrifuge.

At present, it looks as though inhalation of 100 per cent oxygen at

5 psi will not prevent serious arterial anoxemia in subjects exposed to 10 transverse G for 80 seconds. Furthermore, the recovery is going to be appreciably slower than it would be if there were nitrogen in the inhaled gas.

WOOD: I think, in addition to the decrease in oxygen saturation, which is bad, people don't generally realize what a distressing sensation it is to take 5 G for two or three minutes in this position. It is a very distressing situation; I have experienced it myself. At the end of five minutes you wonder whether you can take another minute of it, it is that bad.

FREMONT-SMITH: Which position is this?

Pulmonary Effects of High G Forces

WOOD: In the Mercury couch position one gets an intense feeling of dyspnea. It is one of the most disagreeable situations that I have experienced.

Usually, the tendency is not to pay much attention to these subjective sensations. I have a great deal of admiration for these astronauts. They are really taking a severe subjective stress when they are exposed to high sustained accelerations in this position, let alone the decreases in arterial oxygen saturation and other effects.

FREMONT-SMITH: There is quite a lot to contend with while flying the craft.

ROTH: Is dyspnea a mechanical effect, compressing the chest, and could this be aided mechanically in any way? What is causing the dyspnea?

WOOD: We don't really know this. I think a good deal of it may be mechanical; some of it may be the drive because of the anoxia. It is a sensation that builds up progressively as the exposure to acceleration is continued. One minute is not too bad, two minutes is much worse, and three minutes is getting much worse; and the longer the exposure, the worse it is.

BJURSTEDT: Perhaps I should add here that the type of hypoxemia we observe during and after acceleration differs from that resulting from breathing low oxygen mixtures, since there is no respiratory alkalosis, the arterial *p*H and CO_2 tension staying more or less constant during acceleration. The defective blowing off of CO_2 may cause unpleasant effects, such as breathlessness, which are not present in simple hypoxic hyperventilation where no pulmonary shunts operate to prevent respiratory alkalosis.

HENDLER: I would like to discuss some work we recently did on impact acceleration effects, because I think it has a bearing on the subject we have been covering.* A review of data on human tolerance

*This program was supported by the National Aeronautics and Space Administration under Defense Purchase Request T-9645(G).

to impact acceleration revealed that more was needed with respect to its effects following application through certain body axes. One of these axes was along a line from head to foot, the so-called "negative," "eyeballs-up" or "$-G_z$" acceleration. When this kind of acceleration is applied to the body, the viscera tend to move headward. The NASA people were concerned with the effects of negative impact acceleration on astronauts during capsule contact with the ground after returning from the Apollo mission. Oscillation of the command module containing the three supine astronauts, or its horizontal displacement with respect to the ground due to cross-wind, etc., could result in application of impact negative acceleration to the occupants. The main question concerned designing the proper packaging for the astronauts to protect them by attenuating applied forces. Available data were obtained primarily from downward ejection seat tests performed by the Air Force in the early 1950's. They seemed to show a tolerance limit of about 7 or 8 G for a fraction of a second.

The linear accelerator shown in FIGURE 29, which was used in our tests, consists essentially of a pneumatically driven piston that is

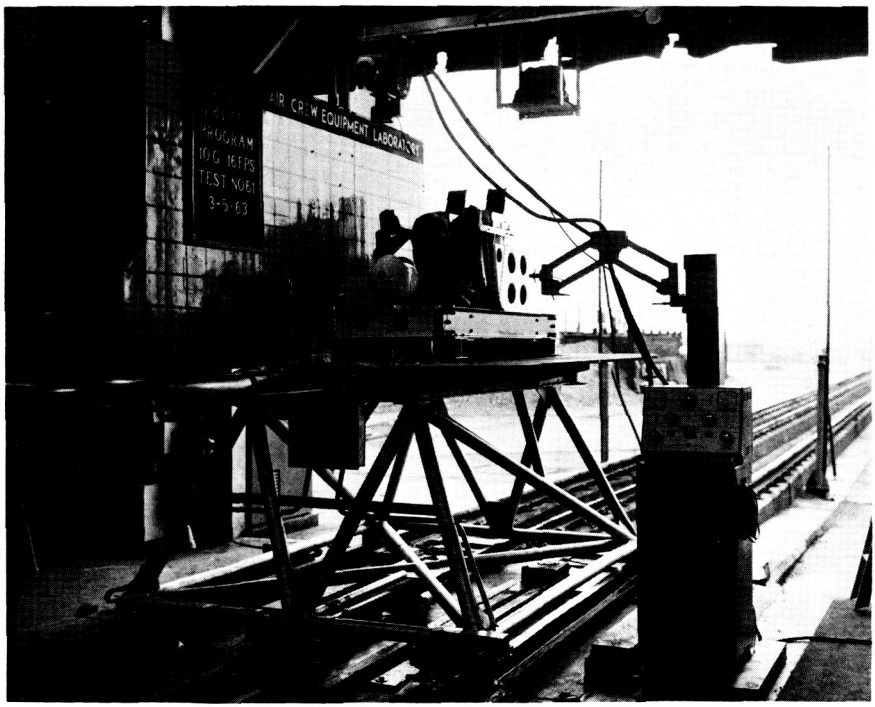


FIG. 29. Horizontal linear accelerator for application of negative impact accelerations to supine subjects. View shows equipment for obtaining X-rays of subjects during acceleration event.

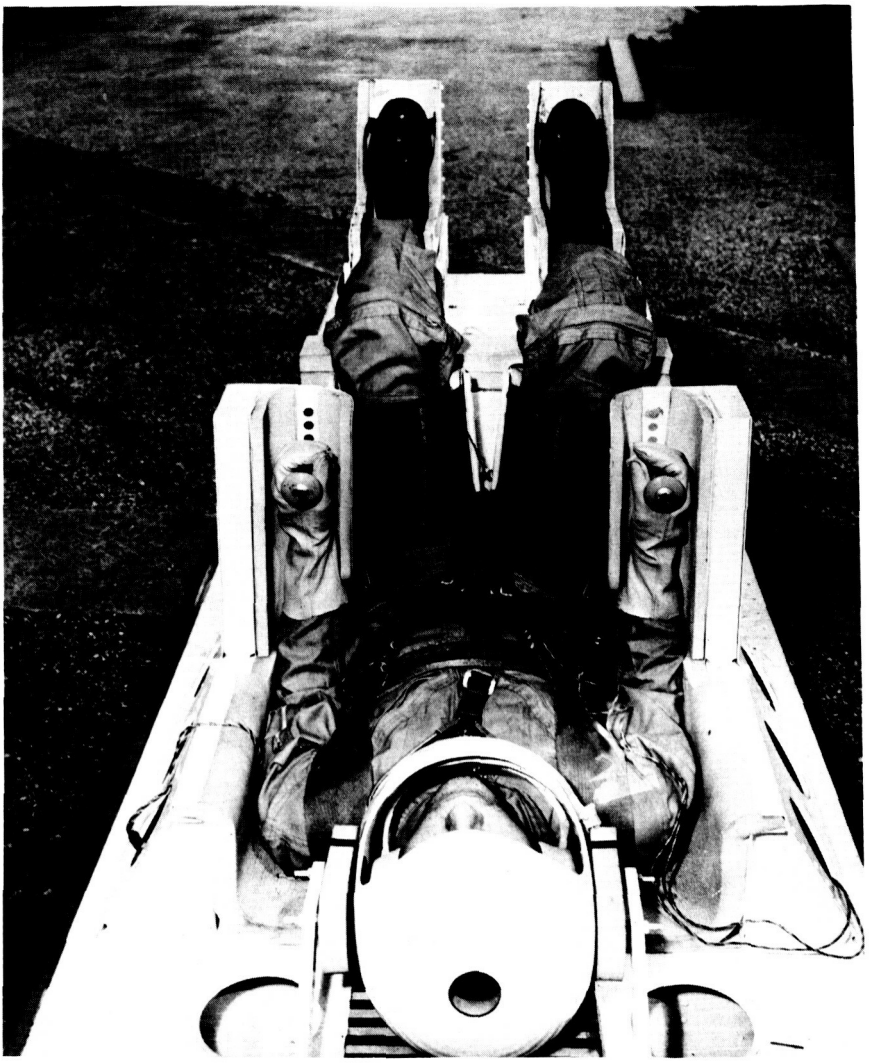


FIG. 30. Restraint and support system developed to provide protection against effects of negative impact acceleration.

hydraulically braked. The sled bearing the test load is brought initially into contact with the piston, the latter being retracted into a cylinder. When the accelerator is "fired," the piston suddenly moves out of the cylinder, propelling the sled along a track. The full piston stroke is about 9 feet, during which time the sled can be accelerated from zero velocity to a maximum of about 150 ft./sec. A test load of

about 1,500 pounds can be accommodated. The acceleration to the sled and test load is thus applied initially in the sequence. The sled then continues to run out on the track and is slowly stopped by a cable and arresting gear arrangement.

FIGURE 30 shows the restraint and support system evolved jointly by NASA and our people during the course of the tests.[103] Notice that the subject is restrained by shoulder harnesses, a chest strap, an integrated lap belt and pelvic retention assembly, special thigh retention harnesses, foot anchor straps, and a lap belt tie-down "V" strap. All of these restraints were made as tight as possible before each firing. This was necessary to minimize overshoot of the acceleration measured on the subject as compared to that on the rigid couch supporting him. Incidentally, we did achieve an acceleration level of 14.5 G as measured on the couch, in this way. My point here is that the only way we could get our subjects to tolerate these high impact acceleration levels was to very securely tie them into the rigid supporting structure. Others have conducted tests for tolerance to impact loads applied along other axes, and I presume that they too have evolved restraint requirements. The over-all result may be a rather complicated tie-down system, which could have a marked effect on normal respiratory mechanics. So far as I know, this aspect of the problem hasn't been fully considered yet.

FREMONT-SMITH: Did you measure vital capacity in the restraints before acceleration started?

HENDLER: No, we haven't done that. The intention is to continue these kinds of studies at higher rates of G application, higher rates of G onset.

FREMONT-SMITH: A chest restraint will definitely reduce vital capacity, depending upon how much restraint. I have measured it and it goes way down.

BJURSTEDT: Would it be difficult in this situation to draw a deep breath or would it be difficult even to hyperventilate?

HENDLER: These people were cinched in as tightly as possible, and this was the only way we could get them to tolerate these high G levels. If any of these straps were loose they had tremendous overshoot and there were a lot of subjective symptoms and other indications that made it very undesirable to go any higher.

DUBOIS: Not only is the vital capacity reduced by the external strapping, but also there are secondary changes in the lungs as a result of reducing the lung volume. If you compress the chest so that the lung volume approaches residual volume, and maintain it that way, the lung compliance will become reduced and there will be shunting of blood. You tend to exaggerate the phenomena that we have been discussing by compressing the chest.

ROTH: How permanent does this have to be? Can you have a solenoid-loaded system that can be used and just prior to impact, to cinch up all your restraints? Then you don't have to worry about this long-term restraint.

HENDLER: I think this might be possible, but, from an engineering standpoint, not only would weight be added to the system, but also considerable complexity.

HELVEY: Are you familiar with the work Carl Clark is doing at Martin* on an air bag for shock impact as well as vibration? They are using an air bag primarily as a source of attenuation. It is found very effective for particular vibrations that were intolerable on, I believe, the Titan missile, and also impact that shows some promise. It has the advantages of being able to be deflated and stored, during the flight. What the shortcomings are, I don't know.

BJURSTEDT: When trying to come up with means of protection against the pulmonary disturbances resulting from increased acceleration stress, it is evident that we have so far mainly discussed those effects that are caused by increased hydrostatic gradients, such as arterial desaturation, atelectasis, and collapse of the pulmonary tissue. Is there any other possibility you might think of that may contribute to imparing the gas exchange in the lungs or producing cough or other kinds of pulmonary disturbances?

FENN: I had a question and maybe it is pertinent here. I know there have been studies of the effect of gravity on the relaxation pressure curve, and the way in which that moves. Has anybody measured other aspects of ventilation, such as resistance to breathing? It has been suggested that you might kink a bronchus more one way than another. Has the resistance to breathing been measured? Have there been measurements of pressure of balloons in the esophagus? Has the compliance of the lung during exposure to acceleration been measured? What is the effect of expanding the alveoli in one part and collapsing them in another on the compliance and the resistance?

BJURSTEDT: A great deal of work has been done in this area. However, it seems that mechanical changes largely contribute to the effects we have been discussing.

FENN: A resistance to breathing might be another effect, in addition to the hydrostatic effect, if there were any change in the resistance.

BJURSTEDT: Yes. It would be interesting to know what happens if the mean pressure in the lungs is made negative so that blood is sucked from the systemic circulation into the pulmonary circuit. In other words, what happens if you increase the blood volume in the lungs?

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*Baltimore, Md. (Friendship International Airport)

Would this exaggerate the desaturation or the atelectatic changes?

WOOD: One can simulate some of the effects of exposure to eyeballs-in and up acceleration by negative pressure breathing, but the big factor not simulated is the hydrostatic pressure differences in the chest. With negative pressure breathing there is no hydrostatic effect over and above that of the normal 1 G environment. In contrast, during acceleration, the hydrostatic effect on the lungs and other structures is multiplied in direct proportion to the G level to which the subject is exposed. This, therefore, is a critically important aspect in which exposure to acceleration and negative pressure breathing are very very different.

FREMONT-SMITH: Couldn't negative pressure breathing in some way be analogous to the same condition as mitral stenosis with accumulation of blood in the chest, in the pulmonary vessels, and therefore decrease in vital capacity and tendency toward edema if it lasted any time?

DUBOIS: I can give you the current view of pulmonary physiologists on that. The old view of mitral stenosis was that the accumulation of blood in the vessels caused a decrease in vital capacity, but since about 1955 some people have thought, instead, that the change in vital capacity was due to the episodes of pulmonary edema that caused fibrinous deposits and a change in the parenchyma of the lungs. The decreased vital capacity was not caused by an acute engorgement of the vessels, but by the secondary accumulation of fluid and protein in the interstitial and alveolar space. That, I think, would be the current view.

FREMONT-SMITH: And no accumulation of blood playing any role at all?

DUBOIS: A slight role, but not the major one.

BJURSTEDT: Couldn't the distress under acceleration be explained in a similar fashion as in left heart failure? some of the vessels are greatly engorged and may give rise to reflex coughing.

DUBOIS: This hinges on the other. I would like to ask Earl Wood if anybody has injected Evans blue dye in a dog during acceleration to see if it leaks out of the pulmonary capillaries and into the lung tissues.

WOOD: No, not that I know of. One of our pathologists is going over histologic sections of lungs of all the dogs we have exposed to acceleration. There are changes that he interprets as pulmonary edema as well as atelectasis. Apparently, there is very little evidence of actual rupture of blood vessels. The experiment of studying the movement of dyed plasma protein during acceleration, to my knowledge, has not been done. There is evidence, however, from these histological slides, of the occurrence of pulmonary edema.

BJURSTEDT: Doctor Schmidt, would it be possible to introduce some space pharmacology in this area? Would you be able to dream up some sort of experiments where you use drugs as a tool to find out what actually happens?

SCHMIDT: To a limited extent, though we haven't really begun to explore the possibilities. For one thing, what about the cough? Do we know what gives rise to it? It is an outstanding symptom isn't it? It certainly was in the British fighter pilots and in the people exposed to high transverse G on the centrifuge.

In the experiments that Sandler did last summer on dogs on the centrifuge,[104] he tried the effect of blowing into the tracheal tube when the centrifuge had stopped and the arterial oxygen saturation still low. He found, as you did, that there is a momentary rise in saturation, but it comes right down again and resumes the same slow rate of recovery as before. The lungs just don't seem to reinflate promptly and completely.

This leads to the guess that there is a factor of organic obstruction of the respiratory tract. Whether this is done by edema fluid, by secretions pushed by G into the dependent parts of the lungs, by adhesion of fine air passages forced together by G, by bronchospasm, or by something else, I don't know. Some light may be cast on the picture by the use of appropriate drugs, and perhaps space pharmacology might contribute appreciably to the safe return of the Apollo astronauts. At present, there is no evidence one way or another, as to the cause of this respiratory obstruction. We are by no means certain that it occurs, as a matter of fact.

DUBOIS: To continue the subject of chest compression, if you simply compress the chest to reduce the lung to a small size and then allow the straps to be released, you find that the lung compliance; i.e., the pressure volume of the curve, has been shifted in the direction of a reduced compliance to about half its value, indicating that some parts of the lung are presumably stuck together and they don't expand easily. The conducting airways become dilated because there is more traction from the tissues on the airway wall.

There is shunting of blood at that time, perhaps a five per cent right-to-left shunt. This is not serious, because when you take a deep breath, even though you have maintained this compression of the chest for an hour, a single deep breath, or two or three deep breaths will reexpand the lung immediately, and the compliance comes right back to where it was, the airway resistance returns, and the shunt goes away.

SCHMIDT: Presumably, a cough would do that same thing.

DUBOIS: A deep breath just pulls open the lungs. What we are

worried about here in this acceleration is that a deep breath may not always reexpand the lung, and that leads you to think that there may be changes that have occurred other than simple approximation of lung surfaces. These secondary changes could be in the nature of transudation of fluid as in pulmonary edema, or loss of surface-active material, or both.

That, I think, is the major concern—not simply compression of lung, because that is reversible in one or two breaths. It is whether there are secondary changes.

SCHMIDT: This brings us back to the slow recovery, which strikes me as one of the most interesting features in the effects of high transverse G, as well as one of the most obscure.

BJURSTEDT: May I mention, as side line to this, that we have had anesthetized dogs on the operating table in an attempt to find out to what extent the pulmonary gas exchange might be affected by some drugs. Among other things we found that acetylcholine, infused into the pulmonary artery, caused an immediate fall of the arterial oxygen saturation. A certain degree of resaturation occurred on inflation of the lungs, but mostly it turned out to be difficult to bring the arterial saturation back to its original level. Perhaps one could use atropine or choline esterases to improve the pulmonary gas exchange in this situation, and also to counteract arterial desaturation and perhaps other adverse effects on the pulmonary circulation under gravitational stress.

ROTH: Has an aerosol bronchodilator been tried? If it is a surfactant defect, could you use an aerosol antisurface tension agent?

BJURSTEDT: As I say, this may have an effect on the bronchus.

SCHMIDT: The effects of acetylcholine might well be due to bronchospasm rather than vasodilatation.

The Question of Residual Effects of Atelectasis

ROTH: This brings up two more problems. What about the actual effect on the mission if you have an atelectasis? People say, "Yes, it predisposes to infection." Are there any numbers or any way of getting at this as a hazard? The question again: How dangerous is atelectasis in healthy people under these conditions?

The other question is on surfactant destruction. I know at first, Stu Bondurant and others showed at high pressures of oxygen there may or may not be destruction of lung surfactants. Studies are now in progress.[105] Other people showed that *in vitro*, on surface tension balances, if you let surfactant hang around in oxygen, there is destruction; in nitrogen, no destruction.[106] Whether this is oxidation or not is still questionable, because the surface tension, itself, will affect pro-

tein. Has this actually been pinned down? Is surfactant destroyed by elevated oxygen?*

FENN: It hasn't been shown.

HELVEY: Doctor Roth touches on a point that I think is very pertinent. I presume we have no answers but he mentioned the effect of atelectasis—does it predispose to disease. Conversely, let's assume that over prolonged periods in space the astronaut has his usual share of upper respiratory infections. What is the role of the lungs in pure oxygen in the pathologic state? This may be very critical.

If we assume, just for purposes of discussion, that the atelectasis problem here is marginal to safe, what we have had no experience with is, when he gets a transient episode of respiratory illness, would this same environment be very serious or will it have no effect? If you assume exudate and other such things, which would predispose to blockage, I would presume that this might be serious.

SCHMIDT: I suppose this becomes a matter of importance for astronauts who will be in space for weeks on end. The long-term pulmonary effects of repeated exposures to G worried the British considerably. In the report I referred to,[102] they leave the matter open, saying that proof can only be obtained by comparing two groups of pilots over a number of years—one of fighter pilots, the other of bomber and transport personnel—looking for a higher incidence of chest disease in the former. They point out that a flyer would have been quite incapable of completing his mission if he had experienced a 40 or even 25 per cent dimunition in vital capacity and the attendant severe pain and coughing while in the air. They also state that the fact that no such occurrence has been reported may be referable to the regulation that only pilots who are 100 per cent fit are allowed to fly. For these reasons they leave open the question of long-term pulmonary effects in their fighter pilots on repeated exposure to G stress.

DUBOIS: Some one asked about the changes in the lungs of fighter pilots. During the last year there has been published a report[107] on autopsies for the purpose of determining whether there were changes as the result of breathing oxygen. The changes were not extensive. These were pilots who died accidentally for reasons other than pulmonary. They did have a little fibrosis, a thickening of the alveolar tissues, although the changes were not extensive, and the interpretation in the report was that these might have been due to the prolonged use of oxygen. But they neglected the fact that these people are also

*Jamieson, D., K. Ladner & H. A. S. van den Brenk report (1963) a decrease in sulfhydryl and increase in disulfide groups in rat lung membranes after 45 minutes exposure of the rat to 5 atm. of oxygen. (Pulmonary damage due to high pressure oxygen breathing in rats IV Quantitative analysis of sulphydryl and disulfide groups in rat lungs. Australian J. Expmntl. Biol. and Animal Sci. **41**:491-497.)

subjected to increased gravitational stress during their occupation.

BJURSTEDT: The problem is different in this group of people than for the astronauts who are perhaps on a mission once in their lifetime.

SCHMIDT: But there is still the question of residual effects. Perhaps the lung isn't the same after such an episode for a long period of time. Of course, the astronauts presumably would have an unlimited period in which to recuperate after their hit-and-run expedition.

DUBOIS: The astronauts are not just going into this fresh, never having been exposed to these stresses. They are test pilots and fighter pilots, so, presumably, their lungs start with the same base line as the material which has been described.

SCHMIDT: Are there no corresponding data on bomber crews who presumably breathed oxygen over a corresponding period but were not exposed to high G? Were these all fighter pilots?

DUBOIS: No, as a matter of fact, it did not discriminate in the description of the material as to which ones had been fighter pilots and which ones had been bomber pilots. The reason they didn't discriminate was because the authors didn't recognize this factor of acceleration as causing changes in the lung.

WOOD: I would like to make two comments. We had the impression (and I cannot prove this) that in the healthy subjects in whom we measured the changes in arterial oxygen saturation on the centrifuge that some subjects were much more susceptible to the decrease in oxygen saturation than other subjects. Just what the basis of this is, I am not certain, although (and this may have been completely coincidence) subjects who had a prior history of attacks of pneumonia seemed to be more susceptible. This is based on a very small series, but this is another aspect of this phenomenon that should be looked into. The second comment is in relation to the slow recovery and the fact that the slow recovery does not respond to deep inspiration, which may be interpreted as evidence that there is obstruction. There may be another mechanism operative in this regard that is a reflex in nature. Subjects, after they have been exposed to acceleration, have almost certainly some degree of reflex inhibition of their ability to breathe in. In fact, one gets an unpleasant tickling sensation apparently in the retrosternal pulmonary airways, which is aggravated during inspiration. I suspect that no matter how hard one tries in this situation, one cannot generate a maximal inspiratory effort—perhaps not due to obstruction but due to the fact that one is incapable because of reflex inhibition of taking a real deep breath after this experience. So, the effect of a deep inspiration on atelectasis is not that it is not there, but that under this circumstance one just does not take the necessarily deep inspiration required completely to inflate the lungs.

FREMONT-SMITH: There is a reflex mechanism. If you expose a person to a blast of air across the nostrils, for instance, such as leaning out of an automobile when it is going fast, it is absolutely impossible to inhale, and that is a reflex; so maybe this would give the basis for finding what this reflex inhibition of inspiration is.

SCHMIDT: This would not apply to experiments on dogs under anesthesia, in which there is the same slow recovery, in spite of an attempt to reinflate the lungs by forced ventilation through a tracheal tube or cannula. I think Doctor Bjurstedt had the same experience.

WOOD: One would have to control that by determining the change in volume produced by the artificial inflation before and after.

SCHMIDT: Quite. In other words, there are still some things to do.

FENN: You have been talking about this reentry problem and the high (15) G that one is exposed to. You are investigating, however, after adaptation to 1 G. Would it be very difficult after a prolonged adaptation to 0 G?

BJURSTEDT: Yes, that is a good question.

FENN: It might be a lot worse from 0 G and you have to have a little more reserve, perhaps.

HENDLER: I think it has been shown that subjects who had been submerged for a while in water, to simulate somewhat the 0 G environment, had decreased tolerance to acceleration.

SCHMIDT: Do you agree, Doctor Wood, that this is the most important physiological limitation to man's ability to tolerate high transverse G?

WOOD: It is my feeling that the Achilles heel of the human system is the pulmonary system. It is the limiting factor.

Water Breathing

RAHN: Can I, therefore, now propose a radical procedure to eliminate it? I think this is the time to mention it, in case it should have an application 20 years from now. This is breathing of water, I mention it because if we can breathe water and put man inside a water bucket, then you can go to any acceleration that you wish, and maybe this will become important when we want to go very far, very fast some day. Doctor Kylstra at the University of Leiden has just accomplished the feat of breathing a dog with water for 20 minutes and having the dog recover.[108] This dog now is called a "sea worthy dog" and is maintained by the Dutch Navy. If this is possible in the dog, this might, therefore, be possible in man eventually. I would just like to bring it up for discussion if it doesn't seem too far-fetched.

Doctor Kylstra is now a visiting professor in our department and we can now quite easily maintain a dog for one hour with fluid breathing.

BJURSTEDT: Is that in a high-pressure tank?

RAHN: Yes. All we need is two atmospheres.

FREMONT-SMITH: And there is enough oxygen dissolved by diffusion?

RAHN: Yes.

HENDLER: What is the recovery procedure?

RAHN: There is none. You pick them up and shake the water out and put them on an ordinary gas pump and hope that the dog will recover.

FENN: Do you squeeze the water out?

RAHN: We drain the lung by gravity.

HELVEY: Is this water without any physiological—

RAHN: Doctor Kylstra says the best thing is to use saline.

SCHMIDT: There is no colloid in it?

RAHN: No.

DUBOIS: The question is, how long can you let lungs stay completely wet with saline? We just do one lung and the other breathes air. Under those conditions one lung can be ventilated with saline for several hours, and then go back to breathing air. Apparently, there is no particular deleterious effect. This can be repeated frequently, so I suppose that if you can go 20 minutes there is no reason you couldn't go considerably longer. You say you go an hour. You can probably go longer than that.

RAHN: Yes.

BJURSTEDT: How far does the water enter into the lungs—not into the alveoli?

RAHN: Yes, it is complete.

BJURSTEDT: Without destroying the membrane?

RAHN: All I am saying is that there has been one permanent recovery.

FREMONT-SMITH: But you have been doing it with one lung repeatedly without a destruction of the membrane, haven't you?

DUBOIS: We are going after the surface active material. We have washed some out and we have to find out now whether there is enough left. Clinically, you see, the lung which has been wet appears to expand all right, by X-ray, but we have to find out about the details.

FREMONT-SMITH: What animal?

DUBOIS: These are dogs.

FENN: What is the volume of their ventilation per minute compared to what they have on air?

RAHN: With the use of a gravity pump Doctor Kylstra has been able to ventilate 15 kg. dogs recently with about 3,500 ml. per minute. This is about what you might expect when breathing air.

FENN: What about his arterial saturation?

RAHN: All we have been able so far to look at is the tongue, and the tongue stays nice and pink.

SCHMIDT: I saw a movie of this and the dog looked pretty unhappy.

FREMONT-SMITH: The mice looked nice, though.

SCHMIDT: They were apparently working hard.

HELVEY: You have to admit it is an unusual situation for the dog. He probably had a little anxiety.

I was wondering, Doctor Rahn, looking forward five to ten years before this can be done, how would it appeal to you if the engineering strides and technology were such that you only needed 1, 2, or 3 G's for all the trips out and back?

RAHN: This would be a much nicer way of doing it.

HELVEY: I just wanted to clarify which side you were on.

ODUM: Coming back to the dog, how do you avoid the cough reflex? Usually, when a dog starts swallowing water, he has a reflex action. How is this overcome?

RAHN: These are anesthetized animals.

FREMONT-SMITH: The mice were not anesthetized and the mice were swimming around under water breathing in and out like this, and I didn't see them coughing.

RAHN: They couldn't.

SCHMIDT: The smaller animals don't recover, do they?

RAHN: So far, no.

SCHMIDT: My guess is that the air passages of small animals are too small to get the fluid out in time to prevent extensive froth formation.

FREMONT-SMITH: Perhaps it is worth remembering that this is merely a return to the intrauterine situation where one is breathing amniotic fluid and where there is respiration.

DUBOIS: Should we discuss the state of a man in a tank of water without the lungs full of water?

SCHMIDT: I think we should remember that there is an all-important time element in this situation. You probably are referring to the experience of Flanagan Gray in an iron sarcophagus (the "Iron Maiden") on the Johnsville centrifuge.[109] He was immersed in water up to his eyes and breathed air through Scuba equipment. Under these circumstances he withstood 31 positive G for five seconds and walked away afterward, though he wasn't a whole man for some time. This was about the absolute limit. To stand it for a minute or more would be something else again.

ROTH: Several years ago, I think it was in *The Physiologist*, Pegg, Horner, and Wahrenbrock[110] mentioned this saturated water approach. Do they have any new twists on this?

DUBOIS: Their last report was at the Diving Symposium in Washington; one of them was there.

BJURSTEDT: Do you have any information on the subjective feelings during drowning?

DUBOIS: Kylstra in 1957-59 was ventilating a dog, one lung with saline, to try to use it as an artificial kidney.[111] His technique was such that he did not require anesthesia of the whole dog. He could introduce a catheter and get water in and out with local anesthesia without complete total anesthesia. He used a special cuffed tube in one bronchus. The dogs, according to his report, had little objective signs of distress during this procedure. We have done it with general anesthesia in dogs, but again there haven't been signs of particular reflex changes that would indicate marked distress.

SCHMIDT: It seems to me that Doctor Helvey has the real answer to all these problems. When the results of our deliberations are fed back to the engineers, if they ever are, the physiological makeshifts are going to be so bulky and ponderous that the engineers are almost certain to conclude that they will save weight and time by providing the space vehicles with propellants capable of slowing them down enough to obviate severe acceleration stresses.

HELVEY: I think within some years, they will be able to provide a 2– or 3–G reentry, well within the state of the art.

I am just reminded how sometimes it occurs that when a fellow like John Stapp rides a rocket sled and gets 45 G's, some people begin to think of building a vehicle to that level. This is an extreme example, but it conveys the thought.

Cardiovascular and Pulmonary Effects of Low G Forces

BJURSTEDT: I have a question for Doctor Fenn in relation to the mechanics of breathing during weightlessness. Would the work of breathing be affected, and if this work is less under 0 G than under 1 G, what would this lead to?

FENN: I suppose there would be a little shift in the relaxation pressure curve and the functional residual capacity would change a little bit. I can't see that it would change the slope of the relaxation pressure curve or the elastic work of breathing or the frictional work of breathing very much. Off hand, I should think it would be about the same.

BJURSTEDT: Would the respiration go on at a somewhat more efficient pace so as to wash out some carbon dioxide and you end up with a lower CO_2 level than normal?

FENN: I think the respiratory center would function to regulate the carbon dioxide about where it normally did and would compensate for any changes that might occur mechanically. I wouldn't anticipate

any special changes that would occur that would be very important. It may be that the functional residual capacity would change, just as it does when you go from 1 G to 2 G.

MARGARIA: The removal of 1 G, i.e., the weight of the chest and abdominal could be reproduced by immersion in water, the subject swimming on the surface where the water pressure is practically nil.

FENN: That would compensate for the weight of the viscera, and so on.

HELVEY: Changes would appear to be minor but they would include a slight elevation, resting elevation, of the diaphragm that you don't have independently. Since the perfusion of the lower two-thirds of the lungs is greater, perhaps a function of the gravity state, this might change blood flow through the lung. But this probably, at most, would amount to a very few millimeters change in P_{O_2}, probably not perceptible if the shunts that are there are functioning based upon other stimuli.

In a purely weightless state, without a positive ventilation flow, some people have postulated that you would essentially pump in and out your CO_2. You wouldn't have convection currents and temperature differentials to help you. But I think this is only a theoretical consideration, since you would require a positive flow of air past the astronaut to maintain his temperature and other things.

There have been no respiratory abnormalities noted to date in the brief experience of the cosmonauts or astronauts.

SCHMIDT: The cardiovascular difficulties are likely to be more important than the respiratory, if one can judge from Cooper's experience. What happened to his pulmonary circulation is anybody's guess, but if it was going to pot, and if in this condition he was exposed to a 10-or 15 G stress, instead of the 6 or 7 of the Mercury flight, he might have been in real trouble.

BJURSTEDT: This would, of course, be especially difficult to find out experimentally, since in practice this stress would occur after prolonged periods of weightlessness.

SCHMIDT: The compensations that occur in the systemic circulation are due pretty much to the influence of baroreceptor reflexes, but the pulmonary circulation isn't so protected. When the pulmonary arterial pressure starts down it can't be restored by redistribution of blood, as happens in the systemic circulation from relex vasoconstriction.

HELVEY: The Russians have reported a couple of things which stimulate the interest in what might be happening in other systems like the pulmonary. They reported a delay in A-V conduction time, a prolongation of systole, in weightlessness; I believe it almost doubled in one instance. This was at the recent IAF meeting where the pre-

prints were given out. One can only conjecture what is involved here, but it does suggest that there will be things uncovered that we would certainly not predict.

BJURSTEDT: It would be nice if we had any useful means and methods for measurements of the thoracic blood volume during weightlessness, since there is reason to believe that blood is shifted from the systemic circulation into the thoracic region.

DUBOIS: If it does increase, what is your feeling about the water excretion under these circumstances? Do you excrete more water from your kidneys and therefore dehydrate the main part of the blood stream?

BJURSTEDT: Yes, you should.

DUBOIS: Is this certain? It seems to me this is one of the experiments it is most important to do in a biosatellite.

Most astronauts have come back having lost a great deal of weight, and everybody attributes it to sweating and other things. But the real factor may be the one we are discussing.

FREMONT-SMITH: Plus excitement which also gives diuresis.

HELVEY: I believe the specific gravity of the urine would be important.

DUBOIS: If he has a normal urinary specific gravity and yet you know that he is dehydrated, doesn't this mean that he had diuresis? Otherwise, you would expect him to have concentrated urine.*

FREMONT-SMITH: May I point out, wouldn't you expect, under tension—and these people were certainly under tension—that you would get diuresis and this diuresis would take place even at a level of some degree of concentration? I think this would be the expectation, because just going into an examination, you get a diuresis, and certainly I should think you would expect the astronauts to have a diuresis at least at the two points of going up and reentry.

RAHN: On the basis of Gauer, you would expect it also on the basis of 0 G, so that would add fuel to this whole diuresis concept.

BJURSTEDT: Time does not permit us to continue the discussion on various means of protection. As to the effects of G stress on the lungs and on pulmonary function, I think that much work is still needed before we will know how serious these effects really might be, for instance with the G profiles now contemplated for the Apollo

*M. S. Carpenter voided 2360 ml. urine, specific gravity 1.003, during eight hours, including prelaunch and orbital flight time. W. M. Schirra, Jr. voided urine of specific gravity 1.018 based on a 292 ml. sample; total volume is unknown because of failure of the collecting device. L. G. Cooper, Jr. voided 949 ml. during approximately 30 hours of orbital flight; the specific gravity of the last 107 ml. was 1.026. The specific gravity of his first post-flight urine sample was 1.031. Data are from NASA reports of the Second, Third and Fourth Manned Orbital Flights, NASA SP-6, 1962; NASA SP-12, 1963, and NASA SP-45, 1963, respectively.

project. I would personally like to see continuous measurements of the changes in O_2 saturation or tension up to 15 G in the centrifuge. In general, most of the effects that have already been observed at lower G levels might become more drastic, but it would seem to be especially important to look into the time history of critical effects, so that the hazards involved in any chosen G profile can be properly evaluated.

FENN: I thought I would call on Doctor Graybiel next, because he has worked so much on some of the sensory aspects of space flight. Doctor Graybiel, if you would introduce the subject for us, we will proceed with our discussion.

Vestibular Function in Unusual Gravitational Environments

GRAYBIEL: Very briefly, I will outline our area of interest and hope that you will take it up from there.

We are interested in the role of the vestibular organs in unusual gravitational inertial force environments. We are attempting to distinguish, where it seems important, the role of the otolith organs which respond to linear accelerations from those of the semicircular canals which respond to angular accelerations and under specific circumstances, Coriolis accelerations.

In talking about the force environment, an important thing not to neglect is the forces generated by man. Moreover, it is necessary to take into account the position of man and the structure and orientation of the vestibular organs. The otoliths don't work the same if you are head down in 1 G, for example.

A chief objective is the practical application of our findings to space flight; hence, we are particularly interested in weightlessness, the subgravity states, and rotating environments in the event that it is decided to rotate a space vehicle to generate an artificial field force.

With regard to the generation of gravitational-inertial force environments these fall into two categories, namely, those which attempt to simulate force environments in space and those which are essential to the study of the vestibular organs singly or collectively. Jointly with the USAF we have conducted experiments in weightlessness and subgravity states. Moreover, during the brief periods of weightlessness we have exposed subjects to angular accelerations or Coriolis accelerations which served to stimulate the canals at a time when the otoliths and other gravireceptors were largely deafferented. We have used a slowly rotating room (SRR)[112] for simulating the rotating environment aloft. Here you have shortcomings; firstly, inasmuch as you are experimenting in 1 G or 1 G+ and not in weightlessness and, secondly, in the usual conditions you have man oriented parallel to the axis of rotation rather than at right angles to it.

In the second category, we are interested in stimulating, selectively insofar as possible, the otolith and canals. With regard to the former, this is possible in a counterrotating environment. If you have, let's say, a centrifuge with an eccentrically placed rotating room which goes exactly counter to it, the subject revolves and is not exposed to an angular velocity. We have a parallel swing but await vertical and linear horizontal oscillators which generate rectilinear accelerations. A variety of devices which rotate a subject about his own axes are used to stimulate the canals.

With regard to subject, we have used normal persons with varying susceptibility to motion sickness and subjects with partial or complete loss of function of the vestibular organs.

What sort of problems or classes of phenomena have we been dealing with? Well, we began right away with a first-class problem; namely, that while there are quite good tests of function of the semicircular canals, tests of function of the otolith apparatus were pretty crude. We have made, for us in a small laboratory, a tremendous effort to come up with functional tests, and I think that we have done a fairly good job. I believe that counterrolling, if this is done very carefully, is a fairly reliable test. Another test, using an illusion which people observe when the direction of resultant force is changed with respect to them also has quite good reliability. But to make the reliability very good you have to do it under water, which we did, but this, of course, is a big chore. So, tests of function of the otolith apparatus have taken up a lot of our time and attention.

Then, of course, we were interested in the stimulus-response relations of these organs. You have to understand their characteristics if you are experimenting in this field.

We studied the symptomatology and separated, somewhat, problems of disorientation from the symptoms and signs which people manifest on exposure to these unusual force environments. In doing this we compared the effects in persons who had lost the function of the vestibular organs with those in normal persons.

Then we got into the problem of adaptation, the problem of transfer, and, of course, the whole business of prevention.

FREMONT-SMITH: What is transfer?

GRAYBIEL: You can be susceptible to one force environment or adapt a person to one force environment, and this may have a greater or lesser transfer to his susceptibility in another force environment. Glenn, for example, is susceptible to seasickness, and yet is far less than average susceptible to other force environments.

I will mention in a little more detail a couple of experiments we did in this area of adaptation and transfer. We used our slow rotation room for these particular experiments. At constant rotation, if you

also rotate your head, you generate a Coriolis acceleration, which is a sufficient stimulus to the semicircular canals. This is in a plane orthogonal to the plane of the two rotations. One of the very simple tests was carried out by having the subject observe a box lighted only around its edges in the dark. If you are watching this box and you move your head to the left shoulder, the box will appear to go up.

FREMONT-SMITH: This is when the room is stationary?

GRAYBIEL: No, in a rotating room. When stationary nothing happens, but if you are in a rotating room and you move your head to your left shoulder and are watching this target, the box will appear to go up.

FENN: Does it make any difference which way it is rotating? Does it go down if you rotate it the other way?

GRAYBIEL: Yes, it does. This is for counterclockwise rotation.

WOOD: The subject is facing centripetally?

GRAYBIEL: Actually, it doesn't matter much where you are, almost anywhere in there you will get pretty much the same effect.

FREMONT-SMITH: The target is right in front of him?

GRAYBIEL: The target is directly in front of him.

FREMONT-SMITH: If he turns his head to the right, will the box go down?

GRAYBIEL: Yes, or after his head is down and he brings his head up, then the target goes down.

But the particular thing that I am interested in is that here is an evoked response. Varying from minutes to days, if you are continuously rotating, this response will decline and be extinguished, and it is extinguished very quickly in certain subjects and only after prolonged exposure in others.

FENN: Is this purely a subjective response or is there a corresponding eye movement which accompanies it?

GRAYBIEL: There is an associated eye movement and we have also measured this. I will show you a slide and discuss the nystagmus response.

FREMONT-SMITH: Another way you can put this is that he tests this against reality and eventually realizes that the box isn't going up and therefore, he doesn't see it go up. Is that it? I know that in the Ames studies on illusions, in the distorted room the subject sees the room distorted and he fails to hit a target; and then after a certain amount of time he adapts to this and now he can hit the target; the room no longer seems so distorted. Is this the same kind of phenomenon or is this something different?

GRAYBIEL: I believe it is something different. This is one of the very points I want to make. We have discovered a mechanism which seems to account for it.

Anyway, here the man is now. He is operating in the room, doesn't have any symptoms, is adapted to everything and is specifically adapted to this illusion. Now, if you stop the centrifuge, let's say on the morning of the third day, and then you ask him to make this same movement, now the box will go down—and remember, he is not being stimulated by a Coriolis acceleration. This must be a conditioned stimulus.

Doctor Guedry,[113,114] who was a guest with us and participated in this first experiment, became extremely interested in the phenomenon, and I am glad to say that he is now a permanent member of our staff. This was done in a series of experiments, and I will show you very quickly some of the results.

In the first experiment (FIGURE 31), the illusion was used, and the object was to find out if, after you had adapted to a particular movement, there was any transfer to a movement, let's say moving the head to the right shoulder. Before rotation, if you move your head nothing much happens. There is a little parallax effect, but the box doesn't appear to move. At the onset of the period of rotation, of course, you observe the apparent movement and it is about equal when moving the head right and left.

The subjects in this particular experiment were fixed. They were allowed to move their head only in this one direction, to their left

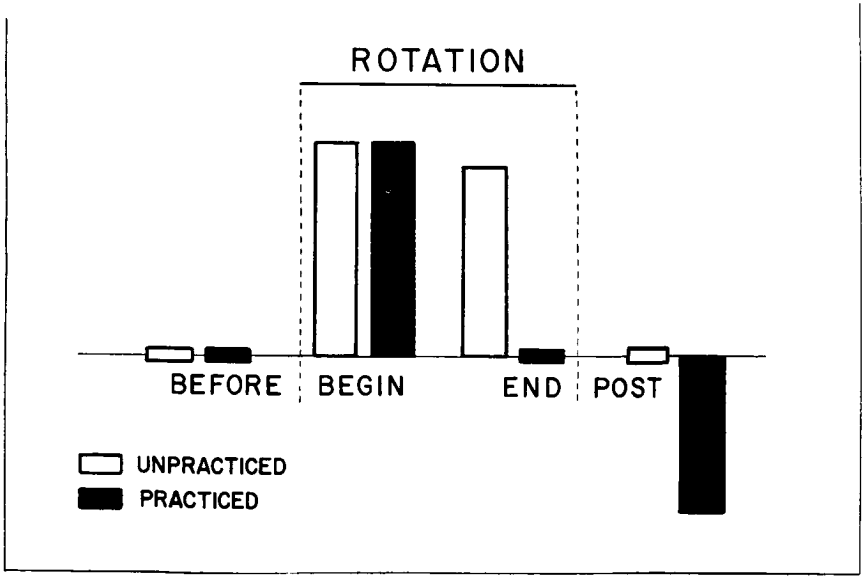

FIG. 31. Comparative magnitude and direction of the Coriolis illusion associated with single head movements before, during and after prolonged rotation at 5.4 rpm; tests carried out at 7.5 rpm. (From Graybiel, 1964.[115])

shoulder. They did this four to 700 times over the course of five to eight hours until they were pretty well adapted, and by the end of that time they didn't get much of any illusion when they made this movement. But if they moved the head to the right shoulder they got about a normal response, indicating a very small or just almost negligible amount of transfer.

Then you stop the centrifuge. Moving the head on the unpractised side, to the right shoulder, nothing happens, but moving the head to the left shoulder results in an illusion but of opposite sign; the box appears to go down.

FREMONT-SMITH: Is it a rapid movement or a slow movement?

GRAYBIEL: It is quite rapid.

FREMONT-SMITH: I mean the movement of the head.

GRAYBIEL: The movement of the head, yes. This was timed with a metronome. I would say the movement occurred in about a second or a second and a half.

FENN: How do you record the magnitude of this illusion?

GRAYBIEL: That is a good question. We have recorded it in terms of the width of the box. Isn't a very accurate way. On the other hand, the movement is so prominent that, within limits, I think it is an ade-

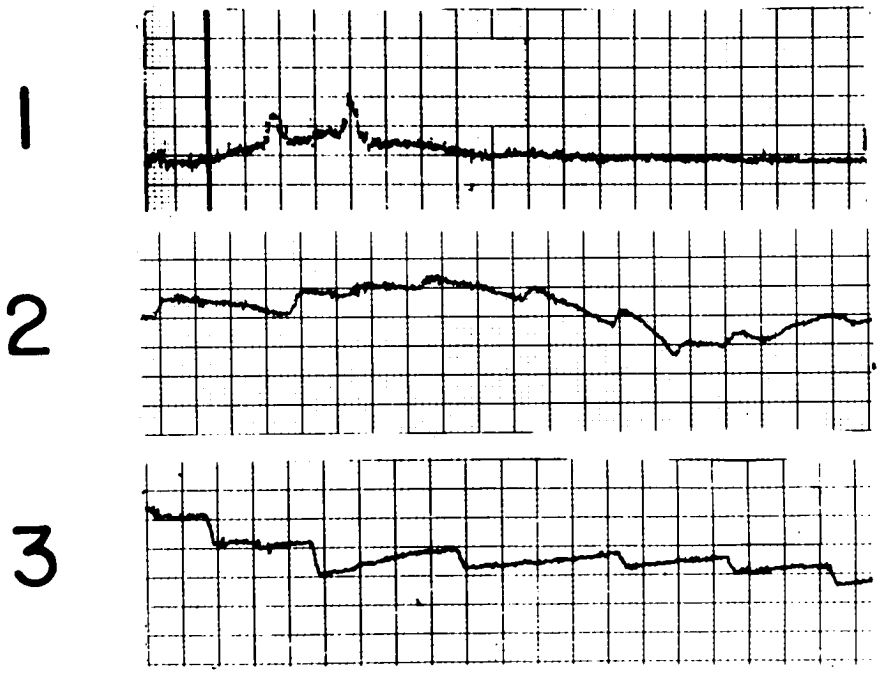

FIG. 32. Nystagmus associated with head movements (*1*) before, (2) during and (3) after prolonged rotation. (From Graybiel, 1964.[115])

quate indicator. It is perfectly obvious that you need something more than this on which to rest your case; so the next thing we did was to take nystagmograms during rotation and after stopping. This shows (FIGURE 32) that before the onset of rotation you didn't get nystagmus when you moved your head to the left shoulder; that at the beginning of the experiment you got nystagmus. It isn't a strong beating nystagmus, but yet it is definite enough, and you can see the direction of the fast phase. After adaptation and cessation of movement, you see that it is in the reverse direction, so that the phenomenon, as such, we feel is shown objectively by these recordings. There is much individual variation.

FENN: Are these nystagmus movements around a vertical axis?

GRAYBIEL: Yes, the initial phase—the fast phase is up and after cessation of movement the fast phase is down; so it seemed to us that here were two important things, a compensatory mechanism and a conditioned response.

I failed to say that in the course of adaptation, the nystagmus would diminish. You might get a little, but it wouldn't amount to much.

FENN: When you say up or down, do you mean when the head is on the side, so it is horizontal axis relative to the head, but the head is tipped?

GRAYBIEL: Yes, I am speaking relative to the head. So, here were two things, it seemed. One, that this was a conditioned compensatory response and that this should be regarded as a mechanism of adaptation different from general suppression which we think of as an adaptation mechanism. Second, the fact that a response was evoked with the room stationary indicates that it was a conditioned response associated with the head movement, but not Coriolis stimulation of the canals.

From this, we feel that this whole phenomenon of transfer is very important and it isn't so simple as it looks here. Actually, there were positive transfer effects. If the subject adapted to counterclockwise rotation had then been rotated clockwise, there would be an exaggeration of the response followed by a curious sequence of events. Also, there is a question of how long these adaptation effects will remain.

It would appear from these findings on adaptation that during rotation a new functional state was created in exchange for the old functionally integrated state. We feel that there is a very good likelihood that instead of substituting a new state for an old one, you could add a new state, thereby preserving your adaptation to a stationary environment while adapting to rotation. I think that figure ice skaters probably are an example of this.

In a more general way, it seems to us that while this adaptation oc-

curring in the rotating room is extraordinarily well arranged for man to operate in this new environment, and, as such, a beautiful example of homeostasis, yet, it falls short of a typical example in that, on cessation of rotation, the new state tends to be preserved at least for hours. We don't yet know how long but we are wondering whether it is preserved until new inputs alter the integrative pattern, thus creating something different. Is this example a unique thing or does it apply more generally? Is postural hypotension after a night in bed or after a few hours of submergence in water another example?

We had subjects submerged in water for a period of a few hours and stood them up, and they had postural hypotension. We thought it was because their superficial vessels were probably dilated, since the temperature of the water had to be almost body temperature. On the other hand, the possibility exists that just the lack of an input from the usual circulatory reflex mechanisms which are generated all the time when we are up and around accounted for this hypotension.

We are also wondering whether it might not be a good experiment to have subjects submerged in water for a period of time and then test them out on a centrifuge, at small amounts of G force, with the object of studying adaptation mechanisms. We might learn whether there is some generality to the concept which seems to be true for the specific instance dealing with vestibular adaptation.

FREMONT-SMITH: Isn't it true that a conditioned reflex will not persist indefinitely—on the one hand, it fades out through time if it is not reinforced; on the other, it can decrease very rapidly if it is put through the process of extinction.

GRAYBIEL: Yes.

FREMONT-SMITH: In your instance, as I understand it, you are giving no stimulus for a period of hours and then you try it again. But if you were to start an opposite stimulus immediately afterwards, it would fade out fairly quickly, wouldn't it, through the process of extinction?

GRAYBIEL: That is right, it will certainly fade out very quickly.

FIGURE 33 shows a view of the counter-rotating room. This room is at Toronto and we used it by courtesy of Walter Johnson and his group.[116] It consists essentially of a turntable and a centrally-placed capsule, and they are geared in such a way that the one goes exactly at the same angular acceleration as the other, but in the other direction.

The canals aren't stimulated. You can deal now with unusual patterns of stimulation to the otolith apparatus in the absence of stimulation to the canals. This contrasts with the experiment in 0 G when we stimulated the canals with angular or Coriolis acceleration while the otoliths were deafferented for practical purposes.

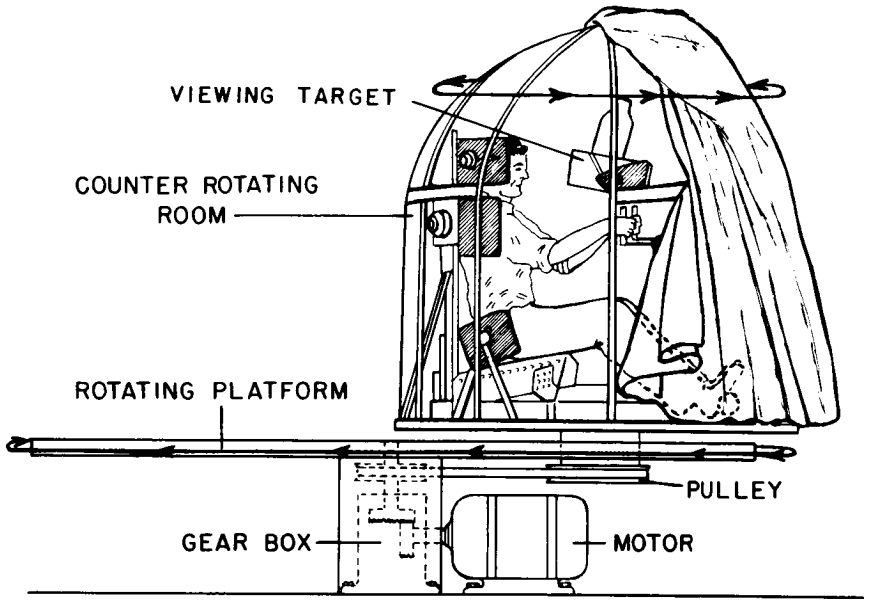

FIG. 33. The counter-rotating room apparatus. (From Graybiel & Johnson, 1963.[116])

FREMONT-SMITH: Is this as though the person were going along in a straight line?

GRAYBIEL: No, you have more of the feeling of being revolved in a funnel.

FREMONT-SMITH: But if the one rotation balances the other, then all you would theoretically have is a situation as if you were going ahead on a train in a straight line.

FENN: Back and forth.

GRAYBIEL: The centripetal force is continually changing direction. You are eccentrically placed so you have generated, in effect, a curvilinear or linear acceleration which is continually changing direction.

FREMONT-SMITH: So it is, as Doctor Fenn said, back and forth.

GRAYBIEL: The subjects react to this somewhat differently. Most characteristically, as I say, they feel as though they were going around inside of a funnel.

FREMONT-SMITH: In what direction is the vector of forces?

GRAYBIEL: The vector sum of forces, the angle that you generate with respect to the vertical, the angle *phi*. This is continually going around you. This is the first time that these subjects without vestibular apparatus felt that they were really rotating. They were sharper than the normal subjects in picking this up right away. They said "we were rotating" and stated which direction, although I don't know how they determined which direction.

TABLE 5
SYMPTOMATOLOGY IN 9 STUDENTS AND IN 6 DEAF SUBJECTS
WITH LABYRINTHINE DEFECTS UNDER DIFFERENT CONDITIONS
IN THE COUNTER ROTATING ROOM[128]

EXPER. CONDITIONS	STUDENTS	I 15 RPM 30 min. ϕ 8°43' HEAD FIXED EYES CLOSED														II 15 RPM 30 min. ϕ 8°43' HEAD FIXED EYES CLOSED														III 10 RPM 30 min. ϕ 3°54' HEAD FIXED EYES CLOSED													
		UNFIT		CONCERN	EXPER. DISCONT. (min.)	AWARE BREATHING	AEROPHAGIA	AWARE STOMACH	NAUSEA	VOMITING	PALLOR	SWEATING	OTHER	GEN. DISCOMFORT		CONCERN	EXPER. DISCONT. (min.)	AWARE BREATHING	AEROPHAGIA	AWARE STOMACH	NAUSEA	VOMITING	PALLOR	SWEATING	OTHER	GEN. DISCOMFORT		CONCERN	EXPER. DISCONT. (min.)	AWARE BREATHING	AEROPHAGIA	AWARE STOMACH	NAUSEA	VOMITING	PALLOR	SWEATING	OTHER	GEN. DISCOMFORT
	LR	II	1	9	0	0	II	1	0	1	1	1,2,3	I		I	20	III	0	III	II	0	1	1	1,2,3,4,5,6	III		I	14	II	0	III	II	0	1	1	1,2,3,4,5,6	III
	GO	I	II	13	III	0	III	II	0	II	1	1,3,5	III		II	16	I	+	III	III	0	II	II	1,3,5	III		II	**	0	+	II	0	0	1	1	1,5	0
	HA	III	II	17	0	0	III	II	0	1	1	1,3,8	II		II	19	1	0	III	III	0	1	1	1,3,5,8	III		II	0	0	0	0	0	0	0	0	2,5	0
	LE	III	1		III	0	1	II	0	III	1	6,8	III		II	1	0	III	0	III	III	0	1	6,8	III		II	0	0	0	0	0	0	0	0	0	0
	AD	II	II	8	0	0	1	1	0	1	1	1	II		II	0	0	1	0	0	0	0	0	0	1													
	RU	II	II		III	0	III	III	0	II	1	1,2,5	II																										
	RE	0	1	18*	0	0	1	0	0	1	0	0	0		1	0	0	0	0	0	0	0	0	0	0														
	PA	0	1		0	0	0	0	0	0	0	0	0																										
	SA	1	1		0	0	0	0	0	0	0	0	0																										

EXPER. CONDITIONS		IV 30 RPM φ31°31' 30 min. HEAD FIXED, EYES CLOSED											V 30 RPM φ31°31' 30 min. HEAD MOVING, EYES CLOSED											VI 30 RPM φ31°31' 30 min. HEAD MOVING, EYES OPEN, ROOM LIT											VII 30 RPM φ31°31' 30 min. HEAD MOVING, 15° PRISMS, ROOM LIT										
		CONCERN	EXPER. DISCONT.(min.)	AWARE BREATHING	AEROPHAGIA	AWARE STOMACH	NAUSEA	VOMITING	PALLOR	SWEATING	OTHER	GEN. DISCOMFORT	CONCERN	EXPER. DISCONTINUED	AWARE BREATHING	AEROPHAGIA	AWARE STOMACH	NAUSEA	VOMITING	PALLOR	SWEATING	OTHER	GEN. DISCOMFORT	CONCERN	EXPER. DISCONT.	AWARE BREATHING	AEROPHAGIA	AWARE STOMACH	NAUSEA	VOMITING	PALLOR	SWEATING	OTHER	GEN. DISCOMFORT	CONCERN	EXPER. DISCONT.	AWARE BREATHING	AEROPHAGIA	AWARE STOMACH	NAUSEA	VOMITING	PALLOR	SWEATING	OTHER	GEN. DISCOMFORT
STUDENTS	AD	II	13	0	0	III	0	0	I	0	I	II																																		
	RU	II		0	0	0	0	0	0	0	0	0	II		0	0	0	0	0	I?	0	0	0	II	23	II	II	II	II	0	II	I	0	III										
	RE	I		0	0	0	0	0	0	0	0	0												I	††	0	0	I	0	0	0	0	0	0	I		0	0	0	0	0	0	0	0	0
	PA	I		0	0	0	0	0	0	0	0	0	I		0	0	0	0	0	0	0	6	0	I		0	0	0	0	0	0	0	8	0	I		0	0	I	0	0	I	I	0	0
	SA	I		0	0	0	0	0	0	0	0	0	I		0	0	0	0	0	0	0	0	0	I		0	0	0	0	0	0	0	0	0	I		0	0	0	0	0	I	I	0	0
LABYRINTHINE DEFECTS	GR																							0				0	0	0	0	I	0	0	0				0	0	0	0	0	0	0
	GU																							0				0	0	0	0	0	0	0	0				0	0	0	0	0	0	0
	MY																							0				0	0	0	0	I	0	II	0				0	0	0	0	0	3	I
	PI																							0				0	0	0	0	I	0	0	0				0	0	0	0	I	0	0
	ST																							0				0	0	0	0	I	3	I	0				0	0	0	0	I	3	I
	ZA																							0				0	0	0	0	I	0	0	0				0	0	0	0	I	0	0

I = Slight, II = Moderate, III = Severe, 0 = Absent or Nil, + = Present, * = Misunderstood; Stopped on First Symptom ** = Not Fully Recovered from Exper. Previous Day

‡ Other: 1 = Dizzy, 2 = Disoriented, 3 = Headache, 4 = Increased Respiration Noted by Experimenter on Egress, 5 = Fatigue, 6 = Desire Move Bowels, 7 = Retching, 8 = Increased Salivation

†† = Closed eyes off an on, one period 5 minutes

SCHMIDT: Are these deaf mutes you are talking about now?

GRAYBIEL: Yes, deaf mutes with loss of vestibular organs. TABLE 5 shows a comparison of the symptomatology between the two groups, and here the dramatic thing isn't that healthy people get sick and these avestibular subjects don't, it is the mild symptoms which healthy people experience. The etiology of these mild symptoms often goes unrecognized. The avestibular subjects usually enjoyed the experience in contrast to the normal ones.

The data shown in FIGURE 34 are from subjects with no labyrinths compared with normal medical students in the counter rolling test. In this test, if a normal person is tilted to the left, his eyes tend to compensate by a roll to the right. In the apparatus we have, the subject is rotated around the eye that we are using for measuring, we use a photographic process and match the landmarks on the iris. This isn't an excellent test, but we think it is better than any other one that we have. If you take four photographs of a person, I don't care whether he is upright or leaning a little bit, and let's say you measure these, then make four prints from any one of those four. Measurements on the four prints are a test of reliability which is good. Measurement on four different photographs shows greater variance, and we believe this may be due to slight spontaneous movements. The eye is never quite still, and there is some movement, and probably this involves also some torsional movement.

So it is true that if you observe counterrolling within this range, you aren't sure whether this may or may not be due to a little residual otolith function. The reason we think it probably isn't is because this rolling reflex is lost so easily if there is any damage to the ear. We believe that it is important to carry out functional tests on the otolith apparatus as well as on the canals before selecting subjects for experiments involving the vestibular apparatus.

Although this test is tedious to carry out in some respects, yet you can do it very quickly and it lends itself to the short parabolas of 0 G, and other subgravity states. We have explored the entire range, concentrating somewhat on 0.165 G which would be the gravitational attraction of the moon. and also at 0.2, a value that some people feel is the smallest amount which would be worthwhile to generate if you are going to rotate a space vehicle.

FENN: Upon coming ashore after a long sea trip, you still feel the deck rolling under you for some time. Is this the same kind of persistance of conditioned reflexes that you were talking about?

GRAYBIEL: It is. There is probably this difference, that when you come ashore you are inclined to think that the dock is moving. We have never been able to get this information from our subjects who

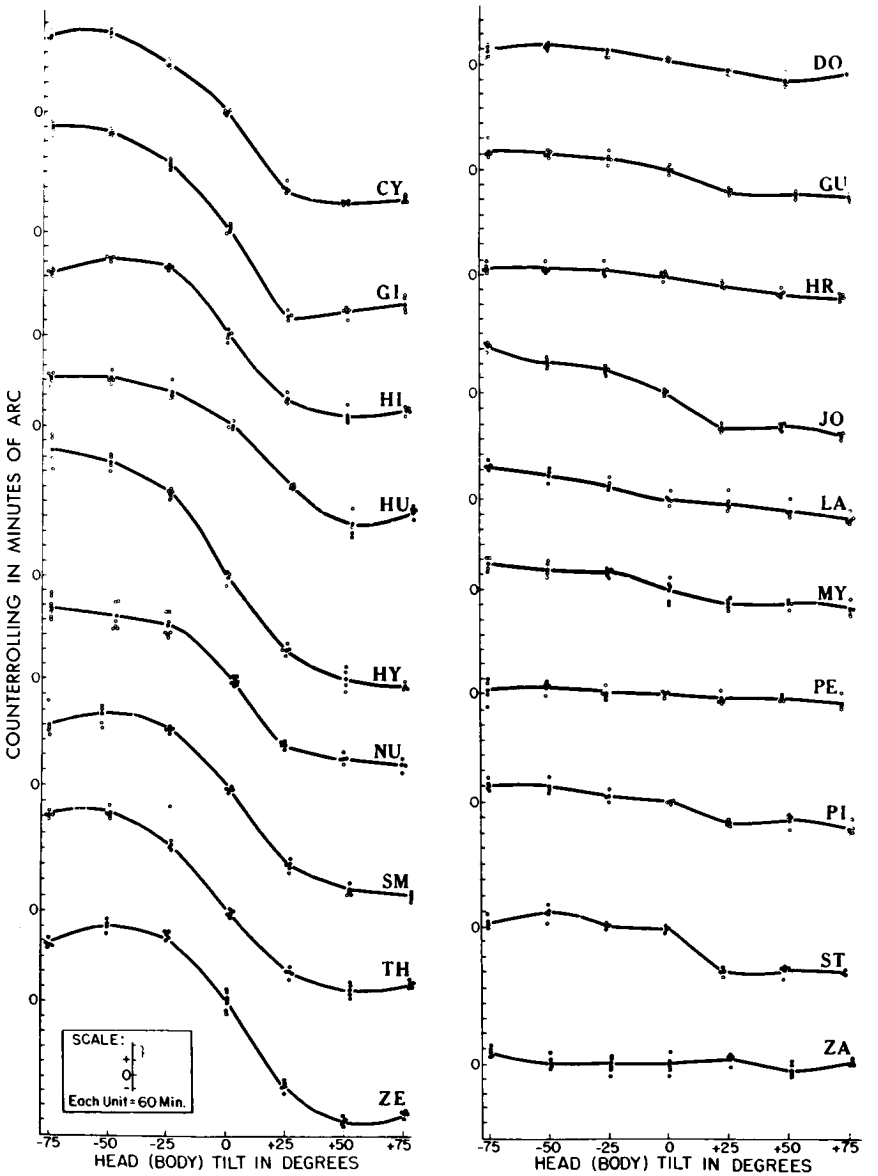

FIG. 34. Mean counterrolling values plotted as a function of leftward and rightward tilt. *Left:* normals; *right:* L-D subjects. *closed circles:* average values in minutes of arc; *open circles:* value for different trials at a given body position. (From Miller & Graybiel, 1963.[117])

come from this room. They always say that they seem to be moving in relation to a solid level floor.

FENN: What do you think is the mechanism of this persistence of sensation? There is no stimulation going on to initiate conditioned reflexes and it isn't in phase with anything. Something must be revolving in the synapses in the brain cells, but at what speed and why is it synchronized the way it is?

How do you think of this going on? What is the mechanism of this remembering? What is happening?

GRAYBIEL: Some believe that it is mainly the result of intralabyrinthine "conflict" and others that it is a more general intersensory conflict. Without denying these possibilities we would like to advance a third possibility, namely, that it is due to the bizarre impulses from the canals per se and that this is independent of other inputs. If Bob Livingston[118] were here, he could tell us about some experiments they carried out using noise. They subjected the animals not to just a click, which is the usual thing, but to a loud noise for a period of time and following that, they found changes at different cell stations along the auditory pathway which made them believe that they had actually established a different functional state at those different stations. Moreover, they found that other influences had a modulating effect.

It would seem here as though in this terrifically complex integration which must go on, probably mainly in the brainstem, inputs from without, from subcortical, and cortical regions, etc, are somehow combined into a global pattern which enables man to deal with his outer environment. Of course, the receptors responsive to the gravitational-inertial force environment account for a very important input. If you alter this input you disturb the normal pattern. Just how this adaptation is so cleverly accomplished without our taking thought is amazing and a fascinating area for further study.

For example, to some extent this adaptation process might be quantified at least in terms of the number of stimuli. Moreover, we could investigate the time-course of the loss of adaptation, minimizing or maximizing other influences. This is open for exploration.

FREMONT-SMITH: What about the movement rate of the head to shoulder? I would think this might influence it if it is quite a rapid one or very slow motion. Have you tried variations on this?

GRAYBIEL: No, we haven't. In our experiments the movement has been made quite quickly. Adaptation will occur almost equally well whether it is an active movement on your part or whether it is a passive movement.

To get back to your question, Doctor Fenn. Sometimes we run into a curiosity which reminds me a little bit of some of the curious phenomena you see with bends. Ordinarily, at 22,000 feet you don't get

bends, or if you get them they are minimal, and at a little higher altitude, they might be prominent for a short time and then disappear. But in particular instances, a person will have his significant visual symptoms long after the thing seems to be over, or have symptoms when it seems there wasn't decompression.

Similarly, with some of these postrotation symptoms, usually the transition back to normal is quite rapid and relatively regular, but occasionally a curiosity will occur and the individual, during the night or at some other time, will suddenly have as severe symptoms as he had immediately postrotation. It is a foruitous phenomenon; on other occasions, he won't have it.

FREMONT-SMITH: Symptoms in what respect?

GRAYBIEL: I was particularly thinking of some of the subjective symptoms, of dizziness and nausea.

FREMONT-SMITH: As if the room was rotating or as if he was rotating?

GRAYBIEL: There have been few instances of this and we didn't have the opportunity to question them at the time to see whether they had subjective or objective vertigo. The most I could say for sure was that it was described as dizziness.

RAHN: I am interested in this one exceptional case that had the bends in the eyes, if that is the way you want to put it. Would this case have never come to your attention unless this man had reported—I don't know what he reported to you—this man who went to 22,000 feet, you said, and had some kind of a visual disturbance that he reported?

Is this something that, under ordinary circumstances, if he had closed his eyes, would never have been reported to you? He would not have been aware of it—something subclinical?

GRAYBIEL: This particular instance I am thinking of was the case of Doctor John Patterson* who is at the Medical College of Virginia. Some of you may know him or know of him. He, without a shadow of a doubt, had definite symptoms following exposure. He was an experimenter and he went into the chamber for a short time. I am not sure how long now, this was some years ago, when we conducted Operation Everest. He went in the chamber, assisted in an experiment, came out, and this was a result.[119]

I would say that at least as far as our experience goes now—and I am talking about Beischer's[120-122] work with magnetic fields where he is trying to see whether there is any change in subjects, either at null or high Gaussian fields, and also under other stressful circumstances,

*Patterson, John L., Jr. Medical College of Virginia, Richmond, Virginia Unpublished observation.

we are relying more and more on visual tests. The things which one might look for are changes in flicker fusion, particularly peripheral flicker fusion as against central, but both, and then any changes in the visual field, changes in binocular vision and space perception. We believe that they are among the better indicators of very early CNS changes.

RAHN: Maybe this is off the subject, but we are talking about bends and I am fascinated with this approach. Would you not say that tests for bends at the moment are some of the crudest we have? You either have a pain in the left elbow or left finger or you don't—isn't that about it?

GRAYBIEL: Yes.

RAHN: On the basis of that, you determine the whole decompression program of an astronaut and it seems to me so utterly crude. Can somebody contribute along these lines? Is anyone working in this area?

ROTH: I think there is a good model for these late symptoms from animal work. Vince Downey[123] demonstrated not too long ago that bubbles will exist both in physical systems and in animals for several hours after a decompression event. It takes a rather long time for the bubbles to collapse. I think you can look at it this way, you have a bubble lodged in a large vessel, the distribution area of which has collateral circulation. If after a period of several hours this bubble decreases in size, it can progress along the vessel to a point which is now distal to the input of the collateral circulation and block off circulation in this area. This gives you the delayed symptoms.

It is interesting that most of these delayed symptoms, if not all, are CNS types. You don't get chokes, skin phenomena; it is always of a CNS type, and I think the CNS collateral circulation is of a type that might predispose to this sort of phenomenon.

GRAYBIEL: We have the same feeling in regard to what might be called motion sickness. In the early days, they used vomiting as their end point. We find that we would have subject difficulty if we did all of our experiments with this as an end point, so now we have established and set up other criteria. We recently had Charles W. Wood,* a pharmacologist, working with us, and it was very difficult to persuade him—he almost insisted on using the vomiting end point. After he saw how well these other symptoms worked, how reliable they were as indicators, he agreed that we had a reliable indicator far short of the vomiting stage.

I think also with respect to susceptibility, whether you are talking about bends or whether you are talking about motion sickness, the way to do it is to measure carefully their threshold of susceptibility.

*Wood, Charles W. University of Arkansas Medical Center, Little Rock, Arkansas. Personal Communication.

ROTH: I just wondered if you have had a chance to compare your results in the rotating room with body axis parallel to the axis rotation, with the Langley studies* which had body axis perpendicular to axis of rotation and with Armstrong's studies at General Dynamics/Astronautics† in which they had a gimbaled system. How did the results compare?

FREMONT-SMITH: What is a gimbal system?

ROTH: This is a centrifuge where the subject is in a gimbaled car at the end of the centrifuge arm and so changes his angle of position so that his body axis is constantly along the resultant G vector.

GRAYBIEL: The Langley results[124] have been published and are very interesting because here they did have their subject at right angles to the axis. A criticism of our results is that the symptoms would be ever so much more severe if the subject were at right angles rather than parallel to the axis of rotation. If you are parallel to the axis of rotation and swivel your head, or body, or move up and down in that plane—the canals will not be stimulated by Coriolis acceleration; whereas if your head is at right axis to rotation, and you roll over, it is almost as if the direction of rotation has changed with respect to the canals. These movements should cause symptoms.

It just so happens that the Langley Field results, as they were reported, would indicate less susceptibility at 10 rpm than we had found. The conditions in the Stone and Letko experiment[124] were, of course, very different from ours, which I believe explains the differences. Our subjects were free to move about and rotated their heads in all positions with respect to the axis of rotation. Their subjects were fixed in a supine position and head movements limited to left-right swivel. Speaking of restraint, a susceptible squirrel monkey gets sick very quickly if freely moving in the rotating room; but we have never made one vomit, if restrained. It may get sick but it won't vomit. Restrained, they just go to sleep. You can hardly keep them awake.

With regard to the experiments at General Dynamics in San Diego the results haven't been published, and I don't feel free to mention them here except to say their experiment was carried out at higher G levels and other factors in the experimental designs were different. I think the differences between their results and ours are due to a number of factors including the different G forces.

BJURSTEDT: I am interested in the specific effects of low oxygen on the CNS system. Have you noticed any effects of low oxygen per se on these measurements?

*Stone, R. W., Jr., 1963, Rotating space station studies (unpublished), Space Mechanics Division, NASA Langley Research Center, Virginia.

†Armstrong, R. C., 1963, Personal communication, Chief Life Sciences, Convair (Astronautics) Division, General Dynamics Corporation, P. O. Box 1128, San Diego 12, California.

GRAYBIEL: I regret to say we haven't done that. We have only had one rotating room until now, and all I can say is that we just haven't done it.

FENN: Doctor Margaria, you have had a lot of experience with this sort of thing.

MARGARIA: We have considered this problem from another point of view. We thought that in 0 G condition, we have, first, the deafferentation of the labyrinth which may involve a profound disturbance on the functioning of the central nervous system. The labyrinth is working normally on high level background noise, which is the normal gravitational pull (1G). In the satellite we shift suddenly to 0G, and in this condition the sensitivity of the apparatus may increase very appreciably, in accordance with the Weber-Fechner Law.

The afferentation from a sense organ does not seem to be of great importance in disturbing the function of the central nervous system: by analogy, closing the eyes or being in a soundproof room is not an unbearable experience. The change of sensitivity of the labyrinth on the other hand may have a very disturbing influence. Furthermore, this problem is complicated by the fact that the labyrinth is made up, as Doctor Graybiel said, of two distinct apparatuses, the otolithic system and the semicircular canals: the semicircular canals work on a different basis, on a different principle from the otolith, and are not affected by static gravitational pull.

All this depends very much, of course, on whether these two apparatuses work independently or whether they work together. As a matter of fact, the fibers from these two apparatuses go together in the eighth nerve, and the impulses that reach the centers may then be integrated in such a way that impulses from the otolithic apparatus operate similarly as impulses from the semicircular canals. In this case, the absence of gravity would not change very much the sensitivity of the otolithic apparatus.

One thing that we should know more about, possibly, is the normal physiology of the otholithic apparatus and the semicircular canals; that is why Gualtierotti and others[125, 129] in my laboratory started to investigate the sensitivity of the otholithic apparatus in normal gravitational field. To this end, some electrodes were inserted in the flocculus nodule lobe of the cerebellum, which is the first central station reached by impulses from this sense organ. Experimenting with cats and pigeons set on a small centrifuge, we found that sensitivity is terrifically high. With this method it goes down to 1/10,000 of a G, which is much higher than the sensitivity of the sense organ. This means that the sensitivity is partially lost going from the lower centers to the upper ones.

RAHN: Would you describe again for me exactly what you mean by this change in sensitivity of 1/10,000 of a G? I don't know what you measure, actually.

MARGARIA: What we measure is an appreciable change of the action potentials in the flocculus nodule, as a consequence of the stimulus.

RAHN: As you tilt the animal?

MARGARIA: As we tilt or accelerate the animal as where the centrifuge is started; then the electrical activity of the flocculonodular lobe of the cerebellum increases until the end of the rotation or of the tilt; then we have one more burst of impulses lasting a fraction of a second as an effect of the acceleration.

FENN: Then you increase the sensitivity by—

MARGARIA: No, we cannot increase the sensitivity. We just see that the sensitivity is that high.

FENN: Do you think it would be higher in a zero gravity situation?

MARGARIA: Yes, presumably, following the Weber-Fechner law it would be higher in conditions of zero gravity because we don't have the ground noise which is due to the normal gravitational pull.

GRAYBIEL: You also found it was higher in a magnetic field, didn't you?

MARGARIA: Yes, we found another interesting thing, that this electrical response is different in homing pigeons than in conventional, domestic pigeons. After a gravitational stimulus in a domestic pigeon, a short burst of impulses is observed at the flocculonodule level and then the electrical activity comes back as prior to stimulation. In homing pigeons, on the contrary, this burst due to stimulation is followed by a series of bursts of impulses, after-discharges that are typical of this homing animal.

We thought that this effect could give a clue to understanding homing activity, that still is very obscure; it may indicate that this property is based on gravitational stimulus. This would require, however, an extraordinarily developed memory for gravitational changes, in addition to great sensitivity to this kind of stimulus; in fact such a hypothesis requires a perfect memorization of all the changes of direction and of all the movements (and direction) of the head.

We did not feel like concluding that homing pigeons have the ability to remember all the acceleration disturbances that they had during their flight, and therefore, we did not support the hypothesis that the "homing" ability is based on the gravitational or acceleration process.

GRAYBIEL: But you found that this was increased when you put them in a high Gaussian field, isn't that right?

Influence of Electromagnetic Forces

MARGARIA: Yes. The electrical response to acceleration or to changing position of a pigeon in the centrifuge is more pronounced if the head of the pigeon lies in the magnetic field of a strong electromagnet.

FENN: How do you explain that effect? Why should magnetic field increase the sensitivity?

MARGARIA: Magnetic field has a very peculiar effect on the sodium pump.[130] This has been studied on frog skin which in this connection, behaves very much like a cell membrane, because sodium is normally actively extruded from the inner to the outer surface, just as in the cell membrane. This sodium pumping is for the frog skin, as well as for the membrane of any cell, responsible for the transmembrane resting electrical potential. The sodium pump activity is decreased some 20-25, in some cases up to 40 per cent when the field intensity increases over a well-defined critical level of about 400 Gauss, if I well remember.

NEUMAN: This is invariant? You said if you varied in the direction of a magnetic field—or is it in relationship, say, to the potential?

MARGARIA: Yes, I think this is independent from the direction of the magnetic field. The presence of such an effect of the magnetic field has been confirmed by poisoning the preparation with ouabain, which inhibits the sodium pump. In a membrane treated with ouabain the magnetic field no longer has an effect on the membrane electrical potential difference.

ROTH: Has anyone ever checked for iron carbonates in the otolith organs of birds as potential magnetic sensors? There is an hypothesis that some birds orient themselves with respect to magnetic fields. They remember their direction by responding to magnetic fields. I just wondered if any iron, excessive iron, has been demonstrated in the otolith of birds?

MARGARIA: I don't think it has been demonstrated: besides, it is hard to visualize how a weak magnetic field, such as the earth's can have an effect, in consideration also that this iron is immersed in a fluid medium. The biological effects mentioned above have been obtained only with magnetic field intensities of a much higher order than the earth's magnetic field.

FENN: This was demonstrated to me in Milan and it was a very beautiful demonstration. If I remember, you looked at the face of a cathode ray oscilloscope and you saw the magnetic field in one direction and the sodium pump current in the other—something like that—and as they increased the field the sodium current diminished.

NEUMAN: Was this magnetic effect also present if they bucked the current with an opposed potential?

FENN: Yes, they did. They bucked the potential and followed the current. I think it works both ways.

MARGARIA: The experiment runs in the following way: a flat chamber of Perspex is divided in two halves by a frog skin of about 7 $cm.^2$ bathed on both sides by phosphate-buffered Ringer solution. A couple of calomel electrodes about 2 cm. apart, set across the membrane lead to a potentiometer that feeds a counter current that is led to the two half chambers to keep the potential constant across the membrane. The membrane is perpendicular to the magnetic lines of force. The current intensity is measured and this is an indication of the electrochemical gradient which is normally sustained mainly by the sodium pump. A change of the activity of this is therefore evidenced by a change of the current intensity.

The whole preparation is set between the poles of an electromagnet: the field intensity was measured and related with the intensity was measured and related with the intensity of exciting current. The excitation of the electromagnet did not show any effect on the feedback current across the membrane until the field intensity reached a critical value of about 500-800 Gauss. Above this, a sudden definite drop of the current was observed that disappeared with the removal of the magnetic field: I seem to remember also that the current shift increased with increasing intensity of the magnetic field.

ROTH: I don't think we can really sell short the sensitivity of biological systems to magnetic fields, because the people working with electric fish have demonstrated that these fish can detect currents as low as seven electrons per receptor cell. These threshold currents are determined by waving small magnets across the front of the aquarium and detecting the threshold response by gross evasive movement of the fish. The African electric fish will respond to incredibly small changes in current fields, much smaller than previously expected.

There is one other factor, the earth's orientation of magnetic components of rocks. When rocks crystallize in the presence of the earth's magnetic field, small as it is, they retain the molecular orientation of their iron particles which occured at this time. Geologists can use this orientation to determine rotation of strata away from the earth's prevailing magnetic field. After a geological cataclysm the direction of molecular magnets in neighboring strata may be radically altered. So fine molecular magnet systems in otolith organs may yet respond to Gaussian fields as small as those found above the surface of the earth.

With both of these considerations, I just wonder whether there might actually be a parallel mechanism in the biological systems under question.

MARGARIA: With rock crystals I can well understand that these particles have plenty of time to obey to the small gravitational field

and get oriented in that peculiar way. But it is much more difficult to understand how in a biological system which is always in a dynamic state molecules can be oriented and keep oriented in an obliged direction.

ROTH: Fernández-Morán,[131] the electron microscopist now at Chicago, has been studying the electron microscopy of special sense organs in fish and higher animals. It might be worthwhile comparing the vestibular organs of homing pigeons with some of the structures in these animals that tend to respond to magnetic fields to see if there are similar transducers in both systems.

MARGARIA: Migrating animals may have developed a particular sense organ. The phenomenon described, however, is not due to a particular sense organ, but it is presumably a very general one, characteristic of all biological systems where cellular membranes are involved: it seems to be just as general as the sodium extrusion through the cell membrane.

NEUMAN: This is why I asked about the position of the magnetic field, because it seems to me to get any net effect you have to have a statistical electrical asymmetry. You have that in the frog membrane and that is why the frog skin is used for membrane studies. Here you have the sodium pumps all oriented in one direction. It has electrical asymmetry and it has a voltage. I was trying to get this electrical asymmetry in terms of either moving the field or possibly bucking the field by an opposed potential.

RAHN: In other words, you would predict that it would change with the orientation of the magnet in relation to the skin?

NEUMAN: Yes.

FENN: You haven't really changed the orientation.

NEUMAN: In the electric fish, you have an asymmetry which is of quite some magnitude.

BROWN: Doctor Roth, in the example you gave of the electric fish, did I understand you to say that a current of seven electrons —

ROTH: Yes, several electrons per receptor cell. This is done by passing a magnet across the surface of the aquarium.

BROWN: How can you measure a seven electron charge?

ROTH: This is calculated. Knowing the saline concentration of the aquarium and the strength of the magnet, you can calculate what the effective current was across the receptor organ.

There several people working on the problem. We had a seminar at MIT[132] at which this sort of phenomenon was being discussed, and several people mentioned that they had done this calculation in various species of fish and they were all of the same magnitude. Bullock gave these specific calculations. Impedance studies indicate that fish can detect changes of $2 \times 10^{-5}\mu$ amperes per cm^2. Since there are

6×10^{18} electrons/sec. in 1 ampere, 2×10^{-11} amperes is equivalent to 3×10^{7} electrons/cm.^{2}/sec. Since each receptor cell is about 10^{-5} cm^2 in area, 300 e/cell/sec. over a period of about 25 msec. or 7 electrons/cell appears to be the threshold. This is an incredibly small stimulus, some 10^4 times smaller than previously imagined. Bullock feels that the organ should allow these fish to detect orientation changes relative to the earth's magnetic field.

Sensitivity of Gravireceptors

BROWN: I am curious about the high sensitivities of the gravity-sensing devices that man and some of the animals have. What really are the limits? How low a G force can be detected?

GRAYBIEL: Man, under ideal conditions, will respond at about 1.00034 resultant G.

BROWN: Didn't I hear a figure, an indirect measurement of a biological accelerometer that was 10^{-4}G?

MARGARIA: Yes, but this is different, because the response was measured at the level of the cerebellum.

BROWN: Yes, I realize that.

MARGARIA: The threshold of sensation, at the cortical level, is much lower.

BROWN: But the sensor must be sensitive at that level.

MARGARIA: Yes that is the point. Changes were detected in the cerebellar electrical activity when the animal was centrifuged at a very low speed; i.e. 1/10,000 of a G. The centrifuge couldn't run at a lower speed.

BROWN: As a plant physiologist, I can't resist the opportunity to point out that plants detect down to 10^{-5} to 10^{-6}G. The lowest limit I know of is for certain kinds of plant growth responses.

Two kinds of botanical experiments have been done. One is to place test organisms along a vibrating rod so that they are exposed to pulses of acceleration and find out how far from the fulcrum you have to go before you get an effect. This is one way.

The other is to grow a higher plant horizontally and rotate it around its long axis so that essentially it is integrating the gravitational effect but it grows in a horizontal fashion. Then at the same time you swing the whole apparatus around slowly. The plant knows whether its "head" is out or its "feet" are out, so to speak, as it goes around, down to about 10^{-5} or $^{-6}$ G.

The two types of experiments give results which are within an order of magnitude in agreement.

SONDHAUS: I think it would be worthwhile pointing out here that these are phenomena of extremely long time constants and, therefore, you would expect to observe perhaps a considerably greater degree of

sensitivity. When you are speaking about the otolith or any of the human sense organs, the time constant is of the order of seconds or fractions of seconds, but in the case of a plant deciding to go in a particular way, it is hours, days.

BROWN: Hours.

SONDHAUS: So, I think it shouldn't be unexpected that there would be a greater sensitivity.

GILBERT: The limitation of the time constant determination might be in the method and not in the biological system.

ROTH: I want to bring up a point relative to the sensitivity of the middle ear in detecting G loads. When we were instrumenting these craft, at the same time we had a series of pilots whom we were trying to train to fly 0 G. I remember sitting in the plane one day and not looking at the G meter while the pilots were training and I said, "My God, that was an awful parabola." I then got to wondering how much of a deviation from 0 G I could detect as the plane fluctuated at the hands of an inexperienced pilot. I had a little pad of paper and I would write down the fluctuation rate of G that I suspected, and then look at the accelerometer tracings to see how close I came. The figure I remember is about 0.05 G. I could sense a fluctuation and I could say whether it was $\pm$ 0.05 G or $\pm$ 0.1 G as the plane fluctuated along the 0 G path. So, you do have a remarkable sensitivity in these low ranges. I don't know if this was ever followed up.

GRAYBIEL: Yes, they have recently carried out a systematic study of this kind, but the data are not yet available.

Factors Affecting Responses to Changes of Force

FENN: We read that Titov in his flight had particular sensations and difficulties from Coriolis forces, I suppose, when he wagged his head quickly, out in orbit. Ordinarily, I think of stimulation by moving the head when you are in a rotating field as changing the distance of your semicircular canals from the axis of rotation.

If you are out 100 miles and you are a long ways from the center of rotation, the center of the earth, a few centimeters distance wouldn't seem to have any effect whatsoever. Then, why should Titov have detected any effect from wagging his head and nobody else got any? Is there any sense to this?

GRAYBIEL: If you are asking me, I think there is a lot of sense to the question, and so far as his great rotation of one orbit in 93 minutes is concerned, I just don't think this was a factor, because at 1 rpm in a rotating room, even the most sensitive person is just barely aware of symptoms.

The first question that was put to the Russians was: Was this capsule rotating at all? They flatly denied that it was rotating, but

rumors still persist that there may have been some rotation. Indeed, his control over the capsule with respect to attitude may have possibly been important here because he began to make these corrections or manipulations, if I remember rightly, on the sixth and seventh orbits. That is when he began to get his symptoms of what they called sea-sickness. This correction movement might have generated a Coriolis acceleration.

There are other possible explanations, too. We have certainly observed subjects who were sufficiently susceptible to unusual force environments so that if you would put them in this same situation they certainly would have bad symptoms far more severe than Titov experienced. I think that, initially, he had symptoms of bodily disorientation and then later on he had symptoms more of the nausea syndrome. If you aren't in possession of all of the facts, then you can only speculate.

There might have been certain changes in terms of fitness. We have found that this is a very important factor in certain individuals, anyway. We have observed them catch cold in the room while they were rotating and re-experience symptoms that they had adapted to previously.

FREMONT-SMITH: Does this suggest that adaptation is a continuous positive action, not a static state that one reaches and then it is there? That there are continuous feedback mechanisms operating and that then when you get a cold or something, this disturbs this positive dynamic adaptive process?

GRAYBIEL: There are many factors involved in producing a symptom like nausea, and it isn't simply the input alone from the vestibular organs. It can be a matter of what the man is thinking about or whether he is alerted or in an ataractic state—many different things of this sort.

FREMONT-SMITH: Expectation is terribly important in human experiments and I just want to emphasize that in any human experiment, suggestion, whether it is suggestion from the outside or self-suggestion, can be crucial and varies greatly with different people.

In these experiments which you have all read about with LSD, which is supposed to produce psychotic reactions, in very small doses, the expectation of the individual as to what is going to happen to him when he takes it profoundly influences whether he gets hallucinations.

I mention this as just one example of something which we know about, and I am quite sure that this is going to be a very important element in the human experiments. We know very well, as you said, that what he is thinking about can have an influence. All you

have to do for some people is to see somebody else vomit promptly to have nausea and vomiting.

GRAYBIEL: It is a good point, but I think the canals are more likely to have been involved than deafferentation of the otoliths and nonotolith receptors.

ROTH: In the studies that took place at Randolph Air Force Base[133] back in 1955, we would put subjects through acrobatics in the aircraft prior going through the parabolas. In most cases, subjects, especially experienced pilots, would have no trouble at all in the acrobatics, but as soon as they pulled 3 G, went into 0 G and then entered 3 G again, they would turn green and vomit.

Previous acrobatic experience free of symptoms seemed to have very little correlation with how they behaved during this zero gravity episode. Actually, I think the figures were that half felt ill, a quarter actually became nauseous and vomited and a quarter had no problems at all.

I, myself, had many, many flights as I was instrumenting the plane and had no trouble except on one occasion when I tried violent head movements just as we were transitioning from 3 G to 0 G, and then I was disoriented and felt nauseous.

This seemed to be the experience of most people, that if they tried violent head movements in the 3 G to 0 G transition period, they did feel somewhat disoriented. Those that had no trouble whatsoever in the rest of the flight would experience difficulty at this transition point.

FREMONT-SMITH: I am interested that you are emphasizing transition because I wanted to raise the question whether it is 0 G or whether it is the change of G, the change of rate of G which is the crucial thing.

ROTH: On interview, people felt that when they were already ill, they seemed to be very much worse going into and coming out of zero gravity. Subjects having been well in zero gravity did become ill when suddenly coming out into 3 G. However, there were many variations in the timing of illness.

DUBOIS: It is not uncommon for athletes to get upset and vomit when they are in a big game.

ROTH: These were experienced pilots who had pulled many G's before.

DUBOIS: I wasn't talking about your group but more about this business of going up in a rocket.

HELVEY: It would be more exciting for some of us than for others. As I recall the data (which may not be too accurate) after five or six hours the astronauts tend to stabilize at about resting levels. The Russian data show that during sleep the heart rates were a little less

than during sleep here on earth, and the heart seems to be a fairly good index of anxiety.

SCHMIDT: Isn't there a feeling that the pulse rates of our astronauts were more labile in the weightless state than they normally were? I seem to remember a report on Cooper, in particular, indicating that his heart would speed up excessively on any effort on his part. Do you have the same recollection Doctor Roth?

ROTH: Yes, he was very labile, especially in exercise, during a minor arm-pull exercise his pulse peaked at 145/min. When his AC system went out of kilter and right at the end of the flight, his pulse peaked at 180-190/min.

FREMONT-SMITH: That's a very big increase.

HELVEY: Pertinent to this response, am I not correct that his pulse went up about 17 points higher for the standard exercise but it started out at a level of about 15 higher, and it did take a little longer to come back.

ROTH: During the postwork plateau, the mean heart rate remained higher than that found in preflight baseline exercise (106/min. vs. 85/min.). During the flight, the peak heart rate during exercise (145/min.) was not as high as the peak of 184/min. which he experienced during anxiety at the end of the flight.

HELVEY: About three years ago we would have been a lot more concerned about rates of 180. In the early flights there was a great deal of concern, but now that we have dynamic monitoring, with telemetery, we find that the normal responses are considerably higher than might have been expected.

The group of eight pilots testing the X-15 averaged about 150 during the flights with individuals going up to 190. In the F-105 during high stress maneuvers, they went up to 176. In Galveston they had a racing event in sports cars and for a prolonged period, or perhaps more than one, driver's heart rates averaged almost 200. In addition to the stress of driving, evidently with the suits they wore there was a little thermal stress superimposed.

ROTH: At the Lovelace Foundation in Albuquerque we monitor the X-15 flights and have studied the responses of NASA and Air Force pilots on these missions. The pulse rates are much more labile during critical parts of the maneuvers than any of the results of the astronauts.

SCHMIDT: Then, it is not associated with the weightless state?

ROTH: No, I don't think it had anything to do with the weightless state.

DUBOIS: I want to ask about the cortex and how much it affects things like vomiting and what the inputs are.

Just as a basis for discussion, let us say that the cerebral cortex

receives some information from the cerebellum, from the eyes, and from the ears. Below this level is the brainstem and neural connections with the peripheral organs, such as the stomach which might become upset, and the postural muscles. The question is whether responses come down the reticular formation and from there out to the peripheral effectors, or whether there is some other more direct pathway Perhaps the impulse comes directly to the stomach without passing through the cortex.

I am asking for information. The relationships in the nervous system would determine whether stimuli received from outside the body, that is, information from around you, or internal disturbances which would affect your cerebral cortex, would cause a direct effect on the stomach, the postural muscles and the heart. These are inputs, I suppose. Doctor Graybiel, where are we on this neuroanatomical system? For instance, Doctor Margaria mentioned that there is considerable information going to the cerebellum which is not received in the cortex. This also would govern whether you could condition a response, or whether you can, by training, abolish a response such as nausea.

MARGARIA: I think you should add to this also the efferent innervation of the sense organ. We know that the ear sense organ is centrally controlled and its sensitivity changes with changing impulses from the brain.

Even motion sickness we know to be influenced by the state of the mind directly or through other sense organs, such as the eye: a man may suffer from motion sickness riding a car on a winding road in the mountains, but he will not get it if he is driving. Also, the sensitivity of the labyrinth is bound to change very appreciably for psychological reasons.

DUBOIS: Is that a sensitivity of the receptor organ or is there a change in the modification of the integrative system, or a change in the effector organ?

MARGARIA: I think both. The ear is very well known to receive an afferent innervation, as the work by Rasmussen at Harvard has shown. Recently my friend, Professor A. Bairati, an anatomist in Milan, has demonstrated the same centrifugal innervation of the labyrinth. But besides this mechanism an integration at the central level takes place, not only at the cortical level but also at the lower nuclei.

GRAYBIEL: I think we are a little too quick to lay the blame elsewhere than in the vestibular organs, or at least to recognize that they participate in it. I say this on the basis of systematic use of these subjects who have no labyrinths and exposing normal subjects of varying sensitivity to many different situations. All of these nonlabyrinthine factors are important, but I think that usually it takes

a triggering stimulus through the labyrinth to set this off. We have observed a person who complained of symptoms before the device actually started rotating although the machinery was noisy and vibrating. Nevertheless, it is difficult to produce symptoms, even in highly susceptible persons, without motion. An exception is the nausea caused by viewing a movie which creates the illusion that you are moving. Using a hemispherical projection screen and watching a movie taken from the front of a truck dashing through country lanes, etc., makes some persons nauseous. Actually you are not quite motionless—if standing you make many corrective small motions.

So far as the peripheral organs are concerned, the thing that is most impressive to us is the fact that, if the threshold to stimulation of the canal is raised as a result of some disease or injury, these people are almost insusceptible to motion sickness. This holds true also for people who have lost the labyrinth on one side. It holds true for the small number of subjects we have tested. We are hoping to screen large numbers of divers, some of whom have injured their ears as a result of diving at great depth. If you test the thresholds of sensitivity of their semicircular canals, using the caloric test, the first response is to water of 30°C whereas normal subjects respond to 36°C. Such subjects are amazingly free of symptoms.

So I think in these instances the peripheral organ is very important. Of course, the great argument and I think a constructive one, is whether this whole thing isn't a matter of conflicting stimuli, which are responsible for these symptoms, which can be intralabyrinthine or visual-labyrinthine or things of this sort—or whether another phenomenon is involved; i.e., the effect of bizarre stimulation of the semicircular canals at different stations along CNS pathways.

We have adapted persons to the visual illusion who were blindfolded for two days. The difference between these persons and persons who didn't have their eyes covered was remarkably small. We are preparing to rock persons who are asleep, that is to say, subject them to Coriolis stimulation and determine how much adaptation will go on where inflow from the higher centers at least isn't taking place.

FREMONT-SMITH: May I bring in here a point which I think both supports and also brings in a different dimension. When suggestion operates and an individual vomits as a result of suggestion, he doesn't do it without the use of his stomach. He uses all of his apparatus for vomiting and, therefore, either the semicircular canals or their representation in the nerve stem are operating. Therefore, the fact that the semicircular canals or their connections are necessary for this reaction doesn't in any way remove the cortical activity, because the cortex is tied up with this.

We know very well that under hypnosis an individual can be made

to vomit. This works automatically for anybody who is susceptible to hypnosis, so we know it can be developed through the cortical function.

Also, I bring out that your scheme is at least as complicated as the actual situation, and probably there are four or five more integrative processes involved in addition to those Doctor DuBois suggested. The situation, I think, is in actuality very complex indeed, and the reason I emphasize this is because no matter how much one can bring out the fact that the semicircular canals or their apparatus has to be involved, this does not in any sense remove the influence of what I have been calling suggestion or cortical function.

There are many cortical functions that are quite unconscious, but all the peripheral apparatus is represented at several different levels of the brain, including the cortical, so that you can get blood pressure changes from appropriate cortical stimulation as well as stimulation at various stages down along the line.

This makes it more difficult, but I do need to emphasize this because I think that there is a tendency to say, "Now, if we can be sure it is in the semicircular canals, then we can say that suggestion doesn't play a very important role." I think it plays a crucial role in those people in whom it plays a crucial role, and we have to find out how to discriminate.

GRAYBIEL: I agree, and I think that one can do something of a job by putting these people through a large assessment test battery. In a random group we found that most persons were either quite susceptible, or insusceptible, a sort of bimodal distribution. The susceptibles, some of them, have symptoms more characteristic of anxiety than typical of motion sickness and part of it I am sure is a matter of conditioning. On the other hand some, those with typical symptoms, may be susceptible for physiological reasons. It is a little difficult to ferret out all of the factors accounting for individual variance.

I agree completely with you but I would still like to point out that, in terms of the prevention of symptoms aloft, if we could take people of average, or even somewhat less than average, sensitivity, and raise their threshold so far as the canals are concerned, we would just about have the problem licked. You can do this on a squirrel monkey and whether or not one can do this safely in man, of course, is another matter.

FENN: Can you make a man without a functional labyrinth dizzy by letting him look at moving screens, or not?

GRAYBIEL: We have yet to set up the panoramic screen and the test has not been carried out. We have taken them on ships at sea, acrobatics, 0 G flights, counter-rotating rooms and every other device available, and the general reaction is that either they like the ex-

perience or that, at worst, it didn't particularly bother them. They are amazingly untroubled by all of this sort of thing.

ROTH: I was interested in your visual conflict experiment because when we were running the zero gravity flights, at least the second one that was in, I tried closing my eyes during the period when we went into 0 G and I got the illusion that I was sitting on a bar and rolling over backward. Just the opposite occurred in coming out of Zero G—rolling over forward.

I reviewed Doctor Gerathewohl's[133] previous studies to find out if other people had reported this, and under what circumstances. The illusions were almost always with the eyes closed, and we hypothesized that what was happening was that the plane, which was set at a constant throttle setting, went up into increasing winds as they shot up into the parabola. By decelerating in the horizontal axis (going into 0 G) the vector of the hypothetical otolith stone was in the direction it would have if you were sitting on a bar and started rolling over backwards—the stone would be thrown this way relative to the sensor hairs.

I did an interesting experiment.* I got the meteorological people to send up a balloon and we determined winds aloft in the area where we were doing these experiments and, indeed, when the winds were increasing under those circumstances we did reproduce this illusion, but it was always with eyes closed. With eyes open, in spite of the fact that the otolith was telling the body that it was going through this particular maneuver, there was no sensation of this. Only one subject of several hundred, I believe, claims to have experienced this illusion with eyes open. Have you had any of this experience in your laboratory?

GRAYBIEL: Yes, we have played around with this quite a little bit and there is one interesting thing about the illusions produced by the otoliths or otolith and nonotolith gravireceptors; namely, we have not been able to observe adaptation there. We have had normal subjects for hours with the direction of resultant force at an angle with their body, and they have continued to measure the same angle of oculogravic illusion. On the other hand, with the Coriolis illusion adaptation occurs very quickly.

Another point is that person who have lost their otolith organs, by our test, anyway, will experience very close to the same postural effects that a person with normal otoliths would experience, but of course wouldn't observe the same visual illusions.

We call these illusions but, maybe we shouldn't. Remember that the direction of gravity on the earth is probably in some ways a more real frame of reference to which we should orient ourselves than the

*Roth, E. M. 1956. Unpublished observations.

visual or object environment. On the other hand, if you produce this illusion that you were speaking of—and we call it the oculogravic illusion—if you really want to see it in full display and with a small stimulus, you do it with the room just barely lighted and then the room will assume almost the position of the angle of *phi*. You turn the lights up and the room will appear to drop down and you have only a little illusion. In a contest between the direction of resultant force and what you consider the upright for visual cues, the visual cues will abolish about 80 or 90 per cent of the illusion. This is why it is so important to have visual cues.

HELVEY: Very pertinent to this otolith sensation and the question of visual cues, there is an anecdote that I heard and I was wondering if Doctor Graybiel would validate this. During the war, when the British were developing a new plane with more thrust, more power than previously, they lost a few planes on takeoff; and on subsequent investigation it was determined that the forward acceleration was such that it displaced the otolith, or the G vector rotated it back, so that the pilot, not relying on or perhaps not looking at his instruments, felt that he was nosing up a little too much (the old business of flying by the seat of your pants), so he pushed the stick over a little bit to compensate, and, of course, with disastrous results. Are you acquainted with this?

GRAYBIEL: Yes, I am, and I am sure we have had accidents in this country on this basis and, indeed, I am 99 per cent sure we had one in Pensacola. Undoubtedly, this is a potent cause, especially taking off from a field where there are no lights beyond the end of the runway. Pilots don't usually glue their eyes on their instruments right on takeoff, and the other point is that it is awfully difficult to deny this feeling of change of G vector. After all, we have been living with gravitational-inertial force all of our lives. I would say undoubtedly this illusion is a cause of accidents under certain circumstances.

DUBOIS: There is something that might happen in pure oxygen: absorption of air from the middle ear. You would develop a retracted drum if your eustacian tube were not open, for instance if you were asleep and it didn't clear. I once had a retracted drum following a cold and I felt a rocking sensation and dizzy. I went to one or two neurologists and a psychiatrist, and no one knew what it was but as soon as I blew air through my eustachian tube and inflated my eardrum I was fine.

This must be common in aviators.

GRAYBIEL: It is.

DUBOIS: Do they become unsteady? Do they have these symptoms?

GRAYBIEL: They complain mainly of earache, and I regret to say that we have made very few measurements under the conditions that

you have mentioned. I think it should be done. The only thing that I am strictly sure about is the business of whether or not a person has had alcohol. This certainly increases susceptibility, and a sufficient amount will cause positional alcohol nystagmus. You don't expect anyone to reach this point in operational flying certainly.

BJURSTEDT: Could any of you tell me what would happen if you decompressed rapidly? Would there be a temperature change in the middle ear? I would like to know whether there is a risk that a caloric effect might be produced.

GRAYBIEL: It is a good point but I can't answer it. They say if you plunge into cold sea water, it is enough of a change in some persons to give them the symptoms as a result of so-called thermal stimulation. The Dutch* have observed this.

May I ask one question of the physiologists which may be a little oblique? How do you explain postural hypotension as a result of inactivity? What is the mechanism here?

WOOD: I don't think anybody is absolutely certain about this. Some people think it is due to the fact that the tone of the peripheral vasculature is relaxed, so that the blood pools in the dependent portions of the vascular system when a person stands up. Others think that it may be a change in the reflex mechanisms. There is no question that the reflex mechanisms are very important because people with autonomic nervous system disease are very prone to postural hypotension.

MARGARIA: I think that this problem of the vestibular reflexes is a very important one and needs to be studied all over. We found also that very small centrifugation stimuli elicit very impressive pressure changes in the femoral artery, that lasts quite a few seconds and that takes a long time to recover after the acceleration is removed.[134]

I think that also astronauts may incur such vestibular responses and I believe that the observed increase of heart rate, changes in blood pressure and others that appear during the flight long after the subject is under zero gravity conditions, may have this origin. On Titov for example and on some other astronaut an increase of the heart rate up to 120-130 after seven or eight hours in orbit has been observed.

FREMONT-SMITH: Aren't there two mechanisms involved, one, the proprioceptive reflexes from the distended blood vessels as the gravity tends to push blood into them on the one hand, and on the other hand, secondary reflexes coming from the central nervous system when there is an inadequate supply of blood to the brain as the result of pooling

*de Vries, H. Natuurkundig Laboratorium der Rijks-Universiteit te Groningen, Netherlands, Westersingel 34. Personal communication.

of the blood in the limbs? I would think that there would probably be two related mechanisms, first one and then the other. Even if the reflex takes place when the individual is put suddenly into the upright position, there would still be some pooling. I assume that the reflex takes place more rapidly with a little bit of practice, but this is a pretty inadequate measurement.

GRAYBIEL: It seems to me that you should be able to separate rather local effects in the lower limbs from central nervous system effects. The difference may be just partly an alerting phenomenon and it may be highly specific. It may even be that in these hours you have really begun to adapt to a somewhat different integrative setup. These are the things which seem to me to be important to unravel and would have application to prolonged flight in 0 G and re-entry.

BJURSTEDT: Related to what you last said, there was a series of investigations made at Wright Field some years ago where it was found that, after prolonged bed rest, the resistance to acceleration in the conventional seated position was almost normal.[135] However, these people developed hypotension when they stood up.

GRAYBIEL: Yes. I know that Beckman also found this at Johnsville in studies on water immersion.[136,137]

BJURSTEDT: It may be, as you say, that there is some sort of an alerting mechanism that operates when you put a man in a centrifuge.

GRAYBIEL: It seems to me that we don't know enough about this, even this, even the very simple clinical observations.

SCHMIDT: I understood that Cooper experienced severe postural hypotension when he got out of his capsule and tried to walk on the deck of the carrier, but the tendency disappeared completely after a night's rest. Is this correct?

ROTH: That is right. They did tilt table experiments and there was a hypotensive response that lasted about seven to 19 hours.

RAHN: Did he have moist rales, too?

ROTH: No, he didn't.

BROWN: Was he dehydrated at the time the tilt table tests were made?

ROTH: He was the first time but within four or five hours apparently he had at least taken enough water to compensate for the weight loss, and yet the hypotension persisted until the next morning. I don't know exactly, but I think it was every few hours that they got back on the tilt table.

It was pointed out that the hypotension lasted longer than they felt the effect of dehydration would have lasted, and it was on a basis other than plasma volume deficit.

RADIATION IN SPACE

Discussion leader:
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NEUMAN: Turning to new intellectual fare, I thought, in honor of our Swedish guest, I would present the whole smorgasbord in very brief style, and then you may select from this smorgasbord that which you wish to chew on in detail. I hope to get the whole smorgasbord out so that we don't chew on one item to the exclusion of the others, at least inadvertently.

The hors d'oeuvre of this smorgasbord is the evaluation of the intensity and also the quality of the radiation exposures that we may expect to encounter. The main entree, really, is a bird with stuffing because it is in two parts: the evaluation of the biological effects of such radiation, where we actually have two main theoretical as well as practical considerations (I think I can develop the meaning of that as we go on); and a choice of standards. This is perhaps more philosophical, but it certainly is not less important.

I don't know much about any aspect of this subject but, knowing Frank Fremont-Smith, it should be, under the rules of this organization, possible to lead from behind. I am going to assume that at least some of you are ignorant but reasonably fast learners, and just outline what I know and what I was able to read about these four main areas with a limited library available to me.

The evaluation of intensity and quality of radiation exposures also falls into four categories: the galactic flux, the solar flare or flux, the earth's geomagnetic belts, and, finally, the possibility of exposure from a nuclear propulsion unit that might be part of the system.

Considering the galactic flux, it is generally believed that this is uniform and invariant. I say that it is generally believed but I do think that there is a great deal of uncertainty in this belief, because our period of observation has been rather brief. The heavy particles in cosmic radiation were first observed in photographic films and published in 1948, so we haven't been looking at the galactic flux for any great length of time.

FREMONT-SMITH: Are we saying, then, that the cosmic radiation is galactic flux?

NEUMAN: Yes, these are thought to be the result of intense activity of radioactive (I mean radio in the radio wave sense of the word) stars near the center of the galaxy. These constitute propulsions of matter from these stars and, therefore, are primarily protons, because that is the primary cosmic matter. They have the appropriate composition of our usual guesses as to the cosmic distribution of matter but, primarily, these are protons.

FREMONT-SMITH: The sun is not involved in these at all?

NEUMAN: No, the sun is not involved. These are thought to have been kicking around the galaxy, being accelerated for a period of something like 10^6 years before they get sufficient relativistic energy actually to escape the galaxy.

SONDHAUS: Parenthentically, the composition of the so-called galactic or nonsolar cosmic radiation appears to be distributed among the lighter elements, at least in a proportion more resembling that of biological material than the earth's crust.

NEUMAN: That is right. In TABLE 6 is presented the general abundance of cosmic versus the so-called universal, and you will see that in the lighter elements, as you pointed out, there is much greater concentration, (0.2 per cent compared to 10^{-6} per cent) of the lighter elements. This is also true of the medium elements (1.2 as compared to 2) and it isn't until we get out to the very heavy elements that we are down to 10^{-4}, as we are in the general abundance. The general pattern then, is like general composition with extra heavy loading of the light-medium and light-heavy elements.

These particles, having 10^6 years to be accelerated by rather gigantic magnetic fields throughout the galaxy itself, obtain some fantastic energies. Many of them are really very, very high-energy

TABLE 6

ABUNDANCES DETERMINED FROM COSMIC RAY RATIOS COMPARED WITH "UNIVERSAL ABUNDANCES"*

Group	Hydrogen	Helium	Light nuclei	Heavy nuclei Z 10 30	Medium nuclei CNOF	Very heavy nuclei
Cosmic Rays	100	15.5	0.24	0.5	1.20	10^{-4}
	100	7.7	10^{-6}	0.033	0.20	10^{-4}

*Compiled by E. P. Ney[138]; cited in J. R. Winckler, 1961.

particles, up to 10^{18} electron volts, or a billion billion billion electron volts. I stress this because this is qualitatively different from the radiation that we can generate or study here on earth.

FENN: Do I understand that these are circulating within the galaxy until they get enough velocity to escape? For some reason they are kept within the galaxy; is that right?

NEUMAN: Yes, being bent. They are all stripped of electrons so that these are positive particles and, therefore, they will all bend in a magnetic field. As they hit the magnetic field, they are bent and tend to kick around the galaxy until they get enough relativistic energy to escape.

FENN: Is there any magnetic field of the galaxy as a whole or only when they come near a star in the galaxy?

NEUMAN: In the interstellar spaces there are concentrations of matter that generated, with velocity, magnetic fields—at least, that is what is thought happens.

GILBERT: What is the highest energy that man can approach in the laboratory?

NEUMAN: Roughly 10^5 less than the highest energy in the cosmos. On the other hand, in most of the cosmic radiation the energy distribution is not at all uniform, but in higher and higher energies there are fewer and fewer of these high-energy particles. The number of a given energy is given approximately by some constant over energy to the 1.5 power, so as the energy power increases, fewer and fewer of the particles are present.

FREMONT-SMITH: Did you say this is coming from our own galaxy? If so, then we are already within it and the ones we are getting are not those that escaped from the galaxy at all.

NEUMAN: No, no. As nearly as I can determine, the flux is nondirectional, although there are some investigators who are trying to study the directional aspect of this phenomenon, to see if they can confirm the idea that the center of the galaxy is also the source of the radiation.

DUBOIS: I don't follow your line of reasoning on how these particles gain so much energy. In an accelerator, don't you have to put the particle in a field to accelerate it all the time? You have to keep putting energy in to make it go faster. Where is the source of energy? If you have a magnetic field, the particle could go around and around indefinitely but not pick up speed. How is it accelerated?

SONDHAUS: I don't think anyone can answer that question at the present time.

ROTH: The plasma streams coming from stars supposedly have trapped magnetic fields to go along with the plasma, but how these kick it along is not clear, even in the solar situation, whenever you

have charged particles travelling in what they call trapped fields. With all the stars contributing to these particulate and magnetic gyrations, however they go, there are plenty of sources for kick.

NEUMAN: Don't forget this is not a spherical galaxy and we don't know how many particles are escaping orthogonally to the axis of the galaxy. We are only observing matter that is kicking around the spiral.

I can accept this general picture since I don't know any other way of explaining the observed phenomena. In any event, the galactic flux is supposed to be isotropic and apparently quite stable in time. The only way we have any kind of a judgment on the time aspect is that this cosmic flux is responsible for C^{14} production. If C^{14} production had been altered very much in the last four or five thousand years, C^{14} wouldn't be a valid archeological dating method. Since it is, it is concluded that the flux has been constant with time.

The flux reaching earth is not uniform (even though we confirm that at least the space traversed by our solar system is uniform) because of the interaction of the earth's magnetic field. At the poles, we get the full intensity of the flux. At the equator, we have the bending of all the lower energies. Only those particles above 15 beV actually break through the magnetic barrier at the equator. Thus, there is a strong latitudinal variation in the distribution of energy from cosmic radiation reaching earth.

These are all very energetic particles, of course, but there is much atmosphere between us and space, and the atmosphere's stopping power, particularly of the heavy nuclei, is really quite efficient. The heavy nuclei will interact with nuclei as well as electrons and, therefore, they are pretty well stopped. What we find reaching earth, then, is all secondary radiation: mesons, decayed gammas, etc., from the absorption of cosmic radiation.

It is estimated from measurements in balloons and from measurements on the earth and at the poles, and also from some space probes that have been sent out, that the intensity of cosmic radiation converted to rads is of the order of 12 millirad per day at the surface of the atmosphere. It may be perhaps as high as 25 millirad per day in deeper space.

With several qualifications, (if we know enough about the energy distribution and the quality of this distribution, and if it doesn't have uniquely different biological effects), and if we can use the rad equivalent as an estimate of the hazard, we can say that the cosmic flux is not a serious hazard affecting the future space traveler.

Just as the stars in the middle of the galaxy are supposed to generate these expulsions of gas, so our own sun does the same thing. The difference is that solar flares are quite variable, both in intensities and in frequency of occurrence. Again, the composition is primarily pro-

tons but the energy distribution, not having been accelerated for 10^6 years, is much, much different. There is a much more rapid falloff at the higher energies. These are mostly low to medium energy protons, and I believe the energy spectrum is given by something like the reciprocal of E^5. The distribution falls off much more rapidly at the higher energies.

There is some evidence that the solar flare, as it envelops the earth and goes on out, seems to decay by something like a diffusion process. This rapidly moving solar flare, of course, carries with it a strong magnetic component, as Doctor Roth pointed out; this is responsible for the violent magnetic storms here on earth that accompany intense sun spot activity.

These are actually sufficient to cause a modification in the normal magnetic distribution of the cosmic radiation of the earth. It was observed long before we had any general idea of this picture, by Forbush, that in times of high sun spot activity, which lowered and disturbed the magnetic field on earth, there was a smaller amount of cosmic radiation reaching earth, down by 30 per cent or so. I think for our purposes, today, the important emphasis is that solar flares are, at the moment, almost totally unpredictable in terms of occurrence and intensity. They vary a great deal. I am not up on details, but there are some inferences (drawn by making a correction relating a balloon measurement to a direct measurement in a rocket, and also extrapolating in time back to the initiation of the flare) that radiation fields as high as 10^4 rad per hour may occur in solar flares. Although these are not high-energy protons and, therefore, some shielding can be done, still, if these range between 100 and 500 meV and occur in intensities of 10^4 rad, we are in trouble in the event of solar flare. I think this is the primary basis on which solar flares are considered the primary radiation hazard to solar system travel today. Does anybody wish to comment on that?

SONDHAUS: I could only comment, in general, that a number of different flare events have been studied, and from the admittedly fragmentary data that are available, a rather rough average intensity has been estimated. Presently, we tend mainly to think in terms of flares that would last as long as two or three days and perhaps deliver a total dose of the order of 1,000 rad.

Then, of course, there are smaller and lower energy flares, which would not be nearly as serious. I believe that at the Boeing Corporation and at the General Dynamics Corporation, there have been some probability studies made on the basis of the experience of the last few years as to what the chance of encountering a dose greater than any given dose might be as a function of the length of the trip. However, these are pure estimates and I think, really, one would have to

sum up the situation by saying that any individual solar flare is not yet predictable either as to its exact energy distribution or its exact intensity, or its temporal distribution. We have to assume that there are rather wide limits within which any of them might fall.

NEUMAN: It looks as though, at least until we know a lot more (and I would think it would take quite a while to gather this kind of experience), we will undoubtedly be forced to use a statistical approach to make missions at times in which low sun spot activity is expected on the basis of the known 11-year cycle plus some superimposed smaller cyclic variation. A mission is sent and if there is no flare there is no problem. If there is a flare, you hope that it isn't a big one. This is the way I analyze it for the next few years, anyway.

HELVEY: Is it generally agreed that it is safe to extrapolate back to the time of onset of the flare? I have heard some nuclear physicists say they feel that this is difficult to do.

SONDHAUS: I don't know if the figures for total dose are reliable. This is what is commonly done, to assume a certain pattern of buildup. Generally, the lower energy particles arrive somewhat later because they travel more slowly and, therefore, the flux of particles of a given energy will decrease, but the total flux may go through a maximum and fall off again.

There have been attempts made by people at Boeing to do this, and most of the maxima appear to fall approximately 20 hours after the onset of the flare as far as the total flux is concerned. The dose is based on such a guess.

RAHN: When did we have the last peak year in the 11-year cycle?

SONDHAUS: I think it was two or three years ago.

NEUMAN: 1959 and 1960; there were two big ones in the spring of 1959.

RAHN: So, for our moon venture, we will be hitting a peak year again around 1970?

ROTH: It depends on slippage.

NEUMAN: Going to the geomagnetically trapped radiation, the Van Allen belts, it seems to me, do not pose any serious hazard but they do present some limitations. There is certainly enough room to evade them, and there is plenty of reason to think that the belts could be traversed in a short enough period to result in rather small doses.

The inner belt is estimated upwards from 20 r per hour behind one gram square centimeter shield. This is uninhabitable in terms of putting a vehicle in orbit at this particular zone, but it certainly could be traversed with safety.

The outer zone has lower energy protons and soft electrons and is much more diffuse. Presumably, shielding could be quite effective. Over all, this zone doesn't seem to present too much of a hazard.

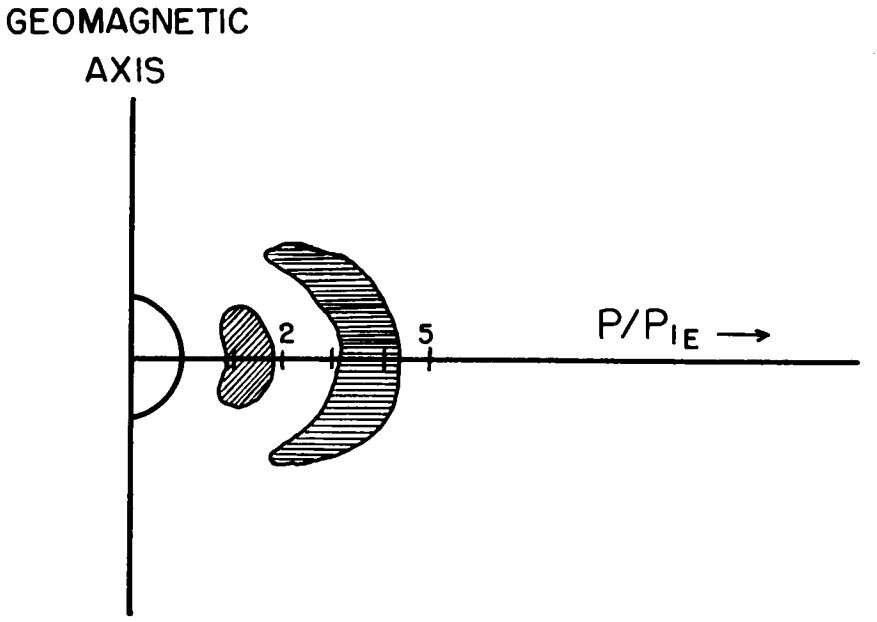

FIG. 35. Trapped radiation belts. (Redrawn from Van Allen, 1961.[139])

All this indicates that, for continuously orbiting vehicles, we have to stay under 400 miles in altitude, preferably on a polar orbit, within a 40° inclination equatorial. Then there is no problem.

FIGURE 35 is a very crude representation of the Van Allen belts[139] as usually pictured with the small doughnut of inner radiation. I don't know the origin of these belts. The inner belt is thought to be due to the decay of neutrons, because the protons have a fairly uniform energy and correspond to neutron decay. They also have an equal number of electrons of about the right energy distribution, to correspond to neutron decay. The outer zone is thought to be mostly solar flare trapping and is quite variable. The inner zone is fairly constant.

SONDHAUS: The space between is quite variable also.

NEUMAN: Yes, because this is a mixture of the two and represents a variable.

ODUM: What is the scale of numbers on that?

NEUMAN: These are earth radii, so from about 400 miles to one-and-one-half earth's radii, we have the hard inner core.

With atomic propulsion units, nobody has designed or decided on what kind of propulsion unit would be useful. The whole problem is one of shielding. If we say that the propulsion unit is going to be essentially a heat or reactor type of unit, then we can use reactor experience to get at least some assessment of the problem, and 50,000

pounds of thrust is equivalent to the production by a 700-kiloton bomb. While this is a small bomb, it is a considerable amount of radiation and would give a lethal dose in tenths of a second at 20 feet without shielding. On the other hand, it has been estimated that a Martian orbital and landing mission with chemical boosters could be made with a 21,000-megawatt reactor. If 25,000 pounds of shielding is used this could be done with about two rad delivered to the crew. If the shielding is decreased, the rad increases.

FREMONT-SMITH: That is two-rad per what?

NEUMAN: Two rad per mission. If there are 10,000 pounds of shielding, 117 rad per mission.

SONDHAUS: This is assuming a particular distance between the reactor and the crew.

NEUMAN: Yes, and the basic plan[140] is what one would expect. The reactor is put at one end and the men at the other. All the fuel is in between. Thus, until the fuel is gone there is a mass between the men and radiation. By putting distance between the men and the reactor, a shadow shield can be used down by the reactor. Then, it is necessary to shield only on the *inside* of the capsule. With this technique, one can use minimal shielding.

It occurred to me that if atomic energy sources were used for ion accelerators, which would be operating under low thrust for long periods of time, it would be possible to have a telescoping device: put the reactor *way* out behind you into space. In this way, the shielding problems would be very much minimized.

So much for the intensities and nature of the radiation to be encountered. Turning to the biological effects, I would like to review briefly radiobiological thinking at the moment; in other words, from geophysics to molecular physics or to the biology of man.

I am sure you have all heard of the target theory. This has been very useful in describing radiation interactions. It is now, I think, modified to include indirect effects from free radical formation in water. Theoretical effects can take place only within very close proximity to the target molecule because of the limited diffusion of free radicals, due to their short life. Both from the standpoint of actual direct measurement and also from the point of view of theory, a hydration shell or a diffusion distance of free radicals, then, constitutes a difference of about 30 Å around a molecular target.

FREMONT-SMITH: What is the life of a free radical?

NEUMAN: It is of the order of fractions of a microsecond.

ROTH: There are stable ones. Probably in biological systems, the folic acid groups or the polycyclics might have a much more stable life.

NEUMAN: I am thinking of water radicals. You are correct, there

are stable radicals. Quinones, for example, are so stable that you can watch them bleach very slowly over minutes of life.

Monomolecular protein films have been irradiated. There isn't an interaction until the energy of the incident radiation is of the order of 10 electron volts or more. Also, the efficiency of radiation is very low, 10^{-4} of this order, until 10 electron volts is approached, where it rises sharply toward unity. For this and many other reasons, most people today believe that the actual damage to molecules is caused by direct ionization. Most ionizations range in the order of 10 to 100 electron volts, so the figure of 100 electron volts is considered the needed energy for a damaging effect on a biological thing.

The old classic basis for believing the target theory, or something like it, is that if you have a target then the smaller the target, the bigger the dose required to hit it, an inverse relationship between dose and target size. This is an assay of molecular weight comparing the target weight determination versus molecular weight, and although there is considerable deviation on a log scale, still the relationship holds over five orders of magnitude and I am quite sure the target theory is here to stay, even though it may have to be modified considerably.

This takes us directly to the heart of the matter, because radiation produces damage in biological molecules by producing primary ionizations, and these are interactions of the order of 100 electron volts. This means that events less than this would not cause any particular damage and events greater than this would be more or less wasted, thus giving rise directly to the theory of linear energy transfer (LET), which is the number of electron volts expended per unit density of the path. It is usually given in electron volts per gram per square centimeter, which, in water, is essentially per centimeter.

SONDHAUS: I think it is also quite commonly used in biology in terms of kiloelectron volts per micron, simply because cellular dimensions are more readily apprehended in microns.

NEUMAN: Yes, you can choose various systems to express the units but this is the basic principle. These high-energy particles can produce tremendous linear transfer rates. In general terms, if a light or light-heavy nucleus has an energy of over one billion electron volts, the chances are it won't just interact with electrons, but will have sufficient energy to penetrate the electron field and collide directly with a nucleus, producing a shower of secondary irradiation fission fragments, and so, whereas below a billion electron volts they generally have a very broad and intense path compared, say, to molecular volumes, a gamma ray would have a very narrow path. It is my understanding that the width at which ionization is occurring is of the order of cell

size in case of primaries and heavy particles. There is also a tremendous burst of energy transfer at the termination; with the particle slowing down, losing its velocity, it interacts more and more with electrons in the surrounding medium, producing primary ionization. This is what is called the thin-down or star formation.

SONDHAUS: If I may comment on that, the thin-down results from a gradual loss of energy along the path because of loss and regaining of charge; as the particle slows down initially, it may be stripped and highly ionized. This causes a greater interaction, but as it slows down it gradually regains charge and becomes less reactive.

In the case of a somewhat lower energy particle than a cosmic ray primary, one doesn't observe the thin-down but, instead, the Bragg peak. This is the very intense ionization toward the end of the path, where in the last few micra of path in tissue, for example, one may get linear energy transfers many times as high as along the rest of the path.

NEUMAN: FIGURE 36 is a picture of the terminal end, that is, the last fraction of a path, the burst of energy release as the particle is slowing to a halt.

FENN: I don't understand why the energy release is so much greater at the end, or can be. Why don't the particles lose energy gradually? Is the path too fast to react?

SONDHAUS: Yes, the fields of the target and the particles in

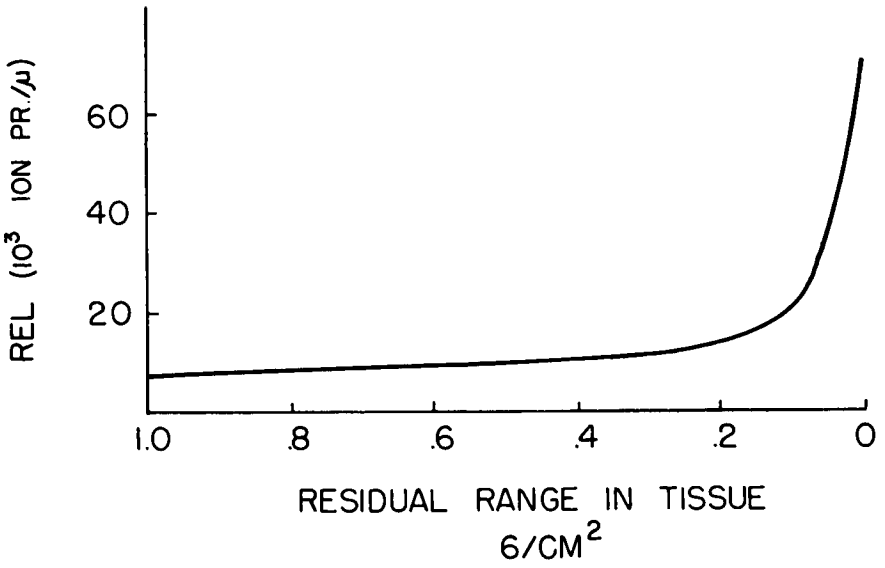

FIG. 36. Calculated ionization peak in terminal thindown of primary: (Adapted from Simons, 1960.[141])

passage aren't close enough to each other long enough to result in much probability of any interaction (either of ionization or excitation) to take place. As the particle slows down and approaches the end of its path, the probability becomes greater and one does see more ionization until a certain velocity has been passed, and then ionization drops to zero.

NEUMAN: Could we draw the analogy between fast and thermal neutrons? Because they are in the vicinity of the nucleus for long periods of time, thermal neutrons are much more reactive and induce more change.

SONDHAUS: Yes, but for different reasons. Protons are charged particles and the fact that the particle is charged creates the electrostatic field between the particle, which is approaching and the target. The neutron has the ability to penetrate through the shielding electrons surrounding the atom and strike the nucleus of the target.

NEUMAN: I think we should point out that here on earth, at least up until very recently, no biologists had worked with radiations of this particular quality and kind. Most of the work has been with X-rays, gamma radiation, beta radiation, and, of course, for internal emitters, alpha radiation. Thus we are faced with the problem: Can we make direct translations of energy absorption from this kind of radiation, primaries, light heavies, etc., to the kind of radiation experience of which we have accumulated a great deal, both in animals and in humans, in the past couple of decades?

The only direct observations from which to extrapolate are those observations made from short-term exposure of animals in balloons and earlier experimentation with Hilac, the high linear accelerator at California and its sister at Yale. At least initially the work with this accelerator was limited to a vacuum condition and, therefore, was limited to enzymes, phage, spores, etc. More recently there have been direct determinations of the relative effectiveness of radiation of protons of the order of 100 to 500 meV.

If linear energy transfer is plotted (FIGURE 37—this illustration is Tobias' data[142]) in electron volts per gram centimeter squared and four different life systems are examined—lysozyme, T-1 phage, spores, and yeast—if there were a constant biological effect per energy absorbed, one could expect to find a linear relationship between the LET and the index or cross section. One finds that there is a divergence in these cases. The more complex the organism, the more the divergence. I think, however, you can also see that there is a tendency for plateauing in all four forms as you go to higher and higher linear energy transfers.

This is another way of saying what you might expect on the basis of just plain logic; that is, if you can knock out a molecule with 100

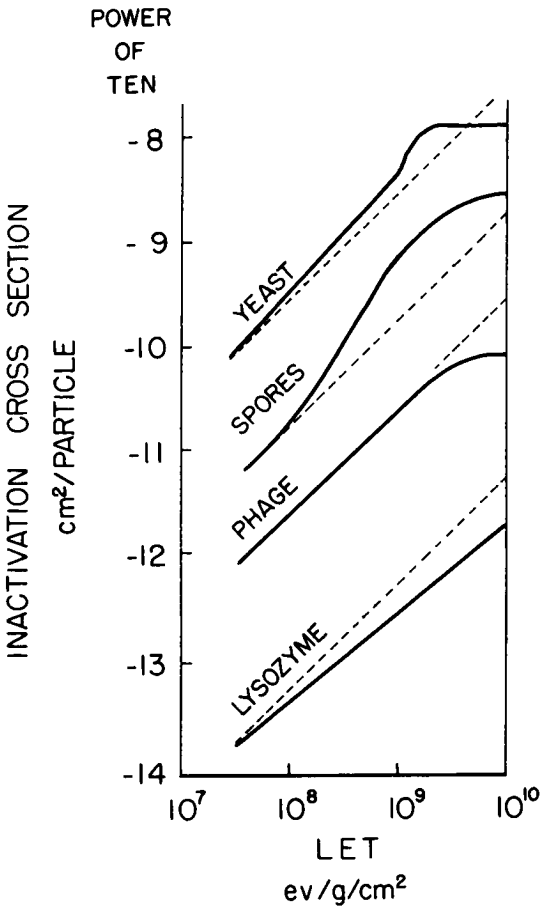

FIG. 37. Deviation of RBE with increasing LET. The dashed lines represent constant RBE; solid lines observed data. (From Tobias, 1960.[142])

electron volts and you have a great big blast coming through a cell, one that is putting out much more than 100 eV, and also over a much larger volume, you are not knocking out one molecule in the cell. Since you are frying the whole cell, and you can't kill a cell more than once, the efficiency of the radiation, although it may be killing the cell very dead, may not be really very effective radiation. From this point of view we would expect perhaps that these higher energy particles might actually be less damaging in total than lower energy transfer radiation.

SCHMIDT: That's not the principle of overkilling at work, is it?

NEUMAN: Yes, I think this is overkilling.

FREMONT-SMITH: What about the adjacent cells, aren't they

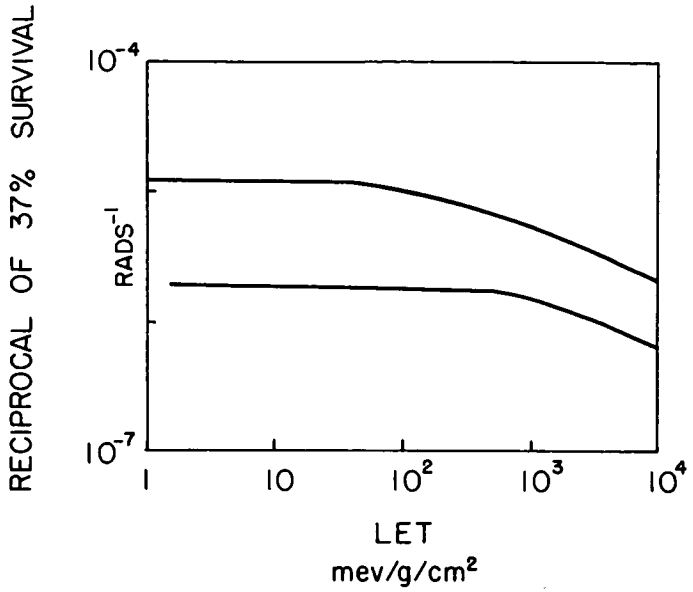

FIG. 38. Decreasing sensitivity of phage (T-1) at high LET. (Redrawn from Brustad, 1961.[143])

going to be killed in this instance, where they wouldn't be in the other, and therefore you get more cells killed?

NEUMAN: The key here is per total energy absorbed, you see. One beam of this would do more damage than one beam of a gamma ray, but it would take many, many, many gamma rays to give an equivalent dose.

With this (FIGURE 38) and other evidence, mostly from California, Brustad[143] has published data on T-1 phage and, indeed, with this organism at higher LET and using, I belive, neon, there seemed to be a decreased biological effect at the higher linear energy transfers. We are really dealing now with a determination of relative biological effectiveness (RBE) as the most crucial part of the biological problem.

We are also faced with the question of a choice of standards; and I want only to point out what we are up against, in setting permissible exposure levels.

You can assume, it seems to me, two completely diametrically opposed viewpoints. You can apply the principle of no injury or practically no injury, in which case you would apply industrial standards or population standards as the limit of radiation to be tolerated. If you use this viewpoint, the engineering costs of space travel are, I think, prohibitive.

The other viewpoint is to set our maximal limit as that which will

get the pilot through the mission. He may die after he gets out of the cockpit but performance during the mission is essential. I don't think we would be able to adopt such standards even if we wished. The public would not accept this on moral grounds. However, we can take the viewpoint to delimit maximal exposures. Wright Langham[144] from whom I have drawn a great deal, has prepared a table of dose limits he considers to be something short of affecting the astronaut's performance. The limiting doses of varying kinds (to the eye, etc.,) range from 200 or 300 to as much as 1,600 rad.

FREMONT-SMITH: Per mission?

NEUMAN: Per mission. He also has a five-year career dose. This is a short career, but you can write up your memoirs in *Life* magazine, and so it pays well.

ROTH: May I dip into the smorgasbord for a second while we are still dealing with the physical problem and not the biological problem? At the Gatlinburg Conference[145] last November there were several issues that created heated arguments and that I thought were quite important in terms of our handling of the situation. I would like to ask Doctor Sondhaus or anyone here if these have been solved.

One was the ability to predict solar flares from the Ca-II lines in the sunspots (Plages). Assuming that these spots have a life of two or three revolutions and the particles we on earth receive are those spewed out from the western limb as the sun rotates (much like a rotary lawn water sprayer spews out water) we should be able to predict flares with a given amount of regularity. A woman astronomer from Sacramento Peak Observatory, New Mexico said, "It is foolish to think you can do this." A nuclear engineer from North America said, "We think we can do it."

SONDHAUS: I think the status of this argument is about as it was. There is a great deal of work being done on attempts to predict flares, but I certainly don't know much about the art of solar flare prediction or any of the parameters that might be made use of. Perhaps someone else here does and might comment on this.

It certainly is a crucial question. In fact, I think in the long run this is the only thing that we can really hope to use. It is going to be a long time before we can put enough shielding up to cut the dose out, once it is there.

ROTH: The other factor was the amount of *pi* mesons that would result from the actions in the shield. This point was raised by Murphy *et al.* from Yale.[146] I think the closing talk was a discussion of shielding and RBE of pi mesons. At that time, he gave a figure of about one per cent of the total input in this form. Gerold McDonnel* from UCLA

*McDonnel, G. M. 1963. University of California at Los Angeles, Los Angeles, California. Personal communication.

told me that this estimate has recently been boosted to about 10 per cent of the total tissue input.

SONDHAUS: The total final tissue dose. This may well be; I don't know these figures. H. B. Knowles has been considering this problem and we discussed this a couple of months ago when he was out in Berkeley visiting. As I recall, the estimates are higher than one per cent. Whether they are 10 per cent or not, I don't know. It is still a small portion of the total dose.

ROTH: The third point was the healing factor. There is a question of the intermittency of dose and how much of a healing factor can we use with radiation of this type as compared to what we know?

SONDHAUS: The recovery factor. Well, I might comment generally that recovery appears to be related to the LET of the radiation. That is, the more or less classical viewpoint that has developed over the past years of radiobiological studies is that a high LET radiation, i.e. of the heavily ionizing type, generally produces more nonrecoverable damage and that, therefore, the rate at which the dose of a high LET radiation is given is less important in the accumulation of total damage. This has been the basis, I think, of many of the estimates of genetic damage to be expected from neutrons, for example, which do produce high LET secondaries.

On the other hand, a low LET radiation, such as the X or gamma radiation with which we are most familiar allows a greater degree of recovery. There are a number of explanations proposed for this, most of them based on the target theory in one form or another, or modifications thereof. I think this still stands: that, in general, a highly ionizing radiation would be expected to produce less recoverable damage and more permanent damage. However, we find some apparent exceptions to this in proton irradiation, for example, which as yet we cannot explain.

NEUMAN: I would comment also on that. I have an example of (FIGURE 39) this dose rate effect. The upper curve is drawn from experimental data on the mouse and, assuming a half time for the recoverable damage of three and one-half days, you get a pretty good experimental fit.

The lower curve predicts for man a 20-day recovery period. Nobody actually knows what the recovery period in man would be, except that it would be longer than that in the mouse.

If we assume that there were no differences in the amount of irrecoverable damage with high LET radiation, then we have to get down to dose rates of the order of one roentgen per hour or smaller before we gain any advantage. My point, then, is that the dose rate delivery in a solar flare would be on the flat portion of the curve and

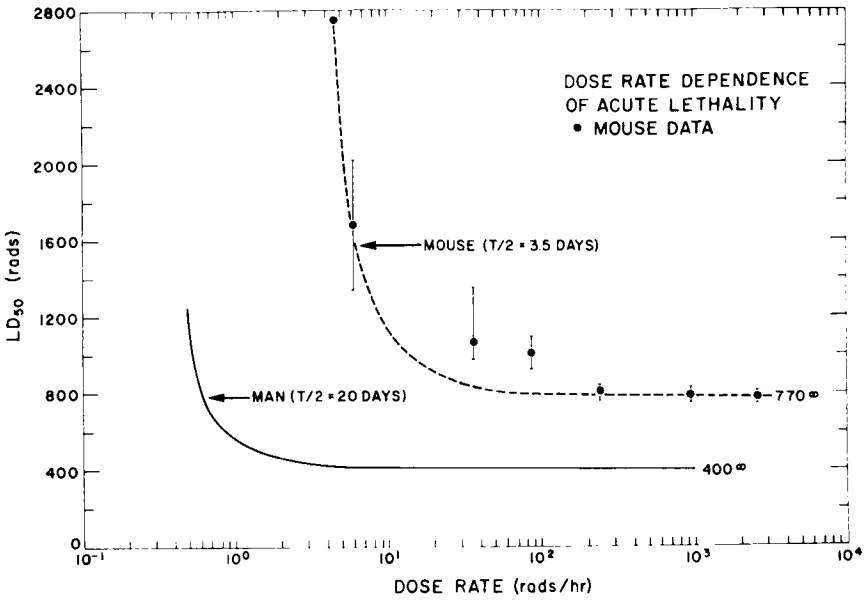

FIG. 39. Dose-rate dependence of early radiation effects (LD_{50}). (From Langham, 1963.[144])

no advantage would be gained from recovery, even though the exposure were intermittent or very time-limited.

FREMONT-SMITH: Whereas there would be in the low radiation damage?

NEUMAN: Yes, galactic radiation, this kind of intensity. As indicated in the Figure, the LD_{50} dose in hundreds of rad is set at about 400 for man. However, the curve rises below 1 rad per hour rate in man, whereas it starts up at about 10 rad per hour in the mouse.

SONDHAUS: Quite possibly these data would fit the other attempts that I have seen to express this dose rate dependence, such as that of Bateman, Bond, and Robertson at Brookhaven, in which they collected about 10 different experimental results of X and gamma radiation on small mammals. (As a matter of fact, I think it was all mice and rats.) They attempted to fit the data with a power function and found that the inverse cube law seemed to express the dose rate dependence; that is, if one decreases the dose rate the resulting effect decreases in that way.

We have been doing some dose rate studies with both gamma and proton radiation, and we observe a dose rate dependence for both.

In this respect, high-energy protons seem to behave as a low LET radiation would be expected to behave. High-energy protons deposit their energy in such a way as to lay down a pattern of secondary

ionizations along their path, which, according to the calculations of Schaefer, for example, results in a distribution of LET very much like that of 250^{kv} X-rays.

I think we should note that in any given case, any radiation energy cannot result in only one value of LET. There is a distribution of ionization; if one expresses it in terms of keV per micron, or some other unit like this, there will be a distribution curve of LET values resulting from the radiation.

In the case of an X-ray beam, since there is a distribution of energy in the beam in the first place, this distribution has a characteristic shape. For proton energies above 50 meV or so, the ionization along the path is quite sparse and it approaches the minimum possible, so that in an irradiation by protons, there should be a dose rate effect rather similar to that observed with X-rays. It is only quite recently, however, that the dose rate effect has been considered important.

I want to make a distinction between dose rate effects and dose fractionation effects. Dose fractionation studies have usually been carried out with periods of days intervening between successive short irradiations. On this time scale, biological recovery processes can result in a partial recuperation, the so-called recoverable fraction of injury. If a high dose rate is given; i.e. the same total dose is delivered, in less than an hour and 10 times as fast, then one has to invoke some other kind of mechanism to explain the differences. I don't think this is very well understood as yet, but we do observe changes in effectiveness with dose rate even on a ratio of 10:1.

JENKINS: What is the present thinking about heat spike?

NEUMAN: I wasn't thinking of heat effects, although the heating effect of local, dense primary ionization, by the time things settled down and the free radicals all got through interacting, might be at least momentarily quite intense.

SONDHAUS: If you took a small enough volume, yes. I think, though, that if you consider even the dimensions of an ordinary cell, this is not very great. The heating effect of a dose of several thousand rad in a few grams of tissue is rather small, of the order of a few thousandths of a degree.

GRAYBIEL: Could it touch off an explosion if there were some very explosive material aboard?

ROTH: If you are talking about mercury fulminate or the azides, yes. Bowden[147] showed that one could trigger some of the primer types of explosives with radiation.

BROWN: Would you form a vapor phase on the track?

ROTH: He has some lovely shadow graphs and X-ray photographs of the events that follow. All that is needed in these primers is a very high-energy input locally; this starts a shock wave along the primer,

causing a detonation. They have actually demonstrated in a single crystal of these primers the radiation effects, and a book has recently come out on this activation of primers by radiation.

I don't know if anyone knows the exact mechanism. Bowden explains it at a lattice level, where once you jiggle the lattice enough you can get a shock wave going through and from an atomic level, this spreads to an explosion of the whole crystal. As for propellants or non-primer explosives, I don't think you can trigger them by radiation.

SONDHAUS: I think I would like to discuss a little bit more this question of LET and RBE, and for those of you who may not be familiar with RBE, I would like to refresh your memory, the RBE of a given radiation is simply the ratio of dose from the standard radiation (which is usually taken as X-ray, 250 kilovolt peak)—to the dose of the given radiation for a given effect.

Relative biological effectiveness is a rather loose term and has many factors built into it besides the quality of the radiation. It involves the species, the tissue and the particular end point chosen. It also involves the degree of damage and we find that it involves a rate factor as well. In the case of systems which are fairly well defined, one can come closer to defining the quantity a little more exactly. Among the best systems for this kind of study are cell cultures.

Some rather recent results on mammalian cell cultures are worthy of summary. If one graphs the data using a log scale on the ordinate for the RBE and, similarly, a log scale on the abscissa for the average LET (expressed in keV per micron), then it is possible to plot most of the experimental data that have been observed—on systems differing as widely as neutron effects in the dog and heavy ion inactivation of enzymes—on the same scale. If we do this, a great many points result and they spread out quite a bit, but, in general, for systems that are subcellular—that is, enzymes, etc.—one observes, as Doctor Neuman pointed out, a decrease in RBE with increasing LET which begins to manifest itself about where a 10 meV proton would be found and beyond. The decrease is continuous. It may fall as low as one or two-tenths of the original RBE of 1. The 250 kv X-ray case would be found at about 3.5 keV per micron.

In a second type of cell, usually smaller plant cells and animal cells, as well as yeast cells, there is observed a very gradual increase, and then around 100 or 200 keV/micron, a peak in the effectiveness at perhaps 2 or 3, followed by a decrease. There has been a great deal of yeast work that has brought this out.

Mammalian cells exhibit the same type of behavior but show a somewhat higher peak in the same general region. The peak is at about six to eight instead of two or three, in the region of 100 to 300 keV per micron. Some very recent data by Paul Todd of our laboratory fit

quite well. He used human kidney cells in culture and irradiated these cells with ions of masses up to carbon and neon, producing an LET of up to about 700 keV per micron. There is some suggestion that the peak is nearer 300 than 100. Other people's work varies slightly as to the peak value but there is certainly a region of LET that appears to be maximally efficient in producing damage on the cellular level.

Finally, just for the sake of completeness, I might mention that there does appear to be class of cells in which the effect may become much higher than this and may increase to values of the order of 20 or so. These generally include dry spores or some system in which a phase change occurs, and they really do not correspond, we feel, as closely to the mammalian case.

For the proton energy spectrum to be expected from a solar flare, there will be large numbers of particles with low energy. The LET is inversely related to the proton energy, so that as the proton is slowed down on its path in tissue and approaches the Bragg peak at the track end, it enters the region where the RBE of the particular particle flux is somewhat greater than at the point of entry. This is one of the complicating factors in a proton exposure that seems to be somewhat different from what has been observed thus far in X or gamma irradiation. Just how important it is, is not yet clear. We do know that there will be a different proton energy distribution in tissue at different depths. We are making some calculations along these lines and later on I will try to indicate some of the results.

At this point I would like to pass from LET and RBE as background to a brief summary of some of the recent results we have found with mice in our laboratory by using the 730 meV proton beam of the 184-inch cyclotron, as it comes from the accelerator. Control mice are placed close enough to the head of an X-ray unit so that the resulting dose rate is comparable to that from the cyclotron.

We have used several thousand mice in the last year. Since the time on the proton beam is severely limited to us, we have had to keep the number of proton-irradiated animals low. Therefore, in order to minimize the statistical variation between animals, we have caged them all individually. Each mouse is kept in a jar and is isolated upon arrival at the laboratory. After being dipped for parasites, they are placed in isolation for two weeks. We then select out of the population the mice that have gained weight in the preceding several days and we discard the two extremes of the weight distribution. We then feel we have a rather uniform and well-controlled population.

The variability in a mortality experiment can be cut down considerably in this way. This has been shown by Ellinger and others in the past; Ashikawa at our laboratory did a very careful statistical study of it a couple of years ago.

So much for the biological parameters. Turning to some results of a proton exposure at two dose rates: 100 rad or 1,000 rad per minute. The total dose levels are such as to give about 98 per cent lethality in both cases. An increase in the dose rate has an effect. In shifts the pattern of mortality toward the four to six day range, which is usually taken as an indication of gastrointestinal damage. For example, if we take six-day mortality, the higher dose rate enhances this pattern by a factor of about two. In other words, something like 70 per cent or so have died in the high dose rate group, whereas about half that number have died in the low dose rate group.

The high incidence of the GI syndrome after these proton exposures appears to be similar to what has been observed previously in neutron exposures, that is, high LET radiation exposures. Yet, as I mentioned, the calculation of the LET spectrum for this energy protons would put them far down on the LET scale and we would expect them to behave more like X-ray.

By contrast, if we use 100 kvP rather soft X-rays, we don't see this pattern at all. In this case, we couldn't use the same two dose rate—the highest we could get was 100 r/min. by positioning one animal at a time. The factor of five here did not markedly enhance early deaths. However, the size of the total dose does.

For an X-ray exposure, when one reaches the lethal range, somewhere around 660 to 700 rad for a mouse, deaths begin to appear in the population but they appear later on. They peak at around 14 days; this is considered generally to be due almost entirely to the bone marrow syndrome, the depletion of blood-forming elements, and all the sequelae. There is no enhancement of early death by dose rate. This is a dose rate effect that is different, then, in the case of protons than it is for X-rays.

In summary then, in an X-ray exposure, if the dose given the animals is high enough to begin to produce mortality (I am speaking of an acute syndrome only) then the pattern of death at first is due to blood-forming element damage. Then if the dose is raised further the gut syndrome begins to supervene and at a high enough dose, the animals will almost all die of gut damage.

In the case of a proton exposure, however, at least from what we have seen thus far in this animal, some of the first deaths are more predominantly due to the gut syndrome even in the low lethal range, and there is no intermediate dose level at which only later bone marrow damage appears. We don't as yet have any explanation for this except an hypothesis that there may very well be a differential dose distribution between the bone marrow and the soft tissue of the intestinal wall. We believe that in the case of X-rays, the distribution of secondary electrons is quite different, in a small cavity, bone, than

it is for other radiation, and even for higher energy gamma radiation. However, there are qualifications to be attached to that and we can only regard it at this point as an hypothesis.

One thing is clear, however. There is quite a marked dose rate effect in a proton exposure, and it is marked in relation to gut death. We therefore can expect that in a solar flare, for example, in which a lot of dose is delivered at a high dose rate, part of the dose would be more effective and would produce this kind of injury more efficiently.

At a lower dose rate, the effectiveness of that portion of the dose, its RBE, if you will, would be less and we would have to weight each part of the exposure. This makes the situation quite difficult to evaluate, and our present approach to this is simply to choose a sort of standardization that we don't really expect will correspond to any one given exposure, but that we can use a reference. Then, if we find that later data on solar flares indicate some vastly different energy distribution or time distribution of the dose, we will have to do another kind of experiment or make use of factors of this kind, as well as time factors, to arrive at a total effectiveness.

The International Commission on Radiation Protection now proposes that in place of the term "RBE", the shorthand notation "QF" for quality factor be used, because, thus far, RBE is felt to be a quantity that we would like to reserve for expressing the differences due to the quality of the radiation itself—LET, in particular—and not apply it to the other variables that I have mentioned: dose rate, etc.

I think if we attempt to do this, we may find that, in addition to the dose rate factor, the fact that there is a distribution of LET in the tissue that might very well cause us to have to weight our exposure by other factors as well.

ODUM: Does this mean that for an LD_{50} for 30 days, X-ray and proton would have about the same effect; that is, the $LD_{50/30}$ would be about 700 r?

SONDHAUS: Yes. In fact, for a 30-day lethality, protons of this energy have been found by several people (Bonet-Maury in Paris, Kurlyandskaya in the USSR and our group in Berkeley) to have an RBE of 0.7 to 0.8. They are actually less effective than X-rays for bone marrow effects. However, when one comes down to the six-day death, the gut death level, this number can exceed 1.0. Let's say about 1.05 or 1.10 at the same dose rate; 1.2 if we take the 1,000-rad per minute data and use that against the 100 in the X-ray.

SCHMIDT: Is it possible to distinguish between the effects of free radicals and those of direct ionizing radiation? Is a common mechanism involved? Are their effects inseparable?

SONDHAUS: There is a great deal of work being done in that area. I don't think experiments of the kind that I have just described will

really shed too much light on mechanisms, but I think some of the work with single cells and with enzyme systems may begin to give us more information on the indirect versus direct effects.

SCHMIDT: The reason I asked the question is that it raises the possibility of physiological antagonists to the one but not to the other. In the case of free radicals, for instance, there are some substances that will increase their rate of decay or decrease their rate of liberation. In the former category, according to Polis and his associates,[148] are the neurohumors serotonin and norepinephrine. Such an action might account for some of your differences between the intestinal mucosa and the blood-forming of organs.

SONDHAUS: This is an interesting possibility.

NEUMAN: I think we could be even a little more definitive in that there is evidence on the basis of exposing an enzyme dry and in water and determining its target volume. The target volume of some enzymes, particularly the smaller ones, is larger in an aqueous medium than in nonaqueous medium. This is how the dimension of 30 Å was derived.

SONDHAUS: Not all the data fit.

NEUMAN: No, and some enzymes show no change in target volume. Many, however, approach a maximum of 30. Thirty has also been estimated as the maximum diffusion distance of water radicals by direct measurements.

ROTH: If your active site on an enzyme is a sulfhydryl group, your enzyme would be much more sensitive to free radical attack than it would be if it had other groups on the active sites. I don't know if enzymes have been systematically studied in terms of the oxygen effect or the water target relative to the type of activity site hypothesized.

NEUMAN: It might be interesting to consider what the oxygen effect would be at 5 psi pure oxygen relative to radiation damage. The oxygen toxicity effect has been explained, at least in part, on the formation of radicals. Now we are asking: What about the energy input? As I said earlier, to form a free radical or an ionization, minimally 10 and more likely 100 electron volts are involved. It was on this basis that I was trying to drag out of Dan Gilbert some statement that perhaps an imposed radiation field was necessary to show the oxygen toxicity effect. However, he kept going back to the production of energy within the cell as being the source of this ionization phenomenon.

I think we can also point out, then, that the oxygen effect in the radiation field is thought to be the formation of free radicals involving oxygen that lead to peroxide through a series of interchanges; radicals that are extremely damaging to biological molecules, that have a finite

life, much longer life than free radicals ordinarily do—at least water molecules. We have, then, these two ideas impinging on each other. The question immediately arises: What about an oxygen effect on radiotoxicity using high tensions of oxygen or 100 per cent atmosphere?

SONDHAUS: To put it a little differently, in contrast to the usual oxygen effect experiments, here, I think we might be dealing with a synergism between oxygen toxicity and radiation damage, both of which involve the question of free radicals.

ROTH: The Russians recently came out with a 200 page document reviewing the oxygen effect.[45] This figure (FIGURE 40), taken from the paper, lost something in translation. The graph on the left side should be entitled "X-ray irradiation," not "oxygen irradiation"; the lower curve should read "oxygen," not "nitrogen." The government translator left it this way and I assume that there is an error in the illustration.

What the Russians did was review all the literature on the oxygen effect, and their major thesis was that the higher the LET radiation, the less the indirect effect involving free radicals and the more direct destruction of the target molecule.

This study is of rat ascites tumor. What they did was count the normal anaphases after 24 hours in these rat cells. They didn't go into detail on the experiment. On the ordinate are the "number" (expressed

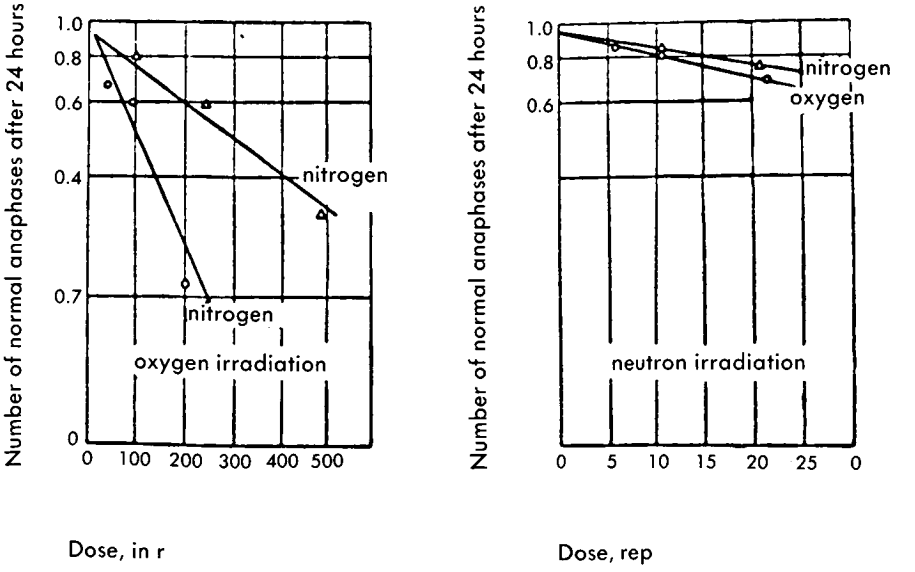

FIG. 40. Comparison of the radiation effects (cytological damages) in the cells of ascites tumors of mice exposed to X-rays and neutrons. (After Shchepot'yeva *et al.*, 1959.[45])

apparently as a fraction of the total) of normal anaphases versus (abscissae) dose (r of X-ray and reps of neutrons). The exposure was made in "nitrogen" and "oxygen" environments. There was no statement as to the exact nature of these environments.

You see that cells irradiated with X-rays in nitrogen had about three times less abnormal anaphases than did the cells in oxygen; whereas with the neutrons, there was very little difference between the two gaseous environments.

The experiments with the highest LET radiation involved frog roe, which were swimming in water heavily bubbled with radon. Radon is an alpha emitter, but I don't know the number of electron volts.

SONDHAUS: Around 5.5 meV, average LET about 70 keV per micron.

ROTH: They didn't use air. They only stated that the oxygen solutions had 15 to 20 times higher concentrations of oxygen than did the "nitrogen" solutions. (The "nitrogen" solutions probably reached hypoxic conditions, since the question arose: "How many of the rats exposed to low doses of radiation and "nitrogen" solutions actually died of hypoxia?") The data distinctly showed that there was virtually no oxygen effect with the radon alphas as with the neutrons of the ascites cell study, and these were thermal neutrons.

NEUMAN: Was this radon exposure a gaseous exposure?

ROTH: They bubbled radon into the water in which the frogs were. The first study was with mouse ascites cells; these were with frogs and frog roe swimming in water. The radon experiment was very poorly described.

NEUMAN: I don't know how you can evaluate that experiment. What is the rate of radon from the water?

SONDHAUS: These data are not shown here.

ROTH: No. I am saying that the closest experiment to proton-oxygen effect situation is this radon experiment. Other Russians[149] also studied AET (aminoethylisothiuronium), which protects quite well against X radiation. I believe Doctor Gilbert and Doctor Gerschman showed this also works quite well against oxygen toxicity.

The Russians are very much interested in the possibility of using hypoxia in the capsule to protect against irradiation, and they were trying to emphasize the point by showing that, since AET also works against oxygen toxicity, there would potentially be an advantage in avoiding the oxygen-radiation synergism.

But the radon and neutron data would suggest, at least with respect to some of the higher LET radiation, that one would have to worry less about the synergism. The question always arises, though, should you worry about primaries or about secondaries and tertiaries, which are ultimately the agents that are destroying the tissue. Where

you have much lower LET in the final analysis, in the final hit event, how much of a factor is oxygen down at that level. Do you have any feelings about this?

SONDHAUS: The secondaries in the case of an X-irradiation have the only LET. As the secondary electrons approach the end of their paths, they increase their ionization and there is a peak of LET, but not very high, due to the secondaries. In the case of a proton exposure the highest LET is confined almost completely to the end of the track of the proton, so that the depth of the tissue or the amount of shielding or absorber, let's say, which slows down the particles before they strike the cell of interest is probably the most important thing.

I noticed that they have been rather cavalier in their treatment of the X-ray on the left side in the figure. The two lines are drawn as straight lines and yet the points aren't really straight lines and it seems to me that one could still draw the classical X-ray survival curve with a shoulder on it through those, but they haven't seemed to do that.

ROTH: No, I don't know why. I don't know if the translator took license and just threw in those dots. This was from a massive review and was not from the original data.*

I was wondering if you were planning to try different oxygen tensions in your lab.

SONDHAUS: I think after the discussion of yesterday and today, we certainly have got to put that up to a little higher priority than we had heretofore considered. I think this would be very important.

ROTH: I don't think we can *a priori* say one way or the other extending to the proton situation.

SONDHAUS: I would like to comment that the presence of a "shoulder" in the X-ray curve leads to a variation of RBE between X-ray and high LET radiation with dose levels. On a log scale, regardless of the unit, the shape of the curve, is exponential but the upper part is not. This so-called hit number is the extrapolation of the straight part up to the axis. This is generally taken to be a measure of the number of events necessary to produce a given inactivation.

But, in the case of a high LET radiation, the shoulder is not observed; for instance, one sees that in the neutron case this seems to be quite well represented with a straight line.

RBE, being expressed as the ratio of effectiveness of these doses, could be defined either as the ratio of their values at a given survival level or of these lines. If one had two exponentials this would stay constant, but since one has a shoulder, the ratio will change with the level of survival or the level of dose. So that the result is to indicate

*Note: I cannot find reference to the original work.

that at a very low dose the RBE is much greater than at a very high dose, and this is, indeed, the case for high LET radiation.

When I discussed the LET versus the RBE curve, I oversimplified; I left out the fact that if one takes a given cell population, say human kidney cells, which exhibit an RBE peak at a given LET, the RBE value for 90 per cent lethality may fall at, say, a value of two or so, but for five per cent lethality, or 95 per cent survival, this RBE peak will be much higher, around six. That is why a range of values in apparent RBE was given.

This is not due so much to an odd behavior of the unknown, of the radiation we are comparing, as to the variation in effectiveness of the standard radiation. That is, it is unfortunate, in a sense, that we use gamma radiation as the standard radiation of RBE 1, because of the effect of the shoulder in the gamma ray survival curve, as I pointed out previously, is to make the RBE a function of dose level or degree of lethality.

What effect this has when you try to extend the data from a bunch of cells on a petri dish to a whole organ system is at this point very difficult to evaluate, but I certainly think it is quite a well known effect now and I am surprised to see that it isn't on there, too. I think the Russians are aware of it. I might also add that they are very enthusiastically performing proton irradiations these days.

ROTH: There are several other interesting points we might make in this area. I was interested to learn that dry spores have such a high RBE. One thing peculiar about many of the anaerobe spores is that they lose a lot of their DNA in sporulation. They take on quite a bit of dipicolinic acid: their chromatin seems to break up into several blebs and up to one half of it leaves the cell. There is a question of how much redundancy there is in the DNA of sporulated bacteria. This increased RBE might represent a diminution in the redundancy of the coded information. It is of interest that spores themselves tend to be more radio-resistant than the vegatative forms. The relative dehydration of the cells, the dipicolinic acid or other metabolic factors may be as important as the DNA factor in determining the RBE levels.

Along this line, I was recently told an interesting tale about the bacteria at the Hanford reactors, in the cooling water. They found bacteria growing that were radiation-resistant. I think it was 1,000- or more fold above the same strain not growing in the vicinity of the reactor. They found these for years. It was not interesting enough and people said, "Oh, isn't it too bad that our water is being contaminated with bacteria?" without stopping to think how these bacteria stay alive under these radiation doses.

But these bacteria have much, much more chromatin—I think the

factor is three or four times as much—than does the strain that was growing in nature away from the reactor.

SONDHAUS: This is an apparent contradiction of some recent studies that correlate the radiosensitivity of different cell lines with their nuclear volume. I think it was Sparrow at Brookhaven who studied this. There is a fairly good correlation. You just plot one against the other and it looks as if the bigger the nucleus, the more radiosensitive the cell.

ROTH: Bacteria, you see, have many copies of the same chromatin; they have several packets of the same information system. *E. Coli* average around two and one-half to three copies of the whole system, whereas I think that in mammalian cells we only have a single copy. But the fact that bacterial spores eject much of this and yet are able to reconstitute their entire genetic complement once they germinate is rather interesting, as is the high RBE.

SCHMIDT: What kind of acid did you say?

ROTH: Dipicolinic is the form in the spores.

FREMONT-SMITH: What kind of an acid is that?

ROTH: It is very similar to phenylalanine, if I am not mistaken. It is pyridine-2,6-di-carboxylic acid. Up to 15 per cent of the dry weight of many spores may be in the form of dipicolinic acid.

FREMONT-SMITH: Is this in the capsule?

ROTH: It is in the capsule, right, but mostly in the cytoplasm. There is a tremendous increase in dipicolinic acid and a decrease in the DNA and a decrease in enzyme content. There is relatively little protein in a spore, and water, of course, is decreased and firmly bound. They become very wet again in germination.

Synergism of Radiation and Oxygen

GILBERT: According to the ideas of Doctor Gerschman,[150-152] the deleterious effects of oxygen are always present. When the oxygen pressure is reduced, then oxygen toxicity is still occurring but the magnitude of the toxicity is reduced. Thus, Doctor Gerschman has pointed out, 70 years, which is considered to be the normal life span of man, is just a survival time of man exposed to 0.2 atmospheres of oxygen. If one could decrease the background radiation, perhaps to zero, then this survival time might actually be increased. We do know that background radiation does play some role in actually producing mutations.

RAHN: I would like to comment upon the concept of radiation protection by anoxia. Doctor Gilbert has emphasized earlier that the oxygen pressure of the environment gives little indication of the oxygen pressure inside the cells. You might protect an astronaut by making

him anoxic, but then he is also incapable of performing properly and not much is gained.

On the other hand, some people propose: Let's make him anoxic and let him adapt to this anoxia, like a high altitude man. But then, I believe, although there are no data available, that the partial pressure of oxygen in the cell of a man adapted to low oxygen is probably as high as it is in a man at sea level; so, I can't at the moment quite see how we are going to get protection by producing anoxia. I don't know whether you would agree with me.

NEUMAN: The Russians propose anoxia, perhaps, but I don't think any of us here would suggest anoxia. I think we are concerned about the possibility, from a mechanistic standpoint, of a synergism between oxygen toxicity and radiation. If it is a synergism, this can be approached theoretically in two ways: (*1*) to test the relative effectiveness of radiation in different oxygenation states and this can be done at the cellular level; (*2*) to study the oxygen toxicity effects in irradiated animals.

I think both approaches are worth doing, and my idea is that, if 5 psi cabin oxygen doubles the effectiveness of radiation, which would be another means of cutting in half the tolerable dose, the tolerable dose may very well in many missions be a limiting factor. This might be a very important factor causing us to reconsider using a mixed gas. If there is a synergism, nitrogen would have an antagonistic effect. We wouldn't propose anoxia but we would insist on a two-atmosphere cabin, or at least advise a two-atmosphere system.

GILBERT: I would like to point out that the primitive organisms on earth were probably anaerobes. As oxygen began to develop in the atmosphere, due mainly to photosynthesis, antioxidant mechanisms were gradually developed. Without the development of antioxidant mechanisms, life in an oxygen atmosphere could not exist.

Man has been living at relatively low altitudes, close to sea level, and possesses certain antioxidant mechanisms. These antioxidant mechanisms were developed as a consequence of the oxygen pressure in the atmosphere. Then I presume that some men adjusted to living in the high Andes and in the high plateaus of Tibet. I also presume that these high-altitude individuals possess the antioxidant mechanisms already developed from their sea-level ancestors. Therefore, high-altitude individuals are living at a lower oxygen tension than the sea-level individuals. Yet both types of individual possess the same antioxidant defense. The result is that high-altitude individuals are better off at their altitude than are sea-level individuals at sea-level.

NEUMAN: May I interrupt? I think you are arguing against a point he did not make. His point was that the adaptation of the man

at high altitude rendered his tissue levels at the same oxygen tension, anyway.

GILBERT: But I think there is some slight difference.

FREMONT-SMITH: Are you suggesting there wouldn't be so much antioxidant needed at the high altitude?

GILBERT: I am suggesting that high-altitude individuals are residing at an altitude where they have more antioxidant defense per unit of oxygen concentration at the essential cell sites than sea-level individuals have at sea-level. I admit that the oxygen concentration at the essential cell sites of high-altitude man may not be very much lower than of sea-level man. How do you think they compare?

RAHN: I believe, and that is all I can say, that it is almost the same.

GILBERT: I would agree that perhaps it would be almost the same, due to the barriers between the gaseous environment and the cell sites. But I would expect some difference, and from what we know, I would think that that small difference could be quite important.

ROTH: The Morococha natives, who live in Morococha, Peru, thrive at 18,000 feet and you see little old ladies carrying loads around and with no trouble. The Andean natives have been shown to have tissue proteins in the oxidative chains which are at higher concentration than in sea level Peruvians. The specific activities TPNH of cytochrome C reductase, DPNH oxidase, transhydrogenase systems are increased.

Myoglobin concentration is also elevated.[153] There are data indicating that some of the respiratory proteins of the high altitude natives have physicochemical properties that differ from those found in sea-level Peruvians. The oxygen dissociation curves of hemoglobin appear to be different.[154] It has been related to me that the tissue oxidative enzyme systems also have qualitative changes in physico chemical properties, such as redox potentials or turnover numbers, etc. Unfortunately, I cannot give specific reference to document these qualitative changes. I know that I picked up the information during a visit to U. S. Air Force School of Aerospace Medicine, Brooks Air Force Base, Tex. in October 1962. It seems that there may be a terrific selection pressure at these altitudes that allowed hypoxia-resistant mutations to persist. The mutations permit the people to function normally at lower oxygen tensions. They also have different settings in their CO_2 mechanisms in that they can tolerate more hypocapnia than a ground level person.*

BROWN: The only enzyme that would be at all important here would be cytochrome oxidase and I doubt if its redox potential is

*Balke, B. 1957. Civil Aeromedical Research Institute. Federal Aviation Agency, Oklahoma City, Okla. Personal Communication.

known, so I suspect this is simply a table of data and you can't prove an adaptive role for it, even teleologically speaking.

ROTH: There were several papers in the School of Aviation Medicine Reports by Hurtado's group at Lima and Morococha[153,154] that only suggest the fact that these particular changes in the myoglobin, cytochromes, and hemoglobin all had a direction that would make the person more efficient in a hypoxic condition. There was no good proof.

SONDHAUS: I think the most striking adaptation is the polycythemia of altitude in those people.

ROTH: Yes, this is present. They also have relatively larger chest volumes. There are other manifestations. I was thinking of a particular situation where there might have been a mutant arising that would be selected under these conditions.

FENN: I never understood this effect very much because we are told by Doctor Chance[155] that if you have as much as 1 mm. of oxygen pressure, that is enough to operate the cytochromes at full capacity. How can you do much better than 1 mm.? You might go to half a millimeter but you haven't gained much and it isn't much of an adaptation.

BROWN: It may be adaptation to high light intensity or something completely irrelevant as far as oxygen is concerned—purely fortuitous.

FENN: So, it really has nothing to do with their ability to perform better at high altitude.

NEUMAN: It might be related to their long use of coca.

MARGARIA: Could some experiments be made comparatively, differentially, between animals from Morococha and animals from sea level?

FENN: You mean compare their sensitivity to oxygen or to radiation, or both?

MARGARIA: To both.

CALLOWAY: Have any of you studied the influence of high oxygen tension on white cells? Those cells are equally as exposed as red cells and might be just as susceptible to damage. We know something about the sensitivity of white cells to radiation damage.

HELVEY: Pertinent to the white blood cell effect of oxygen, our clinical technician is fairly experienced and she did note what she considered morphological changes in wbc's in our studies—changes in the granularity of the cytoplasm, the membrane. However, these things are rather difficult to quantify and we can make no real significant judgements.

NEUMAN: This is a very good point that Doris has raised, and one that, if it hasn't been looked into, is a fairly easy experiment to approach, namely, what happens to the white cell count in animals?

CALLOWAY: Particularly interesting since the white cells are so high in ascorbic acid, which has antioxidant properties.

HELVEY: The lifespan is shorter, if that is significant, in terms of exposure. I think it is about a week, as I recall it, in contrast to 120 days for the RBC.

Physical Considerations

NEUMAN: I would like to leave the oxygen effect because we still have some areas undiscussed: all the different problems that we tried to outline, including depth-dose distribution, dose rate effects, and so on. We fully expect that anyone in space is going to get a different directional kind of exposure than we ordinarily give animals in our earth-bound experiments. The usual radiobiologist places an animal either in front of an X-ray beam or arranged in an array, a semicircular array, around a cobalt source, or something of this sort. Relative to the animal, this is essentially a beam exposure, whereas, we expect exposures in space essentially to have four-*pi* geometry, coming from all directions at one time. Charlie has some experiments and some attempts to achieve four-*pi* dosimetry. If we could get a brief report, Charlie, it will give us another chance to compare space radiation with earth radiation experience.

SONDHAUS: I think it might be worth while to spend a few minutes on this. This is all on a purely practical basis. We attempted to adapt the cyclotron beam at Berkeley to do two things: *(1)* to make it possible to expose a large animal rather than the mice I have mentioned before; and *(2)* to attempt to duplicate this isotropic or four-*pi* geometry.

I would preface my remarks about geometry with the statement that we have rebuilt the 184 inch cyclotron medical biological irradiation cave by doubling the thickness of the concrete wall, and we have redesigned the beam port. As of about one week ago, the construction work on the new medical cave was finished. We have now roughly doubled the floor area. The beam emerges through a port in concrete and heavy aggregate concrete. We have accessible to us a length of beam, which is, we hope, sufficient to enable us to spread the beam at the scattering target and place a large animal across the cave.

We spread the beam by causing the 730-meV proton beam to strike an absorbing substance. We have done some calculations in a preliminary attempt to judge which would be the best of several possible substances, and we have settled on graphite as being the most practical from the point of view of the conservation of the intensity of the beam.

When a proton beam strikes an absorber, as you may know, the protons are slowed down or degraded in energy. Therefore, if we want

to spread the beam we also have to degrade it. We can't get one effect without the other. For this reason, we will not be able to irradiate a large animal at 730 meV any longer, but, instead, at some lower energy that will correspond to a given degree of angular divergence in the beam. At about three meters from the target we get a beam that is sufficiently divergent to produce a fairly flat profile across a 30-cm. diameter circle.

The original intensity has been reduced by a factor of about 10^4. However, this is intensity per unit area per square centimeter, and the initial intensity was the total intensity of the beam. The practical result is that by running the cyclotron at maximum intensity we can achieve proton beam dose rates of about 10 to 100 rad per minute maximum.

Within this spread beam we want to rotate the animal in such a way as to expose every element of its surface to an equal number of protons distributed equally in angular incidence. That is, we want to simulate with a monodirectional beam the case in which, in outer space, each element of surface of an animal will be receiving a cone of radiation (more than a 180° cone, actually, because the radiation will enter from all sides) containing an equal number of particles from all directions.

If we consider the sphere as a model system and we assume that protons are entering from all possible angles *alpha*, at all possible elements of surface *theta*, and are therefore traveling through different depths of tissue from each direction, we can see that a proton coming in from a given direction will be degraded by an amount dependent on its path length, and will, therefore, reach a given element of tissue with a given energy. However, a proton coming in from some other angle will degrade differently and reach this point with a different energy.

We can see that in rotating an animal we will actually be producing a distribution of energy of the protons that strike a given dose point. We can do two things: We can calculate and, eventually we hope, measure both the dose at a point in tissue and the distribution of proton energies that have delivered that dose. As I pointed out earlier, the energy of the protons determines their effectiveness if it is low enough. However, there is a range of energy, from 700 down to about 10 meV or so, in which this effect is not important. A 200-meV proton still has about the same LET and, therefore, the same RBE, we believe, as a higher energy one. Therefore, it is only the protons near the end of their range that will be expected to contribute a substantial component of high LET at any given point in tissue. This will vary, however, and the way we expect to simulate what we find in the space case will be to use a model system. We can calculate what

the solar flare energy distribution as well as tissue dose distribution will be for the model. By combining an irradiation of the model at several different energies, the energy distribution in the flare can be reproduced. Knowing these conditions, we can then irradiate animals in the same way.

If we use a sphere as a model system and produce in that sphere a distribution that is the same as that predicted for a four-*pi* case, then we can be confident when we replace the sphere with an animal that we will approximate the same thing.

If we assume only that the primary protons undergo elastic scattering and do not take into account the secondary production, we see that the lowest energy protons deliver a dose in the four-*pi* case, which does not have a Bragg peak any longer. The Bragg peaks are all smeared out because the protons are entering from different directions through each element of surface. Therefore, we will lay down a dose but it will fall off very rapidly with depth and, depending on the energy of the protons, this dose distribution will penetrate further and further into the tissue.

However, at no point do the Bragg peaks occur within a well-defined volume. That is, they do not occur in the same place simply because of the distribution of path lengths. When we reach a high enough energy, this begins to change. For example, we see that at 140 meV for a particular sphere diameter of 32 cm., we will get a region of overlapping Bragg peaks. Oddly enough, as the energy increases this smeared out set of Bragg peaks moves back out to the surface. This is because it is due predominantly to protons that have crossed the sphere from the other direction and come to rest there, so as the energy increases this region would come out nearer and nearer to the surface.

We can produce a number of dose configurations in this way, but the important point in practical terms is that, even if we have to degrade the beam down as low as 200 meV, we can still produce a flat dose distribution in the animal. So this is one conclusion we can reach, that we may scatter a 730-meV proton beam and diverge it enough to irradiate a large animal and still produce a uniform exposure. This is a monoenergetic exposure with regard to the initial proton energy. It does not correspond to the solar flare spectrum. However, it is useful to be able to irradiate an animal with such a beam. It will have a distribution of LET, however, in tissue. Suffice it to say that near the center of a sphere, one may expect to get, at great enough depths, around five per cent of the total dose delivered by protons of about 10 meV and below, which will be expected to contribute a high LET component to the dose.

We hope to be able to give the low-energy exposure on the 88-

inch cyclotron rather than on the 184 inch simply because the more we degrade, the thicker the target we have to put in the path of the beam and the lower the intensity gets; we are working against ourselves. We have to deliver the low energy dose at a much lower dose rate if we produce the low-energy particles on the 184-inch cyclotron.

However, it is reasonable to believe that we can give an exposure lasting several hours that will agree in both energy distribution and geometry with the solar flare case. I think the main importance of this is that we have a choice of two things at our disposal: either we can irradiate large animals uniformly, or we can simulate any distribution of solar flare energies that we believe to be a reasonable one. In conclusion, we have begun a study on primates, *Macaca mulatta,* with the Ames Laboratory in which we will expose a series of monkeys over the next several months to the monoenergetic proton flux. Ultimately we will expose primates to a solar flare distribution.

In the latter case, with such an uneven, nonuniform depth-dose distribution, we know that the total number of rad at any given depth will turn out to be quite different than would be the case for a flat distribution. This has been shown very well by some experiments done by Jackson at the Boeing Corporation, in which he simulated the depth-dose distribution with cobalt^{60} gamma rays using a wedge filter. Of course, the LET distribution was not the same as for the protons.

Permissible Dosages

In this respect, what we hope to do is to conduct several experiments. We can't embark upon a large-scale program, but we can choose some dose distributions that we can compare with cobalt radiation or X-radiation for that matter, and thereby see just how important the high LET component in the proton beam will be. We are not in a position to report any results on this as yet, but I think we will be able to get fairly far along in this program in the next few months.

NEUMAN: I am sure there is more discussion to go but we have run out of time, so I am going to take the liberty of concluding this part of the program by citing some calculations that Wright Langham has made on the basis of the limiting pilot factor: those doses of radiation that would carry a high probability of the failure of the mission because of radiation damage affecting the pilot's performance.

Of course, from what you have heard, you must realize that these depend on the quality of the radiation. At the moment we have to specify the penetration of the radiation and the dosage at that depth. This would vary with the flare, the nature of the flare, and the time of the flare. These run from 5- to 15-cm. absorption of the abdomen.

100 rad up to 5 cm.-range for the hematopoietic system, all the way up to 3-mm. penetration of the lens at a level of 600 rad. The danger here is not ultimate cataract but actual opacity of the lens. Finally, a high dose to the skin of the extremities, one-tenth of a millimeter skin depth of the extremities up to 1,800 rad. Here the limiting case would be such a severe erythema and sloughing that the pilot would fail.

FREMONT-SMITH: You have ignored the central nervous system, haven't you, in the low dose effects?

NEUMAN: Yes. Except for the behavioral work done by the Russians, where they have reported effects as low as 10 rad—

FREMONT-SMITH: And this work has been confirmed.

NEUMAN: —easily demonstrable acute effects run up as high as around 2,000.

FREMONT-SMITH: The behavioral effects go down to less than that.

NEUMAN: I want to restrict our consideration to failure of the mission, because setting maximum reasonable levels for astronauts is a job for a large committee that I want to be absent from.

FREMONT-SMITH: But behavioral effects could very well influence the success of the mission if they are subtle behavioral effects. I don't think we can afford to ignore these, because this determines the judgment of the astronaut in his performance.

NEUMAN: At Rochester we are entering the behavioral field, first with chemicals with the view of getting into radiation effects. I think it has been neglected in this country and may prove to be a very sensitive approach to radiation effects. I know it is proving to be a very sensitive indicator in toxicological studies, and unique in the case of chronic effects of mercury. How otherwise do you study chronic mercurialism, which is a central nervous system manifestation?

I will close with this final statement, which is, again, from Wright Langham:[144]

"While more physical data on space radiation and more biological data on effects of high energy ionizing particles and their interactions with matter are being collected, there is no alternative but to rely on effects of more conventional radiations (primarily X and gamma rays) as a point of departure to establish tentative exposure limits and to set up interim design criteria for protection measures during the early phases of manned space flight.

"In doing so, however, it must be recognized that many factors inherent in space exposure conditions (for example, quality and nature of the radiations, their RBE, dose rate, depth dose, body areas or organs exposed, etc.) will modify the dose response relationships. Some of these factors may make space radiation exposure conditions less hazardous and others more."

Biosatellite Experimentations

FENN: I am sorry we haven't more time for the discussion of this important area, but we are anxious to learn from Doctor Jenkins something about the biosattelite program and the ways in which it might answer some of the questions we have raised at this conference.

JENKINS: At the present time, about 150 experimenters have submitted experiments for the biosatellite program, involving weightlessness, zero gravity, radiation, and biorhythms related to removal from the earth's rotation. The spacecraft will weigh about 1250 pounds and the payload will be about 250 pounds. The flights will be more or less equatorial, about 22° North latitude, in a circular orbit at about 200 nautical miles altitude. The duration of the flights will be three days for the radiation experiments and 30 days for the longest primate flight.

The experiments involving cells and plants will be three and 21 days. Six flights will be launched on the Thor-Delta booster. There will be some spin-up on entry and some spin and G force on re-entry. About 30 experiments have been selected, involving cells, plants, and animals, including primates.

When experiments were first invited, many of these involved cosmic radiation and proton radiation. However, when the experimenters met, instead of these studies they have suggested that if the major objective is to study the combined effects of weightlessness and radiation, it would be preferable to supply a known source of radiation. One Curie of strontium will be flown. During a three-day flight the organism being irradiated will receive from 100 to 2,000 roentgens.

The objective is to determine whether there is any synergism, antagonism, or no effect of weightlessness in combination with radiation. This is the same conclusion that the radiation panel of the Space Science Board came to: that this is the most important type of experimentation to carry out first.

In NASA balloon flights, there were about 25 cosmic thin-downs per square centimeter in a 50-hour period. We are referring the cosmic radiation experiments to balloon programs. In weightless experiments, there will be no more than 10^{-5} G for all flights. The primate flights will involve pigtail monkeys, in orbit for 30 days. These will be instrumented with deep brain probes, cardiac output implants and a variety of other studies. The urine will be collected and frozen, brought back, and there will be about six experiments on each primate.

The only flight that the United States has completed was called Nerv. In this program a series of experiments were flown to study weightlessness and cosmic and proton radiation. There were only 22 minutes of weightlessness during a trajectory suborbital flight. There

were many Neurospora mutations but this was not a well-controlled experiment.

At the Ames Research Center, biologists and engineers are working with the various experimenters who have been selected for possible space flight experiments. They come to the Ames Research Center with their experimental material and the biologists and engineers help determine how much space, volume, telemetry and other equipment is required. "Bread board" layouts are developed with proper integration to the spacecraft, at the Ames Research Center.

RAHN: Are you contemplating sending up a pregnant mouse which will deliver after going into orbit?

JENKINS: That is not one of the present selected experiments, but it has been proposed. We have fertilization experiments with polarized frog eggs compared to a sea urchin egg which is not polarized to gravity. These are fertilized after being put into 0 G orbit.

RAHN: If delivery occurs after reaching orbit, then the fetus is delivered and stays in a weightless environment until it returns to earth. What bone changes will be seen after 30 days in orbit? Is this a worthwhile experiment?

NEUMAN: This is, I think, a very important question from the standpoint of far projections in our space program, where we have a proposed capsule involving generations, because we are quite sure that the lines of force on bones very markedly affect the shape and form of bones.

The only thing I can think of in the way of experimental data to bring to bear, would be the culture of whole limb buds in an aqueous suspension, which is essentially mimicking 0 G. There has been a considerable amount of this kind of culture work done, both of limb buds and of teeth.

Strangely enough, if you put a femur in culture, it looks something like a femur after growth, but it doesn't look like a normal femur. I think it would be of great interest to see, in a 30-day period where there would be quite a bit of development in something like a mouse, to see what the skeletal parameters were, and how they were altered by the lack of directional forces on the developing skeleton.

FREMONT-SMITH: But *in utero* you don't have any single G effect. The organism is around in various positions so that there are no continuous lines of force of G, and yet your bones develop in the normal way, don't they?

NEUMAN: Absolutely, because this is the normal way for a bone to develop.

RAHN: Yes, but if you take 1 G away from their further development, that is what I would like to see, and then observe this postural reaction.

NEUMAN: My prediction would be that it would look like a mouse but it would be a very funny-looking mouse.

GRAYBIEL: We propose to send up animals without restraint in the cage and rely on indirection to find out how they are getting along. There will be opportunity for photography, motion pictures, and I am not sure whether they will have telemetered television or not. The panel presumably will be instrumented—I guess a modification of the Skinner box. There will be performance tasks with food conditioning and reward. There will be metabolic measures: how much they eat and drink, provision for excreta collection.

We thought we would match off normal animals with animals that had lost their labyrinth—not completely labyrinthectomized animals but animals that have lost the function of all six canals.

In short, we are looking for whatever might be found in two groups of animals which are given every possible advantage to live physiologically under 0 G. We feel that 0 G itself may be a rather small and delicate variable as compared with any other things which might be happening up there.

ROTH: What is the G load on your spin profile?

JENKINS: It goes up to 11 G longitudinal, and about 450 cycles of vibration per second. The spin-up is for 52 seconds at 100 rpm.

ROTH: What is the G load on the spin?

WOOD: At a given rpm the acceleration developed depends on the radius on which the animal is spinning.

ROTH: Here's the reason I was concerned. I think Doctor Arthur Smith at the College of Agriculture, University of California, Davis, California, has had chickens on a centrifuge at G loads up to 3 G for long periods of time.[156] He has also had eggs develop at high G and finds that many of the eggs die. The blastodisc apparently gets displaced into the yolk. But he could breed a strain of chickens that had blastodics that that were specially resistant to this and could reproduce at high G loads.

Interestingly enough, these animals get very heavy thighs and they are using this centrifuge as a way of increasing the thigh size of the chickens. These studies actually stimulated his experiments where hogs were made to eat from high troughs to develop big hams.

There is an interesting nutritional aspect to the chronic centrifuge studies. They find that there is a serious decrease (67 per cent) in the food intake of birds, both going into and after coming out of the 2 G environment. The dietary intake, digestibility and efficiency of feed utilization all decrease. I don't know why the dietary defect is so outstanding or, actually, why it exists, but this was an interesting finding. These dietary changes may have some significance in transitions from chronic 0 G back to 1 G.

SUMMARY

Discussion leader:
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FENN: I think the mark of a good chairman is to do as little as possible and since no one man could hope to summarize this conference effectively—nor would his afterthoughts be of great value compared to those of somebody who is more closely related to the field—I have asked several of you to assist in this task.

I asked these people who were designated if they would either review what had been said, summarize what had been said, or summarize what should have been said, or summarize what we ought to say next time, or just to give an appraisal or a personal opinion about the subject, so that they can do anything they like, whether it is summarizing or otherwise, or supplementing what has been said.

I will ask Hermann Rahn to give us a summary of the problems raised relative to the gaseous environment.

RAHN: It is obviously difficult to summarize and do justice to all the thoughts that were contributed to this particular subject. There is little question that gaseous envionment of the capsule is very important. It touches on many aspects of a space mission, not only in the area of bioecology but also in the area of bioengineering.

I have enumerated several major topics that may help us see the various influences of the gaseous environment. What gas or gas mixture shall we choose for our astronaut and what pressure? (*1*) Cardiopulmonary-cerebral function; (*2*) acceleration-deceleration; (*3*) bends-atelectasis; (*4*) pressure suit; (*5*) cabin pressure; (*6*) oxygen toxicity; (*7*) radiation hazard; (*8*) food recycling; (*9*) engineering problems: fire hazard, equipment fatigue, single versus multiple gas, total cabin pressure.

(*1*) The atmosphere must provide for a normal function of the lung, heart, and brain. The end goal is not so much a stable cardiovascular system, as a stable and normal psycho-motor performance. Thus, the inspired O_2 must be adequate to provide normal hemoglobin

saturation, and the inspired CO_2 must not be high enough to embarrass the ventilation and acid-base balance.

(2) During entry into orbit and final reentry, the lungs appear to be one of the most susceptible organs to changes in G forces. There is little question that the type of gas breathed, as well as the total gas pressure, must have considerable influence upon the degree of lung collapse and possible reexpansion. Whether an O_2–N_2 mixture would be preferable to pure O_2 is not easily settled, for such a decision might affect the occurrence of bends.

(3) Bends would be produced whenever N_2 gas is present in the blood and tissues. To avoid them, one breathes oxygen and slowly washes out the N_2. However, pure oxygen, particularly when breathed at a reduced pressure, renders the lung prone to rapid alveolar collapse following obstruction. We have long been aware of the fact that we cannot tolerate bends. However, we also know now that lung collapse and arterial unsaturation can occur when O_2 is breathed, particularly during acceleration. Unfortunately, the first condition requires the absence, the second condition the presence, of an inert gas such as N_2.

(4) A pressure suit is not only essential for emergency but also for leaving the capsule, either in orbit or walking on the moon's surface. The higher the suit pressure the lower the mobility of man. What is the lowest pressure that would provide for normal cardiopulmonary-cerebral function and therefore the greatest mobility? This is pure oxygen at a pressure of 3.8 psi or about 197 mm. Hg. Subtracting 47 for water vapor we have an inspired O_2 pressure equal to that at sea level.

(5) Thus, the cabin atmosphere is pure oxygen. This allows the astronaut to resort to his pressure suit at a moment's notice without fear of bends. The engineer is happy for he has to provide only one gas instead of a gas mixture. Furthermore, a low pressure differential (between inside and outside of cabin) substantially reduces the weight requirements of the capsule. Thus for Mercury a pressure of 5 psi or 258 mm. Hg was chosen, which yields an inspired O_2 tension of 210 when breathing pure O_2.

(6) This oxygen pressure is equal to breathing a 29.5 per cent O_2-N_2 mixture at sea level and raises the problems of oxygen poisoning. Tests in simulated atmospheres suggests that this O_2 pressure is tolerable for periods up to several weeks. It should be emphasized that raising the inspired or arterial O_2 tension 60 to 70 mm. Hg does not mean that the tissue O_2 tension is changed by a similar amount.

(7) The radiation hazards were discussed. The inverse relationship between radiation susceptibility and O_2 tension may become im-

portant for long space missions. This is still an area that needs more explanation.

(8) The oxygen and CO_2 tensions of the cabin atmosphere will obviously have to be related to the whole process of food cycling and oxygen regeneration once we must depend upon complete ecosystems. I gather that this becomes important for missions beyond three months' duration.

(9) Finally, I will mention the engineering problems. There is first the fire hazard. We must not only learn about the unique problems posed by these atmospheres, but also how to cope practically with fires.

A one-gas system is obviously easier to regulate than a two-or multigas-system, particularly when our satellites have large leak rates.

The total cabin pressure is naturally of great concern in the basic design of the capsule.

HENDLER: There is one set of pertinent experiments that we conducted and that were not mentioned as yet.* We exposed subjects for varying periods of time to an atmosphere of 50 per cent oxygen-50 per cent nitrogen at an absolute pressure of one-half of an atmosphere (18,000 ft. altitude equivalent). The subjects were subsequently decompressed while breathing oxygen to an altitude equivalent of 35,000 ft., where they remained while engaging in light exercise. We found that if the subjects remained in the 50-50 atmosphere for between 12 and 18 hours before being decompressed, very few got the bends. Shorter stays in the 50-50 mixture resulted in many more cases of bends. Another way to provide bends protection, of course, was to wash out nitrogen initially by having the subjects preoxygenate. The 50-50 atmosphere at an 18,000-ft. altitude equivalent was at one time considered for use in project Apollo.

RAHN: In other words, you get rid of half the potential nitrogen hazard by exposing the subjects to 7 psi in a 50-50 mixture?

HENDLER: When time at 18,000 ft. on 50 per cent oxygen-50 per cent nitrogen is plotted on the ordinate against duration of preoxygenation on the abscissa, a diagonal line can be drawn between 12 and 18 hours on the ordinate and two and three hours on the abscissa. The conditions to the left of this line can be considered as bends-producing, those to the right as bends-protecting. We thus have a trade-off between two methods of getting rid of nitrogen in the body. The subjects we used were relatively bends susceptible when compared to others of the same age, so our times are conservative. We hope to be able to define these times better in future studies, and

*This program was supported by the National Aeronautics and Space Administration under Purchase Order R-40.

to determine the effects of other factors known to affect bends susceptibility, such as decompression rate. The rates we used in our study were determined by anticipated operational parameters in the Apollo program, and for these, there was no detectable difference in bends incidence.[157]

FREMONT-SMITH: This is only 18,000?

HENDLER: This was 18,000 feet and then protection against subsequent decompression to 35,000 feet in 100 per cent oxygen, which would be the base.

CALLOWAY: As presently planned for Apollo, the cabin is at 5 psi pure oxygen and the suit is at one-fourth atmospheric (3.75 psi). Did Doctor Helvey's data show whether the men at 3.8 psi were in a little less bad shape than they were at 5 psi?

ROTH: Unfortunately, Doctor Helvey had to leave early. I reviewed his paper[158] and found that one aspect is still unexplained: his 3.8 people had a marked drop in maximum breathing capacity (MBC) with onset at 10 days. Why this is so, I don't know, but the MBC's went down 30 or 40 per cent. The question arose in my mind whether this is not bucking a tendency for increased secretion and increased mechanical bronchial blockage produced by higher tensions of oxygen against the exaggerated collapse tendency produced by lower oxygen tension, which is Doctor Rahn's concept. You can think of a time-dependent situation where you are constantly blocking bronchi and constantly reopening them. The less oxygen you have in the alveolus, the less time it takes to produce collapse after each blockage event.

However, as you get to the higher level of oxygen, the increased secretions increase the blocking tendency so there might be a zone between the two where atelectasis is kept to a minimum. This might be a possibility.

Why maximum breathing capacities dropped on the low oxygen levels, I don't know. I don't believe the vital capacities changed as dramatically as the maximum breathing capacities.

DUBOIS: Were those measured after the end of the run, after they returned to room air?

ROTH: I think they were measured inside as well.

DUBOIS: At low atmospheric pressure the gas in lungs is much more compressible. For a given pressure change in the alveoli, the volume of the gas is changed so that the external volume pumped would be less than the internal. Air is just compressing in the bellows and they are not moving it in and out of the trachea.

SONDHAUS: The 3.8 psi people showed a higher reticulocyte response also, and some other parameters of the blood seemed to be more markedly perturbed.

ROTH: The higher reticulocyte might be a positive health factor, because Tinsley showed back in the 1930's, using unfortunately, tertiary syphilitics as controls, that there was a marked suppression of reticulocyte response to liver therapy in pernicious anema patients.[159] Even in "normal" controls, basal reticulocyte levels dropped, suggesting that the higher oxygen depressed the reticulocyte response. After a given level of hemolysis, a lower oxygen pressure with a higher reticulocyte count might actually be a healthier situation.

FENN: I would like to ask Arthur what his committee actually recommended for an atmosphere in the capsule. Is that a secret?

DUBOIS: The same thing that this group might recommend. We did not reach a definite recommendation but we went over the factors concerned, the philosophy being that once the factors are brought out, then almost anybody can make a decision that is as good as that of anybody else. The most important thing is to try to elicit all the information available on the subject and then let those people who are responsible for the total situation make the decision on the basis of available information.

FENN: But you didn't make a definite recommendation?

DUBOIS: We recommended that certain possible atmospheres[160] be tested to see if they are any good. For instance, the 50 per cent oxygen-50 per cent nitrogen at one-half atmosphere should be tested for two weeks to see if people can get on well in it. It would be hard to recommend an atmosphere for breathing without somebody having first tested it. In otherwords, you can arrive at a recommendation that somebody ought to try it out. That is where we stood.

FENN: I am going to call on Doctor Margaria next to summarize the discussion of the vestibular senses. We were particularly glad to have him here and I want to thank him publicly for coming over and joining our deliberations.

MARGARIA: The subject of orientation is rather peculiar in a way, because we speak of orientation in space where, gravity being absent, there is no possibility of orientation any more. The possibility of orientation here on earth is only in the vertical direction, we know only where is up and where is down, but we cannot indicate where is east or west, or north or south, if we have no visual clue. The labyrinth only informs us of the vertical direction, which is the direction of the gravitational force, not on any other. So, to speak of orientation in space is a little like speaking of vision in a dark room, in dark surroundings. In space there are no stimuli for orientation, just as in the dark there are no stimuli for vision adequate to excite the retina.

If this is the case, it becomes, then, difficult to visualize how a man in space may feel. As there are no sense organs giving information

about the position or movement in all directions, a three-dimensional space is possibly felt as a bidimensional one. In fact, as normally no substantial difference is felt between left and right or left and front, in space no substantial difference can be felt between left and up or front and down. In absence of a gravitational force "up" "down" do not exist any more, and such expressions have no more meaning.

On the other side, the orientation sense organ is made up not only of the otolithic apparatus, picking up static impulses due to the gravitational field, together with kinetic stimuli related with acceleration. In the labyrinth, another apparatus, the semicircular canal system, responds only to accelerative stimuli. These two apparatuses form a rather complicated system, because, though distinct as sense organs in principle, as they respond to somewhat different stimuli, they are related in the central nervous system area where they feed the same nuclei and where impulses from the two sense organs are integrated.

Besides the mechanoceptors that are in the labyrinth the acceleration or gravitational forces act on other mechanoceptors that are distributed over the skin, at the muscle level, and in the viscera. These all contribute, together with the vestibular responses, to the perception of the orientation, of the acceleration forces acting on the body. The impulses from all these very different sense organs widely spread throughout the body all impinge upon the same area of the central nervous system. The lower main station is the cerebellar nuclei and cortex; here and in other upper stations up to the cerebral cortex, these impulses integrate, the effect of this being on one hand, the proper sensation; on the other, the transmission of impulses to the periphery, both to the muscle system and to the sensory system. The effect is a change of tension of particular muscular groups, which is generally referred to as postural tonus, and also a change of the sense organ system and of the sensations felt. This change in the sense organ system may be responsible for illusions that Doctor Graybiel spoke about, when these sense organs are subjected to a peculiar excitation.

The whole picture is quite complicated, and it is my impression that we need to know much more about the basic physiology of this labyrinth, which has received little attention up to the present, because this apparatus is the most susceptible to functional change in space travel and because of the wide influence that this sense organ has on motor and sense performance and on the stability of the operation of the higher nervous functions.

The investigation of the functioning of the apparatus in 0 G condition seems to be particularly urgent. And, as there is no possible

way of stimulating 0 G conditions on earth, the experiments have to be made on the satellite. By immersion in water, we can get rid of all the gravitational stimulation of all the other sense organs, such as the mechanoceptors of the skin muscles and viscera, but we cannot get rid of the stimulation of the otolithic apparatus. Using this procedure, it is possible to know what happens when the gravitational forces act on this sense organ. However, we have no information how it would work in 0 gravity conditions.

A few years ago I made some experiments on orientation in immersion, on a subject with closed eyes,[161] to obtain information on based only on the response to gravitation of the otolithic apparatus. It appeared from the first experiments that the otolithic apparatus had a very low sensitivity, because when the subject was asked to point to a vertical direction, he made errors that amounted sometimes to 180°. In other words, he seemed to be completely disoriented.

After four or five experiments, however, the subject reacquired the capacity to indicate the correct direction with an error not greater than the error observed in control experiments. Evidently, the disorientation observed in the first experiments was due to the fact that normally the information is received through many channels. The limitation of the reception of the information to a single channel led to a profound disturbance of the appreciation and evaluation of the information, in spite of the fact that the only sense organ left was sending appropriate signals to the centers. A new training process was needed to get back to the correct perception of the information as given by the single, probably the most appropriate sense organ. I think that inconveniences of this type are expected in space where gravitational impulses are completely lacking and where kinetic impulses from the labyrinth are probably appreciably distorted.

Experiments on these lines should be done in space, in my opinion. But besides doing these experiments in space, experiments can be done on earth to try to evaluate the physiological functional possibilities of this important sense organ, the labyrinth, and possibly to train astronauts to meet the experience of abnormal stimulation of the labyrinth, and to acquaint them with the possible fallacies of the sensation experienced in particular conditions.

Doctor Graybiel pointed out the utility of the rotary chamber to stimulate the labyrinth through the Coriolis acceleration forces. How the subject responds to this particular stimulus may well be a profitable test to enable one to predict his aptitude to space travel, in spite of the fact that the conditions are not exactly alike. This practice may also be used to measure the adaptation of the individual to abnormal stimuli of the labyrinth.

In conclusion, I should like to stress the necessity and the im-

portance of performing orientation tests and experiments on the labyrinthic function in man in actual space flight. We know from previous flights that serious disturbances may arise from such an apparatus. Titov complained about such disturbances, and I would point out that this is the only physiological phenomenon that could not be predicted, and the only really new physiological information that an astronaut gave us on his flight report. I think that a proper functioning of the labyrinth is required for a successful flight, for a successful mission, particularly of a long-lasting type that requires a specific activity from the astronaut.

FENN: I will ask Doctor Bongers if he will summarize the regenerative capsule for us, briefly.

BONGERS: In considering life support systems for closed environments, we have to deal with at least three important aspects. First of all, the reliability; secondly, the weight contributed by a given system to the total launch weight; and thirdly, the power penalty imposed by the life support system.

As far as reliability is concerned, bioregeneration by either the photosynthetic or the bacterial system is an open question. To my knowledge, no experimental evidence is available to demonstrate that an ecosystem can be operated without failure for extended periods of time. Therefore, bioregenerative systems are approached with some reluctance, and I am convinced that any step in the closed cycle that can be performed by chemical or physical means should be done that way. A case in point is waste processing.

As far as weight is concerned, the solar-illuminated algal system and the bacterial system are acceptable. The geometric design requirements of the solar-illuminated algal system are disadvantageous in some technical respects.

With regard to power utilization, bacterial regeneration is competitive with systems that rely on food storage and atmospheric recycling. The physical-chemical carbon dioxide reduction methods involve the generation of degraded energy, which must be removed in order to maintain the thermal balance of the environment. Additional energy is consumed in this process. The same problem is faced by the photosynthetic system driven by artificial illumination. The future of this sytem depends upon the development of nuclear power devices of large capacity and low specific weight. Taking into consideration all these aspects of power consumption, the bacterial system has the most promise.

A number of problems pertaining to reliability and the operation of a controlled ecosystem remain unsolved. These include the selection of the organism with respect to genetic and physiological stability. Experience has shown that monocultures degrade after prolonged

cultivation. The cause of this phenomenon is not understood and needs elucidation for our purpose. It is uncertain whether the multispecies culture will develop more stability than the type discussed.

Suspension management is another important problem. In order to maintain the optimal nutrient concentration in a steady-state culture, accurate knowledge concerning the consumption rates of a number of ions is necessary. Furthermore, accumulation of extracellular organic material in the medium must be avoided to insure contaminant-free operation. Conditions that prevent the accumulation of excretory products must be carefully studied for the organism of choice and means of "revitalizing" the suspension medium explored. With regard to fecal and urinary excretion products, the same situation exists. No adequate solution to handle these products is presently available.

Finally, I mention some of the problems involved in the closure of the food and nutrient cycle. No experimental evidence is at hand to demonstrate that conventional foods can be replaced exclusively by algal or bacterial crops. Actually, the composition of microorganisms as food for man is far from ideal if the conventional diets are considered as rigid standards. In particular, the overabundance of proteinaceous material in microorganisms poses a major problem. Conversely, the nitrogen output of a human being, if supported by a conventional diet, would be insufficient to support the microbial culture. This imbalance, which is quite obvious in case of nitrogen, might also exist with other elements. Adjustments of the environments to suit the man might require some adjustments by the man to reach a workable compromise. This compromise indeed might require the inclusion of an animal in the cycle as an intermidiary at the expense of additional weight and power penalties.

NEUMAN: You said nuclear power. You were thinking of snap devices?

BONGERS: Not in particular. Any nuclear device with large capacity and of low specific weight would solve the energy problem.

ODUM: In going from algae to bacterial systems, you are going the wrong way. Why not go to higher plant systems? Is this purely a matter of weight?

BONGERS: I think it's both a matter of weight and a matter of power.

ODUM: Many of the objections you raise to the microecological systems can be solved by going to higher plants. Control would be much easier.

BONGERS: Power, weight, and possibly also the volume demand seem to be the main obstacles in utilizing higher plants.

ODUM: Why do we ignore all our vast experience and go to something we know nothing about?

FENN: We can come back to this. Frank told me we would never get through if we had six people reviewing things, so I am watching the clock. I am going to ask Doctor Calloway to give us a review of the nutritive aspects.

CALLOWAY: We have noted that algae are less than perfect food by themselves. We know absolutely nothing about the nutritive quality of the alternative system that is reasonably well developed, the hydrogen-fixing bacterial system, but, according to Doctor Bongers, nutritional studies are programmed.

We have admitted with some embarrassment that we don't know what man's minimum needs are on earth. Doctor Schwartz pointed out that with the availability of a completely defined diet, it might now be possible to determine these minimum requirements exactly. None of us questioned whether minimum would also be optimum, particularly for the special environment of space.

There will be no gravitational force and this, Doctor DuBois observed, might alter water and salt excretion. It might also affect retention of nitrogen and calcium.

We have talked about reduced pressures, the possibility of oxygen toxicity, the deprivation of atmospheric nitrogen. We don't know, and only briefly mentioned the possibility that biological antioxidants—such as vitamins E and C, selenium—might be of some virtue in alleviating these detrimental influences.

We know that there are radiation hazards and that injury can be minimized to some extent by improving the resistance of the host animal. Good nutrition is one way to improve resistance and again, there may be a role for the biological antioxidants.

The other stresses that may be found in this environment—vestibular impairment leading to motion sickness, heat-cold stresses, toxic gases, and other toxic materials—may be subject to dietary influence. And the diet itself can be stressful.

There will be a certain amount of social deprivation and confinement. We didn't touch on the minimum psychological requirement for man—how long you can lock him in a closet? These factors are of interest even to a nutritionist because a disturbed man shows some interference with his nutrient intake mechanisms.

We barely mentioned the man's "private" ecology, his own flora. Does he need these? Do they serve a useful purpose? Should we wipe them out?

JENKINS: An area not discussed with regard to weightlessness is skeletal calcium loss during bed rest. There are some extremely interesting new data at Houston, Texas, in the office of Manned Space Flight. One of our contractors, Doctor Pauline Mack at Texas Women's University, in cooperation with the Texas Institute of Re-

habilitation, using volunteer men, conducted bedrest studies. In three days, using x-ray bone densitometry and analyzing calcium loss in urine, they have found up to 25 per cent loss of bone mineral in the os calcis (heel bone) as measured by this x-ray technique. When the men were put on 10 days' normal activity, and then put back into bed rest for three days, a small amount of isometric exercise prevented undue loss of calcium apatite.

These studies were repeated during two-weeks bed rest periods. During bed rest the calcium apatite went down slowly.

FREMONT-SMITH: Has this been published?

JENKINS: No, it is not published. The data are still being analyzed. This is a very important field and one that is of great interest to us. The question arises, what happens when an astronaut has lost a large amount of skeletal mineral when subjected to the stresses of reentry, including impact?

Another approach to study is the possibility of using fluorine, which causes the formation of larger fluoroapotite crystals, which are less soluble. This is a possibility, but one introduces a toxic substance and we know enough about them.

FREMONT-SMITH: The dosage is no greater than is given for protection of the teeth?

JENKINS: One could give a dose of about 25 mg. per day.

NEUMAN: For short periods you can give up to 100 mg. per day to humans and this is being done. This is the level just below which one doesn't get dental fluorosis. Ten to 25 mg. is tolerable for long periods of time after your teeth have erupted. One part per million (in drinking water) is around 1.5 mg. per day.

CALLOWAY: Is the calcium spillage mainly urinary or mainly fecal?

JENKINS: The fecal loss is about 2 to 10 (average five times) the urinary loss according to Doctor Pauline Mack.

CALLOWAY: It is usually 200 to 300 mg. at the outside in urine. Many years ago Cuthbertson reported excessive calcium loss in men at bed rest.[162] What is also interesting is the emotional influence on calcium loss. Malm reported it in his Scandinavian studies.[163]

FREMONT-SMITH: What kind of emotional loss?

CALLOWAY: In his prisoners, loss was related to events within the social milieu of the prison, such as escapes that didn't come off. He had his men on studies of very, very long duration and he could plot these nicely. Stearns[164] reported findings on unmarried mothers that follow the same pattern. The loss was largely due to fecal dumping of calcium, which would be less serious, from the point of view of the renal calculi.

JENKINS: Formation of renal calculi is another problem of interest, although maintaining the *p*H of the urine may help.

The men carried out isometric exercises by pulling against an ergometer, which resulted in decrease of the rate of calcium loss.

FREMONT-SMITH: In connection with the influence of immobilization on retaining calcium, or withdrawing calcium, I assume would be the other end of this, it is very interesting to think back to George Whipple's work of many, many years ago in which he showed the only way you could build myoglobin was by exercise; that no diet could increase myoglobin if you lost it without exercise, and you could build it back only by exercise. I think it is quite fascinating that you can perhaps build back calcium in the bone by exercise.

CALLOWAY: I wonder whether weightlessness is going to be a less energy-requiring environment than is living down here.

ROTH: I think there are several studies to the point. Just in brief, the Boeing people[165] have had individuals on air-bearing devices in which they have asked them to do various types of tasks that required their stabilization with other limbs, and in some cases the oxygen requirements have gone up about 70 per cent.

CALLOWAY: That is tractionless, isn't it?

ROTH: Yes. They have some in gimbaled systems where there are five degrees of freedom. They are relatively tractionless. The 70 per cent figure was taken from this study. The more degrees of freedom, apparently, the greater the elevation in oxygen consumption. They explained this on the basis that they are using unusual muscle groups—muscle groups they wouldn't ordinarily use in the task.

Then, there are some Italian studies, which I don't think were really adequate in terms of the locomotion apparatus, where individuals were suspended from the ceiling on a tramway by elastic cords. They were lifted so that their weight on a scale was reduced up to one-twentieth of their normal weight. With this suspension they got increases in oxygen consumption of 30 to 35 per cent above that required for the same locomotor task of horizontal walking. After reviewing the whole experimental setup, I had the feeling that the hookup was probably not at the center of gravity of the body. There was much rotation, much countermovement of the arms. The 30 per cent elevation in oxygen consumption was under 1/20th weight conditions where there was still some traction left.[166]

The NASA group at Langley, Va. has had people walking on inclined planes along the incline, with the angle of incline such that the force normal to the surface was simulating, say, a lunar situation of 1/16 G. I have just seen movies of them walking and they were much, much more stable than in the Italian studies, which makes me feel that the oxygen consumption figures that the Italians gave might be biased by their fixation site.

There is also Doctor Ralston* at the University of California, San Francisco, in the biomechanics lab, who has a contract with Ames to study essentially the same thing—stimulating subgravity by suspension devices.

SCHWARTZ: Isn't this a matter to some extent of conditioning or experience?

CALLOWAY: Partly so, and they are going to put belts on the seats and pressure tapes on the floor.

ROTH: The Boeing people found very little training effect.

FENN: Doctor Margaria must know about the Italian studies.

MARGARIA: I don't know too much. I heard a report about them at the meeting of the European Aerospace Medical Association in Rome last week. It is certainly impossible that at a lower gravity the oxygen consumption increases, because in walking or running on the earth, the greatest amount of work is done against gravity—in walking at the most economical speed, all the work is against gravity. A way of stimulating a subgravity condition is to walk downhill, because then the lift of the body at each step is reduced, even to zero, depending on the incline. Walking downhill is much more economical, and the greatest saving of work is obtained at an incline of about 10 per cent, where the cost of walking is about 0.25 kcal/kg./km, while it amounts to 0.50 walking on the level.[167] Similarly, running at such an incline requires an energy expenditure of 0.52 kcal/kg.km., instead of the 0.98 required for running on a level.[168] Of course, downhill walking or running is not the same as performing on the level at lower gravity, it only implies a decrease of the work performed against gravity.

I agree that the experiments performed by the Italian team were affected by an appreciable error due to an incorrect suspension of the subjects. That was evidenced by the very abnormal posture that these subjects had during the performance, as shown by the pictures of them. Evidently, the increased work to correct posture was greater than the work saved by lifting the subject.

ROTH: The NYU Engineering Department has done several interesting studies for the Air Force, which we reviewed in a recent paper.[169] covering the problems of walking in subgravity. They attempted to analyze the total gravity factor in various limb motions, especially those used in walking. Their calculations suggest that when gravity aids limb muscles, it aids by a factor of 5 per cent and when it opposes, it opposes by a factor of 15 per cent. These are very specific motions of the arms and legs. I think it is an interesting approach.[170]

FENN: Doctor Margaria has been restudying the mechanics of

*Ralston, H. J. 1963. Biomechanics Laboratory, University of California Medical Center, San Francisco, California, unpublished data.

running, and he finds a great advantage in running because you bounce when you run. I would like to point out that you can't bounce under 0 gravity, so what about the efficiency of running when you can't bounce?

MARGARIA: On the moon or a planet, gravity is not 0, but only decreased. Running at 0 gravity has no meaning as the length of the step is infinite as well as its duration. Running at reduced gravitational field such as, for example, on the moon, involves particularly (*1*) a higher duration of the step and (*2*) a decreased stretching of the contracted muscles that absorb the impact of the body falling on the ground (negative work). This negative work is, in my opinion, partially given back as positive work in the next step. On this planet this work is appreciable. The force on hitting the ground in fast running amounts to about 200 to 250 kg.; on the other hand elastic work can be performed only by stretching the contracted muscles, and the contraction costs energetically. It follows that if the time between stretching and contraction is very short, energy may be saved to the profit of the runner. If this time is longer, the cost of maintaining the contraction may become greater than the elastic energy disposable.

In running about 50 per cent of the energy is elastic energy. If this cannot be utilized, it follows that at reduced gravitional force, though the energy cost of running is lower, the efficiency may be lower than on earth.

ROTH: What was the most disturbing to me, in view of our discussion this morning, was that we have recently received some requests for reviews of some engineering designs for lunar suits, hard suits, in particular, where the astronaut is loaded with 400 pounds of suit. They assume that with 1/6 G to aid them, astronauts can easily carry around these 400-lb. suits. I think that is an example where we ought to step in right away and point out these things before engineers push it too far.

FREMONT-SMITH: In a very low gravity situation, wouldn't you have a disturbance of the relationship of agonists and antagonists that might also reduce the efficiency of muscular movement? We think as if the muscular movement is made primarily by a flexor, but there is actual activity of the extensors, too, at the same time, isn't there?

MARGARIA: There is inhibition of the extensors.

FREMONT-SMITH: Inhibition but with continued tension. It is not a sudden loss, is it? Isn't there an electromyographic activity in the tensor as well as the flexor?

MARGARIA: I don't think so. In normal movements, of course, there are some movements that require contraction of both agonists and antagonists, but that depends very much on the type of movement. The main point in subgravity, I think, is that one step may

require a few seconds, so that the succession of contractions is completely altered and the movement has to be learned all over again.

FENN: Doctor Sondhaus will give us his views on the subject of radiation—his afterthoughts.

SONDHAUS: I also feel that there was a great deal that did not get said that might have been considered. There are other types of radiation, for instance, besides the ionizing variety, some of which are certainly useful as energy sources. However, I suppose there was justification in limiting our consideration to the environmental hazardous situation, which we have come to view as the radiation problem.

We had a very brief review of the nature of the radiation to be found. I think we have to leave the questions of its characterization largely to the geophysicists and the astrophysicists. It is sufficient, I believe, for us simply to start with the fact that has been given: that there are a variety of particles, the heavier, more highly energetic ones always being present in the cosmic radiation. Superimposed upon the latter are the sporadic, and we hope only occasional, occurrences of solar flares. The other two sources mentioned, the Van Allen belts and the possible nuclear radiation resulting from a propulsion apparatus, are more tractable because they are either avoidable or can be held to a minimum.

The characterization of the radiation environment is certainly still a long way from being complete. So is the interaction with the components of the vehicle itself. We can make fair predictions about the kind of secondaries that will be produced in the vehicle walls. We know that limits exist between which it is conceivable that shielding would increase the exposure dose. Yet, I think the most important problem in this area is that of a prediction of the solar flare. In the long run, I feel that this is going to be the crux of any realistic protection against radiation.

We are left with a host of partial measures, of more or less really inadequate ways of coping with radiation injury once the accident has occurred. We can ameliorate but we certainly cannot reduce by any great factor the effect that will follow.

Given, then, that we have a fair idea, although an incomplete one, of the flux of radiation that might be present in a capsule, the effects, biologically, of this flux are of prime consideration on a very practical basis. In order to set limits—that is, in order to compare unorthodox, exotic situations in which the energy, transfer, the dose distribution, or the time duration of the radiation differs markedly from what we have experience with—we ought to make at least a reasonable prediction in terms of what we believe are safe levels here on earth.

If we attempt to do this, we will at least reach the point where we can do a good deal of simulation of the problem on the ground. It

seems to me that there is only one case in which an actual orbiting environment is required; that is in studying the synergistic effect of the weightlessness and radiation exposure. This will in due time be studied. There are a host of other combined stress situations which can be dealt with without ever going near a capsule. In regard to the differences in syndrome that might be expected with the cosmic or solar radiation, a fair start at least can be made on the surface of the earth. In fact, this is under investigation in a number of different places.

To me, the most interesting possible synergism that has come up during the meeting is that of oxygen toxicity combined with radiation injury. I think that this should receive very early attention in the immediate future. Of course, this problem can be studied by use of any radiation. The differences in injury pattern are not extraordinarily great but it would certainly be desirable to go as far as possible in simulating the space radiation environment along with an oxygen tension environment in which toxicity might occur.

It seems to me that in the long run the oxygen question may turn out to be far more critical than weightlessness, for example, or even temperature. Temperature, too, is a variable that should be included in combining stresses, and I might mention in addition to that the possible effect of a magnetic field. There seems to be no connection *a priori* here, but some recent experimental work on one insect, *Tribolium confusum*, has demonstrated that the presence of a magnetic field reduces the number of radiation-induced developmental abnormalities. With a magnetic field present, several replicate experiments on a fair-sized population of insects showed the effect of a given gamma dose was reduced from some 95 per cent or thereabouts down to less than 50 per cent.

I am talking about the incidence of developmental abnormalities in the maturation of a beetle. At present it is the only example I know of the radiobiological effect of a magnetic field. I think this is a very curious thing. As yet not much is known about it, but I think it belongs very properly in the area of combined stresses. Of course, if one wants to be optimistic, one might get very wild and propose that all astronauts be suitably magnetized and, therefore, rendered more resistant to radiation stress.

In regard to radioprotection, I think diet certainly should be studied, because it seems to me that this can play a very important part. There may be substances in the ordinary diet that have a protective effect. I might mention, in addition to some of the things that were already pointed out, that fatty acids appear to ameliorate the bone marrow syndrome at least. Here, of course, the problem is, do protons produce the same relative degree of bone marrow injury compared to gut injury? They seem to be more efficient in producing the

latter, as I tried to outline yesterday. Therefore, the lipid protective agent question may be, to some extent, irrelevant. However, this remains to be explored.

This brings us into the area of protective measures, of which diet is one. In regard to anoxia, I don't see any real practicality here in one sense. It seems to me that we have difficulties enough in adjusting cabin atmosphere to produce minimal conditions that are satisfactory in other respects without playing around with it further in trying to reduce radiation hazard. There are still, however, possibilities in this direction that might be explored.

The chemical protectants certainly would be one source of tissue anoxia that might be employed in an emergency situation. I don't think we can really say what their practicality might be at this point.

The possibility of marrow transplantation would seem to require isologous marrow. The astronaut would have to carry along some of his own, quick-frozen, of course. Something of this kind might be a possibility, but in the long run, I think all these measures come into the category of ameliorative or partial or marginal things. To me, at least, it seems that our greatest hope is in the long-term predictability of solar activity. For flights of long duration, we may very well have to combine some of these protective measures with practical shielding configuration.

I think that in relation to all the other hazards, the radiation hazard certainly does not govern. It does seem to me to be the most troublesome one, if for no other reason than because it is not always present to a predictable degree. The low level, heavy particle cosmic radiation does not seem to constitute any immediate hazard to carrying out a mission. What its effect will be as to subsequent genetic effects or even long-term behavioral ones, I think, is entirely an open question and one that requires a great deal more study. Certainly the acute case, the solar flare, is somewhat in the nature of an accident and if it is only one of a whole category of accidents, it shouldn't receive any more priority in terms of what it does to our capability of carrying out a mission to allow for it than any one of the other things that have been touched upon here.

I do feel, however, that we ought not be misinformed in our approach to any of these hazards. I think that regardless of whether we expect the probability to be very high on some given mission of having irradiation exposure take place, we should study radiation exposure. We should study the problems of space radiation exposure, simply because we know that whatever we can do now will stand us in good stead for the more and more ambitious missions that we certainly will be undertaking at later times.

I think this more or less summarizes my viewpoint of where we

stand at this moment. It certainly is one of many areas that are going to require a great deal more study, though, before we can be confident about any of the hypotheses we could make at present.

FENN: When you discover that a solar flare is on the way, how much time do you have to get the boys back under cover?

SONDHAUS: At present it is of the order of a few hours, at most. In fact, it is less time than that, really.

FENN: It would be enough to get them down.

SONDHAUS: It would be enough to get them down from a satellite orbit but not back from the moon.

NEUMAN: I want to make one comment on the magnetic report. The dramatic drop from 95 to 50 per cent might not mean a very large dose effect if the slope of the dose effect curve is very steep.

SONDHAUS: Yes, that is true.

JENKINS: Was temperature measured very accurately?

SONDHAUS: The temperature was but the magnetic field also is bound to introduce a temperature dependence.

As far as I know, the field did not induce a temperature change in the organism. But the radiation effect was temperature-dependent. That is, if you irradiated in a magnetic field at another temperature, you got a different mortality.

FREMONT-SMITH: Doesn't a powerful magnetic field induce a temperature change?

SONDHAUS: It does in a metallic substance but, as far as I know, not in an organism.

FREMONT-SMITH: Did they have a thermocouple in there?

SONDHAUS: Not in the flour beetles but among them. They are rather small.

ROTH: Your summary has reminded me of several things that we didn't cover. One was a very serious attempt on the part of the Russians to go into hibernation as a radioprotective device. As you cool the tissue, you produce a "histotoxic" type of anoxia and protect the subjects that way. Dale Jenkins, I think, is actually supporting some work along that line.

JENKINS: Doctor Musacchia at St. Louis University has some extremely interesting data on hibernation protection against radiation in rodents.

SONDHAUS: It certainly cuts down food consumption, too.

CALLOWAY: Don't they go right into an injury syndrome after hibernation ends?

JENKINS: They go into the typical syndrome, but it is delayed during the period of hibernation.

FREMONT-SMITH: What was the animal?

CALLOWAY: It has been studied in hibernating ground squirrels and bats.

SONDHAUS: It has been done in frogs.

ROTH: The problem is that normally hibernating animals are quite different from nonhibernators in their response to temperature, and I think we have a big gap in making the jump to a natural nonhibernator.

Another factor, I think, is the personal protection equipment of astronauts in case of solar flares. How effective would eye shields or marrow shields, or something like that be? If you are weight-limited, can you really effect a saving by strapping on protective devices? I think this is worthy of some consideration.

The third is that we are now dealing with this new form of radiation where the human's distance from the shield is a factor. This isn't so much a factor in the case of gamma radiation. This is especially true in the case of solar flares where, if you were going to get behind a shield, you would have to well know how to position yourself geometrically to minimize your dose.

SONDHAUS: Yes, from both primary and secondary radiation.

FREMONT-SMITH: This is to minimize the effects of secondary neutrons?

ROTH: Yes, the total postcascade dose, which hasn't come up previously.

There is one last question. In these solar flares, is the radiation isotropic or anisotropic?

SONDHAUS: This is generally assumed to be isotropic at present. I am not really able to give you a very adequate explanation of this, except that the cloud of protons leaving the sun generates its own magnetic field and tends to diffuse itself out and change its path. Thus, if you enter a solar proton flux you may find velocities in different directions.

Also, there is the obvious possibility that the space ship, itself, is rotating or moving. Isotropy is generally assumed to be the case but this is not always so. The configuration of the vehicle itself, where the water supply is placed and the variation of thicknesses in different directions would reduce this.

I think we should start by assuming isotropy and then we can work from there.

NEUMAN: It certainly is not temporal isotropy.

SCHMIDT: The possibility of chemical protection is not limited to tissue anoxia. There are other ways, are there not, than simply by producing tissue anoxia?

SONDHAUS: There is free radical competitive inhibition or competition.

CALLOWAY: Free radical acceptors.

SONDHAUS: Scavengers.

ODUM: You mentioned the nonionizing radiation. Will the spectrum of visible and ultraviolet light be approximately the same on a trip to the moon as it is here on earth?

SONDHAUS: Ultraviolet light is largely removed by the atmosphere at the surface of the earth; in space, all frequencies are present. There will be a great deal more.

ODUM: Does it remain constant after you get out from the earth?

SONDHAUS: Yes, it is just a function of your distance from the sun.

ODUM: That is not considered a hazard—increased ultraviolet?

SONDHAUS: It would certainly be a hazard but far more easily shielded against.

ODUM: This could affect any kind of biosystem, using natural light.

SONDHAUS: And also render windows opaque, and things of this kind.

FENN: I think we will go on to gravity and acceleration. Doctor Wood, you were going to give us your afterthoughts on that.

WOOD: First, I think it is well to emphasize that the discussion was primarily confined, as Doctor Bjurstedt pointed out, to the physiologic effects of exposures to acceleration of relatively long duration. By long duration, I mean exposures of more than a few seconds. This means that we touched very little on the important field of impact acceleration, except for Doctor Hendler's discussion of the possibility of a side effect of the protective restraint harnesses against impact accelerations on pulmonary function during the more prolonged transverse (eyeballs-in) accelerations associated with the launch and reentry phases of space flight.

Also, except for the discussion by Doctor Graybiel, concerning effects on the sense organs, we neglected angular acceleration as we did the effects of vibration, which also is a form of acceleration.

It is generally agreed, I believe, that the problem of long-duration acceleration is without question a potentially serious one, particularly in relation to launch and reentry phases of space flight. In relation to the present and contemplated G time profiles, there is no question that such exposures to acceleration will produce definite disturbances in physiologic function.

It is also pretty well agreed that the most susceptible organ system in relation to these effects is the pulmonary system. The pulmonary effects that become evident are first the decrease in arterial oxygen saturation, apparently due to atelectasis and edema formation in the dependent portions of the lungs; and second, a potentially more serious hazard that was mentioned but discussed only briefly; namely,

the danger of actual disruption of pulmonary parenchyma particularly in the uppermost (nondependent) portions of the lungs.

It is pretty well agreed that the magnitude of the disruption of pulmonary function is affected by the gas mixture that is being breathed; both the composition of this mixture, and its absolute pressure. High oxygen pressures, of course, tend to prevent or decrease the degree of arterial desaturation. However, there is good evidence that high oxygen makes the atelectasis-producing effects of acceleration worse, and, on the other hand, if the mixture contains a large percentage of nitrogen the problem of the susceptibility to the bends must be considered.

We talked relatively little about the effect of posture. The differences between eyeballs-in and eyeballs-out and eyeballs-down acceleration were mentioned. Except in relationship to the pulmonary disturbances, the very dramatic circulatory and consequent central nervous system effects of eyeballs-down acceleration were scarcely mentioned. There is no question that we need to know considerably more about these effects, particularly in relation to the basic mechanisms that produce them. We need to know more, as I mentioned, about the possibility of using variations in posture to protect the pulmonary system. There are some findings that indicate that some of these effects may not be as severe when the eyeballs-out type of acceleration is used.

It would be worthwhile to know more about the possible effect of pharmacological agents on these effects. Doctor Bjurstedt's description of some of the dramatic effects of atropine indicates that more should be done in relation to the effects of some of the pharmacologic agents on the reactions to transverse acceleration.

We need to know much more about the recovery phases from the effects of acceleration on the lungs. It is well known that recovery is relatively prolonged. Just what the mechanisms responsible for the delay in recover are is not clearly understood and should be looked into, as this may reveal more about the mechanisms responsible for the original disturbances.

We discussed somewhat the means of protection against the pulmonary effects of acceleration. There seems to be no question that the most practical means of protection is that which would be afforded by flattening out the G time profile—that is, exposing the individual to relatively low levels of acceleration for long periods of time, and by this means accumulating the necessary number of G seconds required to attain escape from or reentry into the atmosphere. If the levels of acceleration could be kept below 2 to 3 G, the physiologic effects would almost certainly not be important. Of course, this flat-

tening out of the G time profile is very much dependent upon the engineering problems which may be involved.

The next possibility of protection that was considered is so called fluid breathing. I think one of the most exciting things that came up was the fact that a dog has survived after being subject to fluid breathing for a period of 20 minutes. This places the very high degree of protection that would be afforded by fluid breathing within the realm of possibility. The physiologic and engineering problems involved, of course, are considerable. One thing that should be kept in mind, which was not mentioned, was that if one did have an animal breathing fluid with the intent of subjecting him to very high levels of acceleration, it would be important to remove all air from his gastrointestinal tract. The tissue air interphase of any air-conditioning cavity, whether in the lungs or the gastrointestinal tract, is subject to very high hydrostatic pressure differences during exposure to high levels of acceleration.

Very little was said about the possible protection afforded by pressure breathing. There is evidence that has been obtained in humans that pressure breathing does not produce appreciable protection against the arterial desaturation produced by eyeballs-in acceleration, but in some instances does provide subjective protection.

Another mechanism of protection that was not mentioned and that probably from an engineering viewpoint would be rather difficult to achieve is to rotate the astronaut around his longitudinal axis during the launch and reentry phases of space flight so that the period of acceleration in any one direction in relation to the body was very brief. Thus, accumulation of fluid or the production of atelectasis in the dependent portions of the lungs are largely circumvented. It is possible, by use of some type of periscope arrangement mounted at the axis of rotation, that a man could be rotated around his longitudinal body axis without becoming completely disoriented.

Another facet of the acceleration problem is the possibility of the development of increased susceptibility to gravitational and accelerative effects following long periods at 0 G. There is apparently considerable evidence now that the astronauts have had some degree of increased susceptibility to orthostatic effects. Possible means of preventing development of this condition and its importance were not discussed.

In relation to acceleration, there are a number of questions that cannot be answered adequately without the use of an orbiting space laboratory. These include the orientation problems which Doctors Graybiel and Margaria have discussed; the question of development of susceptibility to orthostatic and accelerative effects and others.

FENN: I was going to ask you about the possibility of turning a

man on his long axis. Couldn't he just turn over from supine into prone in the booster—go up in two steps and turn over in between; would it make matters worse or better?

GRAYBIEL: When test personnel are subjected to very high G levels, they might suffer injury, of course, and I am wondering if it wouldn't be a good plan to follow them longitudinally over years. They could be tagged, then have these repeated examinations, including good test batteries for possible brain damage, etc.

WOOD: That is true. Questions have been raised, particularly in relation to positive acceleration where there is no doubt that subjects are exposed to multiple, relatively brief periods of considerable degrees of stagnant anoxia of the retina and brain. A study of this was made in our laboratory several years ago in relation to the healthy subjects who (during World War II) underwent repeated exposures to acceleration with many blackouts and periods of unconsciousness. These subjects have very probably suffered more blackouts than any pilot has ever experienced. As far as can be determined, these subjects are still healthy and have shown no evidence of deterioration as a result of this experience.[171]

FENN: You don't really have a control to demonstrate the brilliant accomplishments they might have had if they hadn't been spun down a few times.

WOOD: True.

GRAYBIEL: But you have a before and after possibility here, which is so neat.

FENN: I suppose the reason you say the chief danger is in the pulmonary circuit is that there is a good means of protecting the systemic circuit. You just put him horizontal.

WOOD: That is true. There is not much evidence at the present time that the effects of transverse acceleration on the systemic circulation are particularly deleterious. There is some clear-cut evidence of rapid hemo-concentration during periods of eyeballs-in acceleration. It is not clear-cut whether this hemoconcentration occurs primarily in the lungs, due to loss of fluid from the blood stream associated with edema formation in dependent regions of the lungs, or due to a combination of leakage of fluid in the lungs plus leakage of fluid from dependent portions of the systemic circulation. Very probably part of this loss of fluid from the vascular system occurs in the systemic circulation, since in most dependent regions of the body there will be an increase in capillary pressure above colloidal osmotic pressure. Consequently, there will be some edema formation in the dependent portions of the body supplied by the systemic circulation as well as in the lungs.

This hemoconcentration is relatively rapidly reversible. The evi-

dence indicates that the increase in hemoglobin concentration has pretty well disappeared in a period of five to ten minutes after the exposure. Apparently, fluid is lost from and regained by the capillaries very rapidly.

FREMONT-SMITH: Have they been using serum specific gravities to check the hemoconcentration, because we do have reservoirs of hemoglobin, red cells, that can come out from the spleen under this kind of stress.

WOOD: This has been done by photoelectric means—measuring a change in concentration of hemoglobin—

FREMONT-SMITH: It is not a good blood volume method, is it?

WOOD: No. There is corroborative evidence, however. When healthy men or dogs are exposed to acceleration for five minutes, or so, not only do they show an increase in hemoglobin concentration during and after the exposure, but after the exposure there is a reduction in right atrial pressure.[172] Dogs also have a decrease in left atrial pressure. This means that either blood volume is reduced or there has been an increase in vascular volume or a combination of both.[173]

FREMONT-SMITH: Or vasodilatation.

WOOD: That is what I mean, vasodilatation would increase vascular volume. We rather suspect, however, that there is a reduction in intravascular fluid volume.

CALLOWAY: Does body size make any difference in the tolerance to these stresses?

WOOD: Very definitely. It is well known, for instance, that small mammals, such as rodents, can take very high levels of acceleration.

CALLOWAY: I mean within man.

WOOD: This has not been proved. On purely theoretical grounds, one might suspect that individuals with a small anterior-posterior chest diameter might be better off.

ROTH: One unusual position that we haven't covered is the man rolled up in a ball with his legs oriented one way or another with respect to the effective G load. I haven't gone through the reasoning to tell me whether it is going to help or not, but has this been looked at?

WOOD: It has been looked at in relation to positive acceleration. In the seated individual, one can get a definite degree of protection by bending over, so as to reduce the heart-to-head hydrostatic distance. Some pilots have used the crouched position during high G maneuvers. It is a position in which, at high levels of acceleration, there is perhaps danger of back injury. I do not know *a priori* any reason to think it should particularly protect against pulmonary effects.

ROTH: If the legs were positioned so that it was going from the back into the legs, it might push the blood into the venous pool of the leg.

WOOD: There is no evidence of which I am aware, at least from dog experiments, that tilting an individual either head-up or head-down affects the arterial desaturation that occurs, or that the head-down position was associated with the greatest degree of pulmonary arterial venous shunting.

FREMONT-SMITH: The dogs don't have nearly as much tendency toward pooling in the limbs, do they?

WOOD: This is true. However, as I said earlier in the conference, when we studied humans in a typical Mercury couch position, and then shifted them so that their legs were extended horizontally on a plane below heart level and exposed them to the same levels of acceleration interchangeably, there was no difference in the magnitude of the decreases in arterial oxygen saturation that occurred.[174] The acceleration was in the eyeballs-in direction.

FENN: Are there any other questions or contributions?

FREMONT-SMITH: May I express my deep appreciation to every one of you, and including Mrs. Swanson, who has been working silently but effectively throughout, for your coming to the conference and for your generosity in participating, and for the great helpfulness that everybody has shown.

Our special thanks to our Chairman. Orr Reynolds knew just was he was about.

FENN: Thank you all for coming and for contributing so willingly, and to the discussion leaders who have served and relieved me of so much responsibility. I think we have had a much more profitable meeting than I dared hope for. The product is one of those immeasurable things that you can't even talk about; most of the advantages may come after it is all over, in the things that we think about when we go home.

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