Proceedings

Symposia on Arctic Biology and Medicine

VI. The physiology of work in cold and altitude

Editor
Carle Helfferich

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ARCTIC AEROMEDICAL LABORATORY
FT. WAINWRIGHT, ALASKA

MAY 2-5, 1966

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VI. THE PHYSIOLOGY OF WORK IN COLD AND ALTITUDE

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Front row, from left: Col. Goltra, Drs. Reynafarje, Horvath, Chiodi, Blatteis, Evonuk. Back Row, from left: Drs. Hannon, Weihe, Saltin, Buskirk, Brauer, Dill, Grover.

PROCEEDINGS

SYMPOSIA ON ARCTIC BIOLOGY AND MEDICINE

VI. THE PHYSIOLOGY OF WORK IN COLD AND ALTITUDE

Symposium held May 2-5 at the
Arctic Aeromedical Laboratory
Fort Wainwright, Alaska

Symposium Organizer

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Arctic Aeromedical Laboratory

Symposium Chairman

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Editor

Carla Helfferich
The Geophysical Institute
of the University of Alaska

Symposium held under the auspices of
The Geophysical Institute
University of Alaska
Colllege, Alaska

EDITOR'S NOTE AND ACKNOWLEDGEMENTS

Only a minimal attempt has been made to force uniformity on the work of the investigators represented here. Whenever possible their own choice of form as well as content has been maintained, thereby hopefully preserving more of the flavor of their meeting as an exchange of complex and individual ideas among highly individual men.

The preparation of this symposium for the presses was made vastly more challenging by the unsolicited editorial assistance of an earthquake, a flood, and the Dead Letter Office of the Seattle post office. At least in part because of these overwhelming aids, undoubtedly certain typographical errors or mental stuffers have been cherished and preserved in this finished product which would better have been pruned in preliminary editing. There is even reason to suspect that a dead gnat has been immortalized as a diacritical mark. For whatever confusion or distraction such improprieties give to authors or readers, I apologize.

Full credit for whatever is right with this publication should be given to Dr. Steven M. Horvath, chairman of the symposium. My thanks go also to Dr. Eugene Evonuk, to the staff of Jessen's printing office for their extraordinary effort in the final preparation, and especially to the staff of the Geophysical Institute for their tolerance, patience, and help.

C. Helfferich, editor

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*Since no official guest list was kept during the proceedings, some names may have been inadvertently left off. Ed.

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ARCTIC AEROMEDICAL LABORATORY

Sixth Symposium on Arctic Biology and Medicine

"THE PHYSIOLOGY OF WORK IN COLD AND ALTITUDE"

OPENING REMARKS

COL. GOLTRA: I would like to welcome officially the participants in this symposium, guests, and staff members to the Sixth Symposium on Arctic Biology and Medicine. Following the opening remarks of General Jones, the Yukon Commander, I would like to say a few other things. Because of the demands on General Jones' time, I will defer those remarks until after his address. Sir.

GENERAL JONES: Thank you very much, Col. Goltra. Dr. Horvath, distinguished guests, I wish to extend to you a warm welcome to the Yukon Command and Fort Wainwright. We are indeed gratified to have such a distinguished group of physiologists at Fort Wainwright and the Arctic Aeromedical Laboratory as participants in this scientifically important symposium. The significance of your work and its relationship to the military mission in this community is not sufficiently appreciated. Military interest is expanding to areas that were once considered uninhabitable and forbidding, such as the Arctic. The geopolitical importance of the Arctic Basin and the Arctic mountainous area neccessitates much greater knowledge and special understanding of these areas. New concepts in limited warfare and counter-insurgency operations such as we are now experiencing in Southeast Asia, particularly in Viet Nam, may be extended to operations in cold and mountainous areas. In light of this, and the constantly changing military requirements, it is singularly important for us to understand the physiological responses and limits of man to these unusual stresses, in order to utilize human capabilities maximally in the accomplishment of our military mission. It is also necessary for us to understand what measures can be taken to improve the functional capability of military personnel in these adverse and hostile environments. Further, it is imperative for us to know how some individuals are capable and others are incapable of adjusting to these environments. It is equally

important to be able to establish realistic physical criteria for military service in these areas, similar to those that we have established for selection of the astronauts. In simple terms, first we must learn to live with the Arctic environment, and after that we must go on and discover ways to make the seeming obstacles of the Arctic actually work for us in the accomplishment of our military mission. Now these are but a few of the problem areas with which we in the military have concern, and I feel that through symposia of this nature, wherein are gathered together eminent and knowledgeable scientists, some of these questions might be resolved; more importantly, you will provide guide-lines for future research. I have been at this post only ten days and I think that I am extremely fortunate to have the opportunity to meet such a distinguished group of people who are giving their lives for study, for this is the keynote of progress. I personally am appreciative of your coming here and participating, because I know that all of you people are very busy. I have looked over your agenda; you have an agenda which is very challenging, so you have the knowledge, you have a challenging agenda, you have a good environment, and I am sure that this is going to be a successful symposium. I would like to give particular recognition to our out-of-country guests. I understand that Dr. Margaria from Milano, Italy, was not able to be here; I would like to welcome particularly then Dr. Balthazar Reynafarje from Lima, Peru, and Dr. Wolf H. Weihe from Bern, Switzerland. If those two gentlemen will please forgive my cold and my lack of being a linguist in pronunciation, I thank you. Again I want to say my very best wishes for a successful, a most successful conference here, and I hope to meet you all personally tomorrow night if not before.

COL. GOLTRA: Thank you, General Jones. I am struck by the malapropism of the entitlement of this meeting. It's labelled a symposium. A symposium is a drinking party, a feast; in ancient Greece it was a drinking together usually following the banquet proper. It was associated with music, singing, dancing girls, and lastly, conversation. Hence, the word has come to mean a kind of social gathering at which there is a free interchange of ideas. Lastly, the word has the meaning of a conference at which a particular topic is discussed and from which ensues a publication. So in truth, this will not be a drinking festivity or a series of feasts; it will be a scientific gathering at which there will be a free interchange of ideas. In the past, these symposia have been extremely productive both from the viewpoint of the scope of the ideas presented and the depth and profundity of the ideas as they are written.

Again I would like to extend to you a cordial and warm welcome to the

Arctic Aeromedical Laboratory and to Fort Wainwright. For those of you who are not familiar with this laboratory, it is one of six laboratories which are parts of the Aerospace Medical Division headquartered in San Antonio, Texas, which is part of the Air Force Systems Command, that command in the Air Force which is concerned with the development and direction of all research and development. All techniques in this direction are under the command of General Schriever. As a laboratory, we are the smallest in the Aerospace Medical Division. We have approximately fifty people working here; we represent a significant cross section of scientific disciplines, to include anthropology, electronics, physiology, botany, medicine, engineering, and so on. We are about one-half military, one-half civilian scientist and/or support personnel. Our mission, as you might well determine, is concerned with the basic problems of the Arctic, which include survival, personal equipment which might enhance the survival, and also an investigation into the basic physiological problems of exposure to the cold. This includes cold injury, cardiovascular physiology, pulmonary physiology, and the physiology of work under the stress of exposure to acute and chronic low temperatures. This has been our concern now for seventeen years since this laboratory has been open, and I am sure that it will continue to be our concern. We have had the unusual good fortune in the past seventeen years of attracting and being able to utilize the skills of some eminent people; some of you in this room have worked here before. No laboratory is worth more than the people who staff it, independently of the wealth of the laboratory or the availability of funds, and as I have said, it has always been our extreme good fortune to have extraordinary men here. We are still in the enviable position of having extraordinary men working here. I would like to turn this over to Dr. Horvath of the University of California, who will act as the moderator of this symposium or drinking feast.

DR. HORVATH: Ladies and gentlemen, actually I think the drinking feast did start a little bit early. Because some of us spent a good deal of time waiting in an airport, we had time to discuss this conference and we may have solved some of the problems that we're going to discuss later on today. I have just a few minor comments to make, first of all, about the operation of the symposium. I would like to emphasize, for the benefit of everyone concerned, that our primary interest is not only in the exchange of the fixed papers which are coming, but more important that our concern is for the discussions which will occur subsequent to these. As many of you know, the discussions are much more important than are the actual factual materials which are being presented,

because it is on the basis of the discussions of new ideas, new thoughts, new concepts, new approaches to problems which at one time were thought insolvable or at least not approachable can now be made much more readily. In order for us to obtain the maximum benefit from the discussions, we are hoping that most of you will remember just exactly who you happen to be and will so inform us at some time during the questions which you will pose. It would be nice for us who are visitors to become acquainted with the people in the laboratory. The only other announcement I have to make relates to afternoon programs. On Tuesday afternoon we're going to have an opportunity to go through this laboratory so that we can talk to the people who are working here and again further an exchange of knowledge. On Wednesday afternoon we will be going over to the University of Alaska, where we will be at the Museum and also at the Arctic Medical Institute.

I'm not going to have much to say about the multiple programs to be discussed at this conference, since the experts have been assigned specific topics and they can do it well. But I would like to spend a little bit of time in setting the stage. In actuality this conference, as it's entitled "Work, Altitude, and Cold," is a definite misnomer, because it would be impossible to discuss the three topics without taking into account the entire knowledge in the fields of physiology, of biochemistry, of medicine and – unfortunately for most of us, I think – in the field of psychology and maybe even a little bit in the field of sociology. What we are trying to answer today has to do with the integrated responses of the human organism, and when you start talking about integrated responses, you are discussing multiple factors of which most of us, I am afraid, know very, very little. Our concept of the way in which the organism responds has been limited for most of us to a few individuals, those whom we have studied. But we're going to have to talk about groups, about hundreds and thousands acting not as individuals but as units, although our basic information will be coming from individuals. It's from the group standpoint that we will have to discuss eventually the problems of the ability of man to adjust to these three major parameters. As my old professor of physiology once told me, and he happens to be sitting here – Dr. Dill – he pointed out to me that the most important information for the understanding of integration or homeokinesis (homeostasis) is to study man at work. When a man has to exercise he undergoes practically all of the adjustments or has to integrate practically all of the adjustments which he as an organism is capable of performing. He has to take all those into account before he succeeds, and the difference between the successful performer in work and the poor performer in work depends upon how well his own system has been able to make these adjustments and adaptations. Now, this

means that the material we are going to discuss is in all the textbooks of physiology, medicine, pharmacology, biochemistry, even psychology; we shall try to get beyond them, that is, to the fields which are not as yet written.

I have considered approaching my task by presenting a few illustrative problems. May I start off with the simplest one and in this way possibly identify the kind of problems, new problems, that have come to our attention in the very recent past. Most people, when they talk about man at work, have been primarily concerned with the responses of the man to hard, intense, severe work, work which measures his utmost capacity, but in most instances very few of us ever perform at that level. Most of us are working primarily at levels which are, say, only those at two or three mets. Because of our social and economic organization, the significance of the total capacity of the organism has been lost to many of us. We look upon it as a figure up on top, as something that is hopefully to be attained. In the process of looking very carefully at this goal, we have forgotten how man responds to a long-term type of stress where he has to work at 33 percent or 50 percent of his capacity. We have been very interested in physiological adjustments occurring in man working for extended periods. In the process, of course, we had to determine the capacity of the organism, so we do make that measure and then we try to set up experiments in which the individual is working at various percentages of his capacity.

In our initial experiments we were able to determine that a man can work for periods of up to eight hours at somewhere between one-third to one-half of his capacity, depending upon his initial endowment. The highly trained athlete or well-trained individual can perform for eight hours a day at 45 percent of his capacity, but the ordinary individual who makes up the greatest percentage of our population is really unable to work at more than one-third of his capacity. Our new experiments, therefore, have been designed to see how rapidly or effectively the individual can maintain his work ability at that level, as modified by a number of factors. In the first instance we used variations in caloric intake and composition of diet, and in the second instance we attempted to determine what would happen if man were exposed to extreme ambient temperatures (hot and cold), and then we try to combine these. When our subjects were working at approximately one-third of their maximum capacity for eight hours a day, we gave them, instead of a 3,000 calorie intake with the normal distribution between carbohydrates, fats, and proteins, a diet with the protein intake as low as possible, one-tenth of a gram of protein in their diet. It was rather surprising that most of our subjects were unable to complete the task without excessive fatigue; they refused to continue to work for more than six hours. Then we tried to determine for how many consecutive days we could ask them to work at this

level and duration. We did this first of all in normal temperatures, that is, 25 degrees Centigrade, fifty percent relative humidity, and then we did it at seven degrees Centigrade, relative humidity about 85 percent. We kept the amount of clothing on them essentially the same, in other words they had nothing on but shorts and shoes and socks. It was a little bit disturbing to find how much more difficult it was for our subjects to work in the cold environment for a series of consecutive days. We were quite easily able to get groups of individuals, we had somewhere in the neighborhood of fifteen subjects who were able to do this outside in normal temperatures without any great difficulty for four days in a row, that is, four days of eight hours at one-third of their capacity. In the cold environment, despite the fact that the individuals were somewhat better off when compared to those lying quietly at those temperatures, we were unable to get them to maintain this level of work for more than two and a half days. The longest period of time that any of these individuals did work was for a total period of 25 hours, slightly over three days of total work. Your appreciation of the problems facing the human organism is completely altered when you are considering these physiological problems in contrast to those occurring when he's being forced to do maximum activity which he then does not have to repeat for two or three days. We are now hopefully going to add another stress, i.e., altitude, to see what is happening to the physiological stability of the exercising organism. We will eventually have to combine this with cold and natural altitudes.

I hope this sort of conference will be interested in trying to develop new ways of evaluating the response of the human organism, to get away from our more straightforward precise ways of handling the problem of man in action. Too often we have been more interested in getting small concrete bits of data on relatively small numbers of people in fixed situations. The use of multiple stresses, such as low ambient temperatures, prolonged exercise, nutritional alterations, etc., should provide us with a new tool to evaluate the ability of men to maintain homeokinesis under maximum stress. I just wanted to bring this up as an illustration of the kinds of attitudes we hold towards man at work in these environments. From our studies of the biochemical things that are going on, we're pretty sure that there are a lot of strange things happening in these very prolonged types of work in contrast to the shorter periods of work.

What are some of the other problems which I hope we will be discussing today? The title of the symposium in a sense implies that we are interested in the cross-effects of different series of stresses. Here we have three major stresses, superimposable, separate, or superimposable to varying degrees. In most cases people who have looked at any one of these have looked at only one, and never

or very seldom looked at more than two. Very few experimental studies have been made in which all three of these have been combined, yet these are not the only kinds of stresses that face the human organism. Take for example something which is very practical both from the civilian and the military standpoints, and that is what happens if you have a mild blood loss. Let's say you lose 500 to 1,000 milliliters of blood, when you are being forced to operate under these conditions of work, of altitude and of cold; the combination or addition of this fourth stress, which is very real and realistic—it happens all the time—has not been adequately evaluated. What will we do for the care of individuals who have lost a fair amount of blood in the cold? You can add another of the major problems which is important in the cold, and that is dehydration. We know roughly what happens to man under normal conditions but the influence of dehydration which so frequently occurs at altitude has not been evaluated under a combined stress load. We can add additional stresses to individuals being under what may amount to a state of sensory deprivation. Being up at high altitude, cold, isolated, can cause in the individual a tremendous number of changes which we have not as yet evaluated. The sensory deprivation experiments in themselves suggest the intensity of the stimulus which is being imposed on the human organism. Here we have now the possibilities of in a single organism adding on practically every stress, any stress that we can identify—and yet we have not considered these very effectively. It's most important that in our discussions we take into account the possible interrelationship of other stresses in addition to those of our primary concern; in order to do a good job, we should take into account the psychological stresses and the social stresses. Most physiologists find it very difficult to appreciate the tremendous role that these factors place on the human organism.

We have another major problem, the question of the effectiveness of our training programs: how effective is cross-acclimization to various other stresses upon the ability of man to respond to a stress such as cold? We know, for example, that the physical condition of the individual, as measured by his maximal oxygen uptake or his maximal work capacity, can modify his responses to heat—we know he can modify his responses to altitude, we know he can modify his response to cold, and yet we have never really precisely identified how this cross-adaptation, how these cross-homeostatic equilibriums, homeokinetic equilibriums, do cause that individual to make better adjustments. Neither can we precisely say that if you have a high level of physical ability, a high level of physical performance, that you will necessarily do just as well at altitude as an individual who is not quite as competent. We think that he can do better, but we have inadequate evidence for such a statement; we need a great

deal more precise work on this before we can accept this concept. We do not know whether an individual can adjust if he is required to perform this work over extended periods of time. Neither have we made another necessary correlation; namely, the influences of the central nervous system upon the individual's response to such a series of environmental and work stresses. We've nearly ignored this factor in the past mostly because it has been, according to us, impossible to study effectively. I am sure that the new techniques which are now available will make it much more possible for us to obtain such information.

Another aspect of all our studies on the human organism which we have to take into account—and it is becoming now I think a very pressing problem—is how effectively have we evaluated the responses of the organism by the tools that we have employed to measure his responses? I think some of you are familiar with the work that Dr. Lamb has been doing, in which he has shown somewhat interestingly and somewhat unfortunately for some of us that the application of a great many sensors to the human organism tends to reduce his ability to respond to a stress; that if you get rid of some of these sensors, you get an entirely different kind of picture of his ability to respond to stress. In essence what this really means is that we must devise ways of evaluating the human organism in such a way that he does not really know that he is being tested, and this I think is going to be a problem which will require a great deal of effort and ingenuity to resolve.

One of the topics which I am sure we will discuss is the question of mountain sickness. We have no idea of the relative incidence of this in a large group of people. We really need to study this in, say, tens of thousands of people, we should send that many up to altitude to see how many of them get it. What are the relative degrees of incidence, what is the severity, how rapidly do they recover, how many times can they go back up and come down again before they get it? This provides a statistical picture, and although I'm not a strong believer in statistics as such, yet I think we need some of this kind of information in order to enable us to make a better evaluation of just exactly what is going on, so that we do need to have a better identification of the problems of altitude and also of cold and of work in a large percentage of the population, rather than in the small portion we have studied. In this regard we have not taken full advantage of the peoples who arenaturally living at these higher altitudes, where they have been exposed for generations to such environmental stress. Usually when we've gone up we have been able, if we've been fortunate, to study ten or twelve individuals. In a sense, the very individuals whom we study at these high altitudes are ones who themselves are somewhat peculiar, because if they weren't they wouldn't let us study them.

Many of our subjects basically have some sort of quirk in them physiologically, biochemically, that almost induces them to want to be subjects. Perhaps we've got some wrong information from this particular group. There may be hundreds of other subjects who would not respond exactly the same way. I'm not telling you these things because I believe them to be true, but I'm raising them as questions because I think unless we answer some of these questions, we'll never be able to give a broad interpretation of the problems that we're facing.

One reason for at least three main contributions in this particular symposium is the failure on the part of most scientists and also of practical individuals to understand that there is a difference in our ability to respond to any stress depending upon our age. It is true that although most of the actual combat or the actual experiences at altitude, in cold and during work are done by relatively younger people, we cannot escape the necessity of sending people of different ages up there at one time or another, and in general I think you can appreciate that it's very fine for you to be sitting down at 400 feet and making decisions as to what may be happening at 18,000 feet, but in order for you to appreciate fully what's going on, you might have to go up there yourself. We must get an appreciation of the ability of the aged to respond. Interestingly enough, as Dr. Dill will be telling you later, we are beginning to obtain information of this sort, and to realize that the kind of things that have happened to younger people do not necessarily happen to older individuals. There's a great deal of difference between the more mature male and the younger male, and then furthermore there's been an appreciation I think recently forced upon us of the fact that there might be advantages or disadvantages to being of one or the other sex, and that these factors too come into the play and make us respond somewhat differently. We must understand what happens to individuals of all ages, of both sexes. I would like to make one last statement, because in essense most of the problems that we have been thinking about, Dr. Evonuk and I, in our discussions of this conference, in a sense we have sort of parcelled them out to you, hoping that you would by consequence of our integrated effort, come up with the other things that we haven't directly assigned to anybody. I really couldn't find anyone who has been thinking seriously enough about the psychological aspects, changes in psychomotor ability, changes in learning, behavior, and so forth, of individuals under these stresses. We have not really spent a great deal of our effort in trying to assess the motivational factors which enable an individual to keep on going against all sorts of stressful situations. There has been no truly direct attack by a combination of behavioral scientists, physiologists, physicians, biochemists, and so forth. This is going to be one of the main areas of endeavor in the future

because one of the problems that face all investigators when they themselves go to altitude is their own failure. They make many mistakes in immediate performance at that time which may have resulted in some erroneous impressions when they return. It's amazing how easy it is for you to forget what you did wrong up at altitude. Of course there's always the hope that there is some way in which we can relieve the organism of all of its responsibilities for adaptation, and that is to provide it with some sort of an agent which would take care of all of these adjustments in anticipation of the stress which will come. Therefore we spend a great deal of our effort looking for the right drug, the right chemical combination, to give to an individual either before he faces the stressful situation or after he's there, and then we'd like to find the same sort of drug to do something for him when he returns so that he can recover more quickly and more effectively. We do have a whole gamut of problems to resolve, from the initial moment when we decide to combine a series of stresses to the actual accomplishment of individuals during exposure to the stresses and then finally their ability to recover from all of these stresses, and their successful recovery therefore determines how easily they will return to make further endeavors under these particular series of environmental conditions. I think it is only fair that I stop now, because the basic information is coming not from me but from those of you who are around the table and those of you who will be asking questions.

DR. DILL: In connection with that very interesting statement you made about your experiments on men with virtually zero protein intake, do you recall the study by Austin Flint about 1875 or so that was reported in about a hundred pages of a New York medical journal? It was on Edward Payson Weston who was a very celebrated walker, at that time 31 years old, and I think he continued walking for another 50 years or so. Flint studied him over a period of five days, in which Weston intended to walk a total of 400 miles, with a maximum he hoped to attain in one 24-hour day of a hundred miles. He didn't succeed; his best performance I think was on the third or fourth day of 87 miles, and he covered a total of--I have forgotten whether it was exactly 340, but it was something of that sort. Flint did extremely detailed analyses of food intake and of the composition of the urine and feces, body weight, daily temperature, and a few other observations. However, the major intent of his study was to answer the question, is there increased destruction of protein during hard work? And Flint found a considerable increase in urinary nitrogen during this period.

DR. HORVATH: I didn't know about this and therefore you can see that I have learned something already. Initially, we see very little change in nitrogen excretion and then as we begin to see more nitrogen excreted in the urine, our subjects start to fail. We also did another one on which we did report, and that was an attempt to keep people in a cold environment relatively quiescent, letting them only work at their metabolic cost of shivering. We have never been able to follow this up, mostly because we have been unable to get subjects who want to repeat it. We put them on these diets, and then just put them lying quietly in a cold room. We were planning to keep them there for twelve days; we were able to keep a group of individuals on a normal diet at that time with a great deal of effort on our part, for a period of just six days, but with none of the experimental diets that we tried, zero protein or 1,500 calories, normal distribution or 1,500 calories with no protein practically speaking, were we able to keep any of our subjects in for longer than 36 hours. They all went out with various minor disabilities, they refused to stay in; more importantly, despite the fact that one of the things that we wanted to measure on them was their ability to work after their exposure, in all these combined exposures of cold and diet, cold and dietary factors, we were unable to make our study of their performance capability afterwards because the men couldn't work anymore. So if you use this as a criterion, they were completely incapacitated, their performance would have been practically nil. One man, the best of the group of nine subjects who didn't last during the cold exposure, the longest period of time we were able to get him to work was one minute on the treadmill, at which time he said–excuse me, ladies–but he said, the hell with this, and he just stopped and he got off and quit. We couldn't get any others to do anything. Well, part of this was the fact that their feet were so cold, and we forget that this is one of the major limiting factors–here in Fairbanks you don't forget, because you live with it all the time, but many people do forget that the limitation for performance really for many people in cold is their feet and their hands. But if you incapacitate them in that regard then you incapacitate them as far as their total performance is concerned. I think these are areas of real interest and concern for investigaton. We haven't been able to spend as much time on long term studies, partly because it's been very difficult to get people to last that long, we get worn out ourselves after a while, and then we can't repeat these experiments indefinitely. We do this for a couple of months in one year and then we're about finished until the next year, and by that time we get into the problem that Dr. Dill is going to talk about, namely, that as we get older our responses are going to be different, so we can't really predict what's going to happen from one time to the next.

DR. EVONUK: You'd better get people in uniform. They can't quit on you.

DR. HORVATH: We don't have those availalbe where we are. When I was with the Army we were able to get subjects in adequate numbers, but I think even now it would be difficult.

COL. GOLTRA: I think this should be a serious consideration, because we are the people who are going to reap the benefits.

DR. HORVATH: I think a great help for the long term studies that give us valuable information would be to have subjects from the service available to us, but this is hard to arrange, and I know most of you in this room actually have been trying to get subjects of this type because this is the group that would give us the best cooperation. We can't depend on the ordinary civilian any more. As you know we're getting a different social attitude towards many things; all you have to recall is the experiences that people have been having in the last few years, at least in the large cities, where someone will be attacked and badly beaten up and robbed or whatever it is, and there may be 15, 20 people standing around the periphery who won't help the victim. This is one of the reasons I have brought up the problem of social factors in the ability of men to perform, because unless we take some of this into account–and we're getting a kind of problem here which makes one shudder, but it's going to be more serious as time goes on, as the attitude of people change as a group, not as individuals. but as a group, then we may find that all the studies we have been doing on the ability of individuals to perform will be negated, completely negated, completely unapplicable, completely useless, because the social environment makes it impossible to utilize this information. I say this is going to be one of our major problems, and I wish there was some way that we here could bring this up. I wish there were some people who were really seriously interested in group behavior so that we could interpret the physiological and biochemical and medical problems of the individual in terms of a group, but I don't know of anyone who is doing this with the intensity and effort which I think we need to put into it.

DR. HANNON: With respect to your comments here about subject motivation, last fall we were doing studies at Brooks Air Force Base, an army group on the Air Force post, and as part of this study, we did a psychiatric examination of the subjects who volunteered for this study. Eight of these subjects were conscientious objectors, they were not in the military, but were assigned to our laboratory as civilians; the other eight were medical laboratory technicians, army people, from Brooks Army Hospital. The psychiatric examiniations turned up many things that most of us had suspected. It turned out that two of the military people were also conscientious objectors basically; of the 16, 11 had psychoses of one sort or another, one was a schizophrenic, who had not yet been diagnosed, and two were normal.

DR. HORVATH: You may have got that completely wrong; maybe of the sixteen, fourteen were normal and two were abnormal, the so-called two that were considered normal may have been the abnormal, in a way. You might be interested in something else which I think suggests the importance of knowing something about the personalities of subjects being evaluated. We have been studying some pre-schizoids, young boys the ages of 16 to 18, comparing them with "normal" youngsters of the same age and physical activity. We used the Balke test in order to determine not only their maximum oxygen capacity but the energy cost of working at different grades (intensity levels). There was a small difference in maximum oxygen uptake but a marked difference in the duration of the exercise to maximum fatigue. The pre-schzoid youngsters were definitely below the levels found in the other young men. For example, the latter walked for some 26 minutes (25% grade) while the pre-schzoids went for only 19 minutes (18% grade). However, most interestingly, the metabolic cost of walking at the lower grades (up to 13 percent) was statistically less for the pre-schzoids, despite their lower maximum oxygen uptake; and the heart rates for this performance of work were much lower. This is very similar to some of the things that Dr. Dill has found. This raises a question about differences between groups of individuals and how the individual responds due to group pressure. This is the sort of approach I think that we must take into account. We don't know enough about our subjects, we don't know enough about people; until we look at all these variables, including group behavior, we're going to get some wrong impressions. What an impression you might have obtained with he prior results compared to another group which had a different normal (?) response. We have utilized psychiatrists and psychologists in our attempts to evaluate our subjects; I have been very much impressed that they have better

than a 50 percent accuracy, a good many of the subjects whom they predict will fail actually do fail.

Unless we know more about the population we really can't make adequate judgments as to the effectiveness of any of our stresses or the adaptive ability to respond to these stresses. We must consider not only the individual but the group. How much different will the individual respond if he acts as an individual or is in concert with a group? Remember mob psychology.

RESPONSES TO COLD, WORK, AND ALTITUDE OF AGING MAN*

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Introduction

We have been concerned during the past five years with the responses of man to environmental stress and to work as related to age. The subjects have included physiologists who took part in high altitude studies in 1929 (two men) and in 1935 (six men). The altitude studies at White Mountain extended from the first day after arrival up to seven weeks later in one man. Subsequently, a study of acute exposures in the altitude chamber lasting less than one hour was carried out on three young men (19 to 35 years) and one old man (74 years). Work performance was of major interest. Hemoglobin and other blood components were studied at White Mountain in 1962 and 1964.

Methods

In the course of these studies much was learned about equipment best adapted to exercise studies in the field. These lessons have persuaded us to adopt some new procedures that have been described elsewhere (1); they are summarized here. The new procedures do not give different results but they require less cumbersome and less expensive equipment than was formerly used.

The ergometer and its use. We use a bicycle ergometer designed by von Döbeln and made by A.B. Cykelfabriken Monark, Varberg, Sweden. It was delivered in Bloomington at a total cost of $297.00. Its weight, 30 kg, and

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design make it readily portable. The load can be adjusted in a few seconds by means of a screw-regulated pendulum. The ergometer is used either for evaluating performance at various steady state levels or during successive increments in work rate up to the limit of aerobic and anaerobic capacity. One observer must devote part of his time to adjusting the work load since frictional resistance may change appreciably during the course of an experiment. Before work starts it is essential to adjust the seat height to the subject: maximum efficiency and peak performance require a seat height that permits nearly full extension of the leg with the feet firmly on the pedals. Our usual procedure for evaluating maximal performance is to start with zero load and to increase it by 150 kpm/min each minute with the pedaling rate, 50 rpm, synchronous with a metronome. An alternative procedure is to begin with a warm-up period of a few minutes with a light load and with or without metabolic and cardio-respiratory measurements. Then the stepwise increase in load begins. The subject decides when he has reached his end point; when one is dealing with athletes or ex-athletes, the spirit of competition stimulated by the observers' words of encouragement ensures all-out performance. Seven indexes of achievement can be obtained: peak work rate, maximal pulmonary ventilation, maximal rate of oxygen consumption, maximal respiratory exchange ratio, maximal heart rate, maximal blood pressure, and blood lactate.

Evaluating pulmonary ventilation and rate of oxygen consumption. The preferred breathing valve is the modified Otis-McKerrow valve assembly sold by Warren E. Collins, Cat. No. P339, $65.00. The dead space is about 30 ml; this estimate does not take into account an undetermined but probably small amount of mixing through turbulence in the expiratory phase.

This valve system is superior to the Hans Rudolph valve in that its resistance at high rates of flow is much less. From measurements made by McKerrow and Otis, the two valve systems compare as shown below:

Flow rate, l/min	100	200	300	400
Resistance, cm H_2O				
Hans Rudolph valve	1.3	2.9	4.6	7.1
Otis-McKerrow valve	0.5	0.8	1.1	1.6

Its low resistance at high flow rates is achieved by the use of two pairs of J-valves and large bore inlet and outlet and mouthpiece tubes; each is 3 cm inside diameter. Collins furnishes a mouthpiece large enough to fit the 3 cm tube. For air connections to and from the valve assembly we use non-kinkable plastic

tubing 4 cm inside diameter (Collins, Cat. No. P521, $2.00 per foot). One length leads from the outside air source to the breathing valve, the other from he breathing valve through a mixing chamber to the gas meter. Rubber connectors, 5 cm long, join the plastic tubing to the breathing valve, mixing chamber and outside air source. They are supplied by Collins, Cat. No. P552, $1.50 each. For cleaning the valve, mouthpiece, and connecting tube, warm water with detergent is used after the unit is detached from the outside air source and mixing chamber. The mouthpiece is left in place. A mixing chamber is used for sampling expired air for analysis; ours is made of stainless steel in the university shops. It is a cylinder 16 cm long and 16 cm in diameter, provided with a baffle to facilitate mixing, and capped at each end by a truncated cone 6 cm long ending in a tube 3 cm inside diameter and 5 cm long. The lower cone is provided with 6 brass tubes about 5 cm apart, 2 cm long, 5 mm outside diameter and 2 mm inside diameter. They are made by drilling holes in brass rod and rounding the exit end. The small diameter of the hole prevents more than a negligible amount of air from escaping when a sampling tube is replaced.

Samples of expired air are drawn from the mixing chamber into glass Syringes, 50 ml, with Luer-Lok metal tip (Arthur H. Thomas Co., Cat. No. 9404, $8.00 each). The syringe can be used with rubber tubing and a pinch clamp if analyses are to be done within a few hours. Since diffusion losses through rubber tubing become appreciable in 12 or more hours, we prefer to close the syringe with a metal stopcock (Becton, Dickenson & Co., Rutherford, New Jersey, Cat. No. XMSO1-T, No. 18, $2.86). For connecting the tubes to a teat of the mixing chamber or to the Haldane apparatus we use amber latex tubing 3 mm bore by 1.5 mm wall. The syringe is lubricated with ethylene glycol and is washed frequently and dried completely before lubricating. Samples are drawn by quickly flushing the connections and slowly filling the syringe. In steady-state exercise we read the meter each minute and draw two successive samples each over a two-minute period. In the Balke test of all-out performance the meter is read at 30-second intervals and samples are drawn during each of the last few minutes of work. The subject attempts to complete a full minute or at least a half-minute; he signals when he is within a minute of his end-point. Sampling-tube racks, holding 4 tubes each, are made of wood in our shop. The tubes are supported plunger down in holes large enough to accommodate the neck of the syringe. The end of the plunger rests in a depression drilled into the base of the rack. In this position the sample is kept under a slight positive pressure.

The mixing chamber is mounted vertically on the intake side of a high precision, low-resistance gas meter, Model CD-4 manufactured by

Parkinson-Cowan, London, England. This meter can be procured from Instrumentation Associates Inc., 17 W. 60th St., New York City, $225.00. One dial reads 10 liters in tenths; the other, 100 liters in tens. A short thermometer reading from 0° to 50° C (Arthur H. Thomas Co., Cat. No. 3599D) is installed in a length of brass tubing fixed to the meter inlet with a rubber connector. A packing nut holds it in proper position. Another thermometer is similarly placed in the meter outlet. Both thermometers are read from time to time; the mean temperature is used for calculating the volume to 0° C.

This meter is superior to the spirometer for maximal performance: its resistance to breathing is the same, but it weighs only 12 kg, and observations can continue indefinitely. Even a spirometer of 600 liters capacity often is too small to permit a complete record of all-out performance. The accuracy of the two is equal although calibration of the meter is essential.

For gas analysis we employ the Haldane apparatus. A skilled worker can learn in a few days all the tricks of operating it and keeping it in working condition. In contrast, breakdown of modern, more sophisticated equipment may be disastrous when the success of a program requires adherence to a schedule of experiments.

In the measurement of all-out performance, systolic and diastolic pressures are read before starting, at one-minute intervals after starting and during each of the first five minutes of recovery. The diaphragm is strapped over the brachial artery; tygon tubes 1/8" inside diameter, 3/8" outside diameter (3 x 9 mm) and about 100 cm long are supported so as not to swing against the subject or any part of the equipment. We use the Kompak Beaumanometer with the Air-Lok cuff (Aloe Scientific Co., St. Louis, Missouri, $43.50). The observer inflates the cuff at about the 30th second of each minute and notes the systolic pressure. If a cardiotachometer is not in use he slows the pressure release enough to count the heart beats for 15 seconds; this count is noted and then the diastolic pressure is read and recorded. With practice, such counts give rates in beats per minute usually within ± 2 of the tachometer rate.

Heart beats are monitored, commonly with a telemetering system, since this frequently is useful in field studies. Either that of Telemedics Inc. or that of the Gulton Industries is satisfactory.

Venous blood for lactate determination is drawn from the antecubital vein in the sixth minute after work ends; this is when the highest lactate level generally is reached after exercise of this type and duration. The enzymatic method is used; a bulletin describing it is supplied with a complete kit adequate for 25 analyses by Roehring Mannheim Corp., 10 Vessey St., New York City, at a cost of $10.00. The blood sample is diluted with perchloric acid reagent and

centrifuged. The supernatent fluid can be analyzed at once or may be held near 0° C for days or weeks before analysis.

The preferred interval timer is sold for $28.00 by the Cole-Palmer Instrument Co., 7330 North Clark St., Chicago, Illinois. It is placed so that one observer, in addition to his other duties, "counts down" the last five seconds of each half-minute, calling out the time at the end of each minute. The timer also is in view of the observer attending to blood pressure.

Four observers are required for an all-out experiment using the above equipment. One attends to blood pressure and adjusts the load. A second makes and records meter readings every 30 seconds, notes expired air temperatures, and records respiratory rate. The third draws gas samples, makes 30-second counts of respiratory rate and calls them out to the meter reader. The fourth attends to the heart rate record and calls time.

A scaffold for field or laboratory studies can be made of 2" x 4" pine in a few hours. It has shelves on each side and in front of the subject. One side-shelf supports the Baumanometer; on the front shelf is the metronome, drinking water, tissues, etc. A central overhead beam running from front to back has screw-eyes and a pulley through which passes the nylon cord supporting the breathing valve. Another screw-eye pulley is at the top of a corner post. In this way the valve can be moved to suit the subject's desires. The overall dimensions of our scaffold in cm are 87 wide, 130 long, and 210 high, with a shelf height of 135. The dimensions are not critical although the width should be slightly less than door openings.

Discussion

The advantages of this system over the treadmill-spirometer system (including the Hans Rudolph valve) are manifold. The ergometer and gas meter together cost $525.00, i.e., from 10 to 20% of the total cost of the treadmill and 600-liter spirometer; the treadmill alone costs from $2,000 to $5,000. The difference in weight is even greater. Shipping and even moving within the same building are easy in the one case and formidable in the other.

When this system is used in conjunction with he Otis-McKerrow valve plastic tubing without cocks, resistance to breathing is far less, especially at high work rates. A continuous series of observations can be made where this system is used, whereas with a spirometer there are interruptions while it is emptied. If a series of Douglas bags are used, the operation of flushing out, emptying and gas sampling is more cumbersome and probably more subject to error. In addition, the series of cocks and the right-angle turns increase resistance to air flow.

One disadvantage of this system is that for many Americans bicycle-riding is a new experience; poorly-trained muscles may result in a lower limit for metabolic rate than if grade-walking or running were measured. Hence for the home laboratory a treadmill is desireable. However, the era of the 600-liter spirometer is closing.

The advantages of the syringe are its light weight, portability, and freedom from the toxic hazard of mercury vapor. When it is used in conjunction with metal cocks there is no change in composition of a sample over a period of time. When it is well-lubricated there is no leakage, whereas the glass cock on mercury sampling tubes sometimes loosens, especially in hot weather.

Acute vs. Chronic Exposures to Altitude

Emphasis in our current studies has been on the responses to altitude as related to duration of exposure. Acute exposures lasting about 30 minutes were conducted in the altitude chamber at Bloomington. Chronic exposures ranged from one day to seven weeks at altitudes of 3080 to 4343 meters. The mean barometric pressures were 740, 535, 485, and 455 mm Hg. Temperature ranged from 14° to 20° C. Within this range of temperature all-out work lasting no more than 15 minutes places no strain on man's capacity for temperature regulation. The four male subjects in the acute exposures ranged in age from 19 to 74; pertinent measurements on them in the resting state have been published (2). In the acute exposures, three observations were made on each man at each pressure in order to attain greater statistical validity. Each man started at a different pressure and progressed in the same sequence; this made it possible to balance out the training effect, on the one hand, and on the other hand, to assess it.

Results. To evaluate the response of the heart rate (HR) in exercise in acute exposures to altitude, the rates in each set of three experiments were averaged for each man. An examination of these averages revealed that neither Dill, age 74, nor Brown, age 19, showed an appreciably greater HR at a given time at 535 than at 740. Accordingly their rates at those two pressures were averaged to give the solid lines of Figure 1. The other points in this figure show that in easy and moderate work there were increments in HR from 535 to 485 at equal work rates but little further increment from 485 to 455. Approximately the same limiting heart rate was reached by Dill, regardless of altitude. Unlike Dill and Brown, Phillips, age 35, and Myhre, age 28, had increments in HR at a given work rate between 740 and 535, as well as further increments at 485 and

455. Accordingly, the solid lines in Figure 2 correspond to HR at 740, with identified points indicating rates at the other pressures. Here, also, nearly as high a limiting rate was reached at the lower pressures as 740.

Systolic blood pressure at 740 increased with increasing work rate at about the same nearly rectilinear rate in the four men, as can be seen in Figure 3. Thus the increases in mm Hg from 0 to 8 min were: Dill, 51; Brown, 52; Phillips, 58; and Myhre, 46. Except in Dill, there was a slightly smaller acceleration in the last few minutes. The responses at lower atmospheric pressures were so similar to those at 740 that they have not been shown in Figure 3. Of the 27 averages at equal work rates on Dill at 535, 485, and 455, only 5 differed from the averages at 740 by more than 5 mm. Brown's systolic pressures at altitude averaged 6 mm higher than at 740; Myhre's averaged 3 mm higher. Only Phillips showed a distinctly different pattern. At 485 and 455 through the tenth minute his systolic pressures averaged about 15 mm higher than at 740; during the last three minutes they were about the same as at 535 and 740. While Dill's systolic pressures increased at the same rate as in the others, his started 10 to 15 mm higher and ended 6 to 15 mm lower.

The individual pattern of diastolic pressures in work and recovery differed little from one altitude to another. In each man it tended to drop during exercise. In recovery there was a further drop in Brown, no change in Dill, and an increase in Phillips and Myhre. The extreme range in average values during exercise was from 65 in Brown to 90 in Dill. Pulse pressure in the last minute of work was independent of altitude. It ranged from 111 to 118 in Dill, 127 to 134 in Brown, and 128 to 144 in Phillips and Myhre.

Average values for $\dot{V}_E$ at body temperature and pressure, saturated (BTPS) are shown for Brown and Dill in Figure 4, and for Phillips and Myhre in Figure 5. The solid line in each figure corresponds to average $\dot{V}_E$ values for the three experiments at 740. Each point except for the last one or two is the average of three observations for a given work rate and pressure. In the subsequent discussion attention will be directed to variations in patterns of response, to the age-related limiting values for $\dot{V}_E$, and to the ability to ventilate the lungs equally well in all-out work over the whole range of pressures–740 to 455.

Metabolic and related measurement made during the last two, three, or four minutes of work have been published (2). The record includes rate of oxygen consumption in liters/min, $\dot{V}_{O_2}$, respiratory exchange ratio, R, and the "True" O_2 in percent. The last figure multiplied by V_E at standard temperature and pressure, dry (STPD) gives $\dot{V}_{O_2}$. Maximum work rates attained and blood lactates in the sixth minute of recovery also have been published (2). Blood from an arm vein usually reaches maximal lactate concentration at about this time.

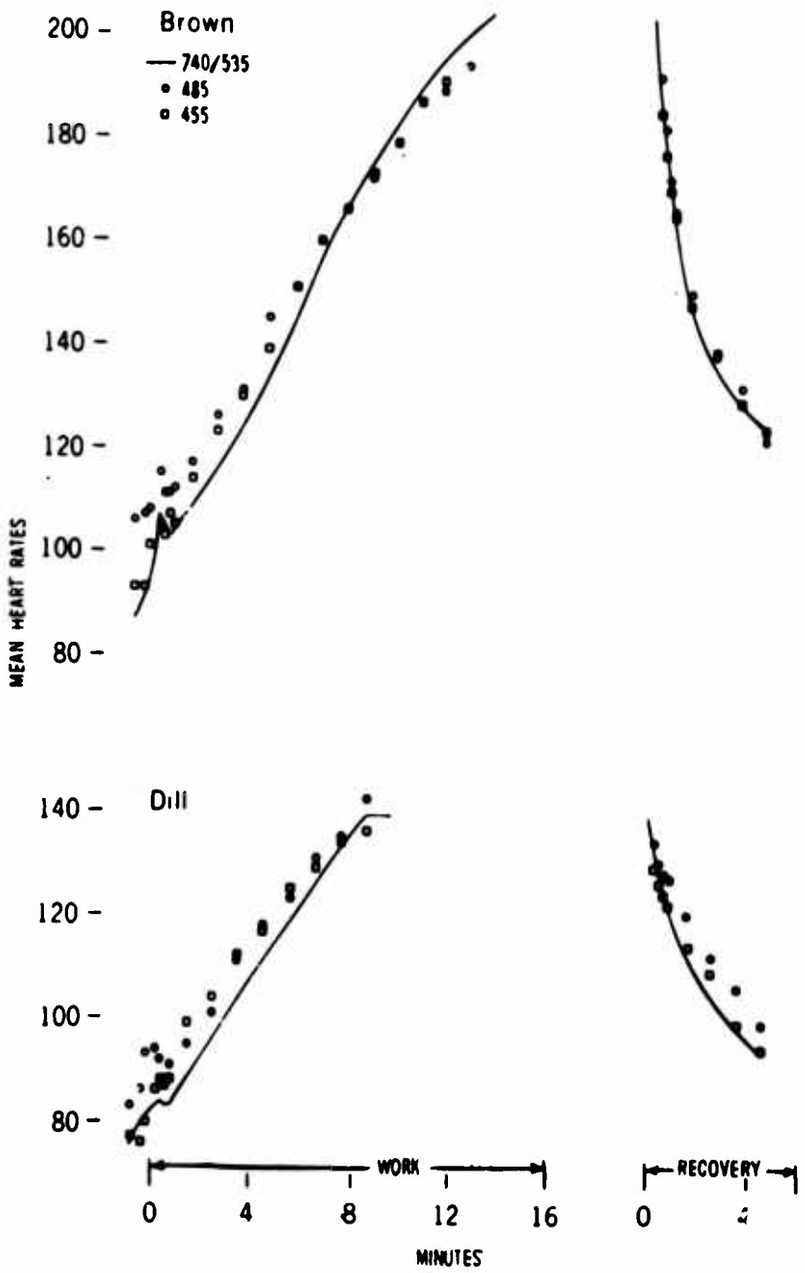


Figure 1

Heart rate of Brown and Dill in the Balke test. The solid lines correspond to averages, minute by minute, of rates at 740 and 535 since in these subjects the heart rates were nearly the same at these pressures. The recovery heart rates of Brown fall on the same curve regardless of altitude; in Dill, recovery was a little slower at 485 and 455 than at 740 and 535.

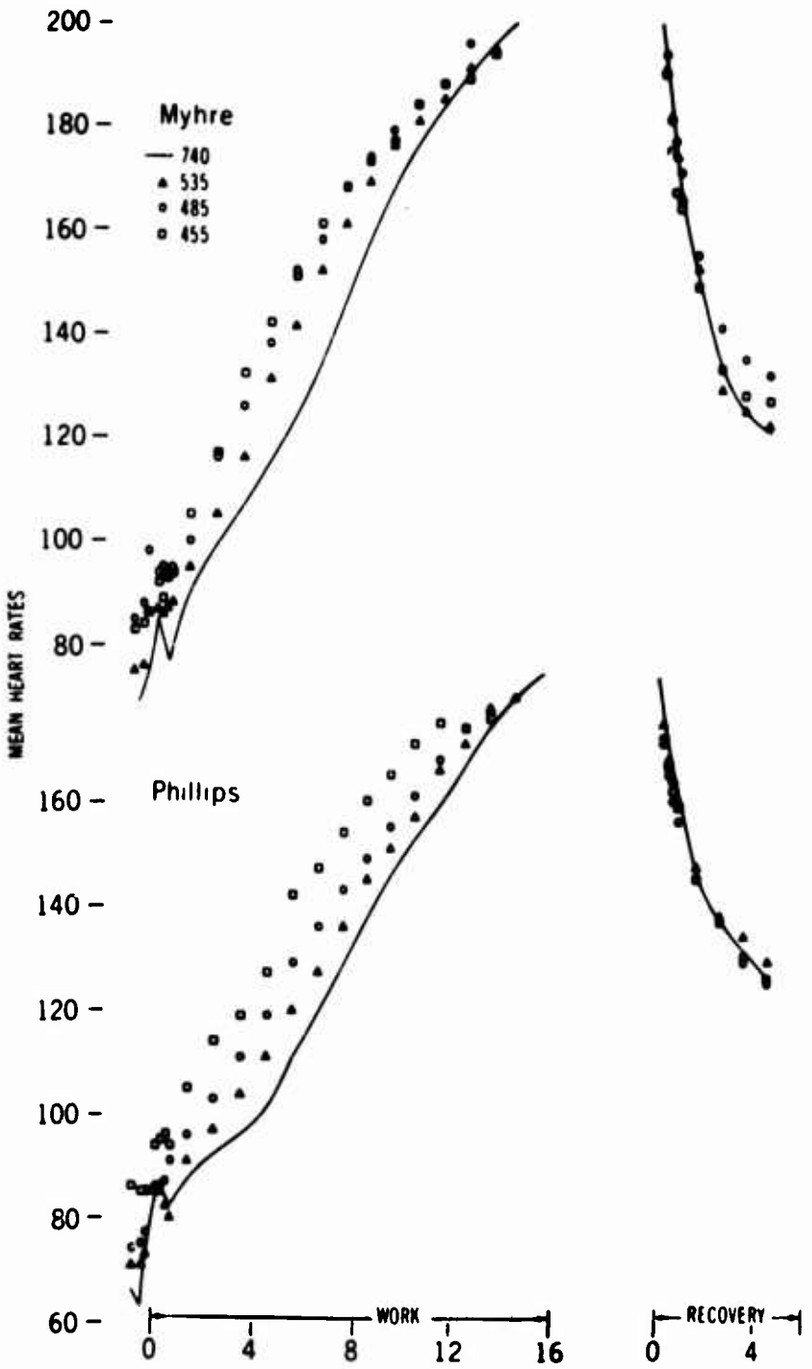


Figure 2

Heart rate of Phillips and Myhre in the Balke test. The solid lines correspond to 740. In each man the heart rate in moderate work increases with each increase in altitude, but approximately the same limiting rate is reached at the end. Recovery rates are remarkably similar for all altitudes.

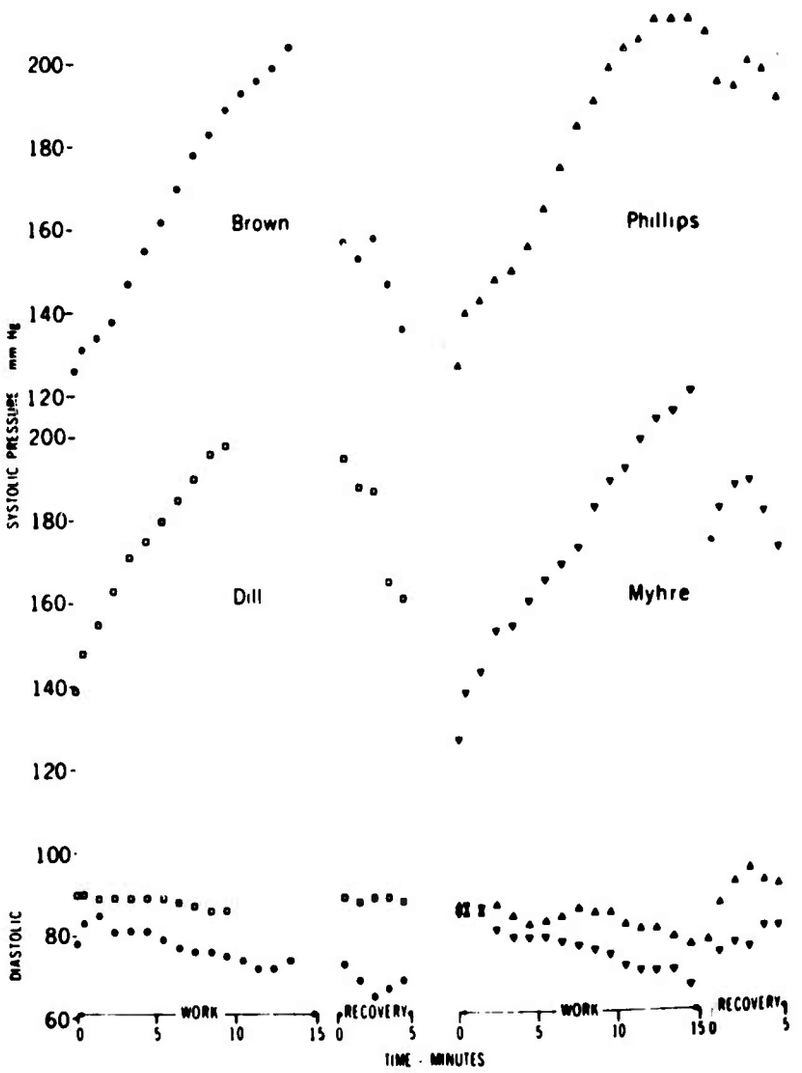


Figure 3
Systolic and diastolic blood pressure at 740. The patterns at the other pressures differed in minor respects.

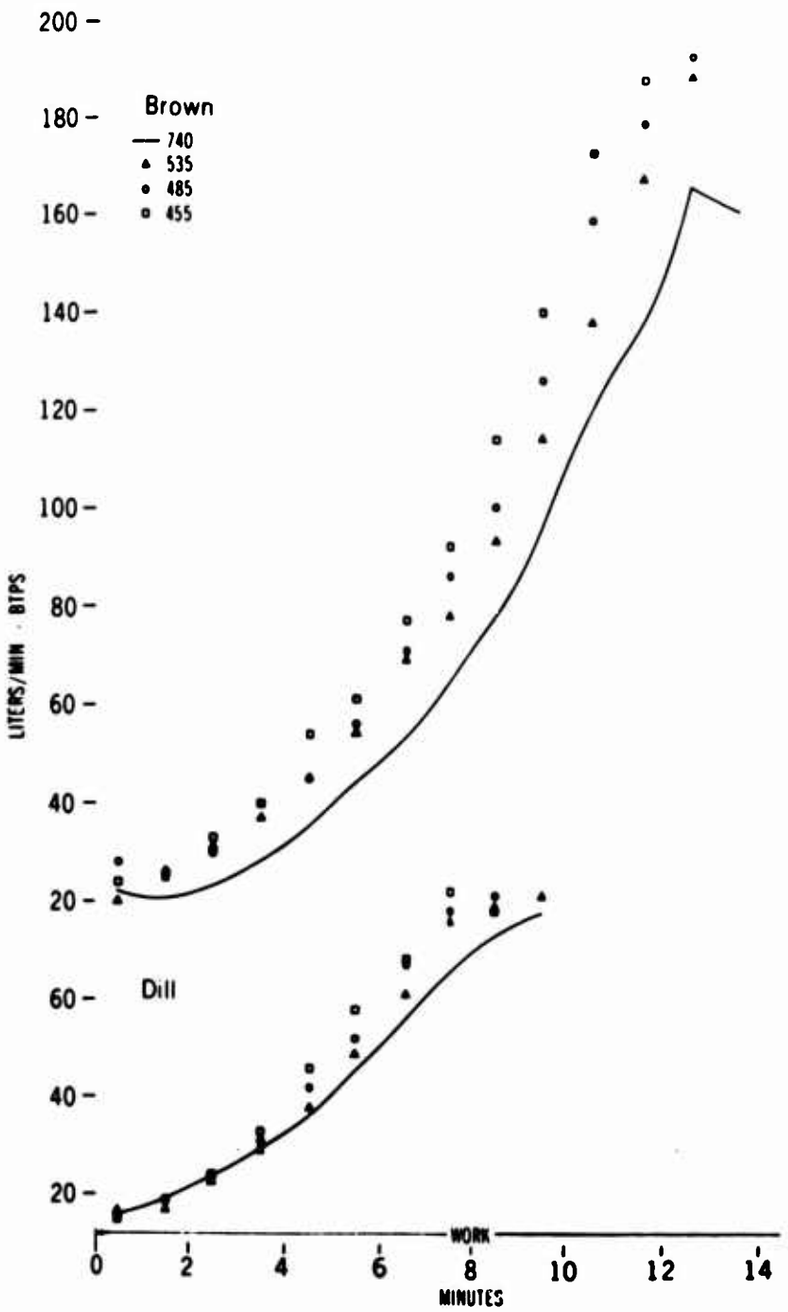


Figure 4

$\dot{V}_E$, Brown and Dill, at body temperature and pressure, saturated (BTPS). Ventilation in moderate work is higher the lower the barometric pressure, but the same ceiling is approached in the last minutes of work.

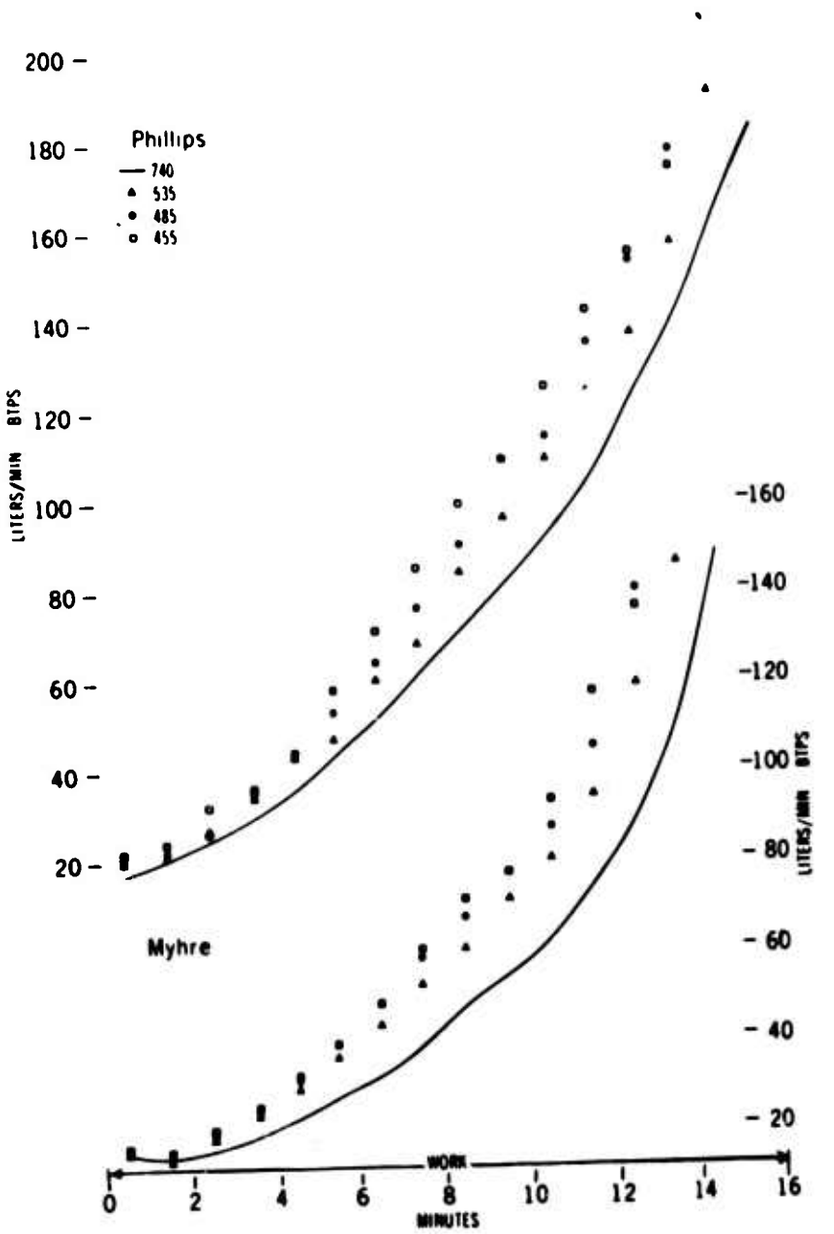


Figure 5

$\dot{V}_E$, BTPS, in Phillips and Myhre.

	At 535 (3093 m)		At 485 (3800 m)		At 455 (4343 m)	
	- ΔHR	days	- ΔHR	days	- ΔHR	days
Dill, 1962 (6)	14	[2] *	30	[9]	28	[28]
			32	[10]		
			33	[20]		
			28	[34]		
Forbes, 1962 (6)	18	[2]				
Balke, 1962 (6)			8	[16]	18	[30]
Dill, 1964 (7)			14	[1]		
			12	[8]		
Phillips, 1964 (7)			4	[3]		
			24	[8]		
Myhre, 1964 (7)			6	[3]	13	[20]
			13	[26]		

*Numbers in brackets are days at 3093 m or above.

TABLE I

Decrements in maximum heart rate (-ΔHR max) in exercise at White Mountain Laboratories. The reference base is the highest HR attained at sea level.

There was an added advantage in delaying the puncture: heart rate and blood pressure recordings could be continued through five minutes of recovery without the disturbance of venipuncture.

Discussion

It is well-established that HR in all-out work reaches higher values at sea level than during the first weeks or even months at altitude. Thus Pugh (3) found that the average HR in maximum exercise in members of the Himalayan scientific and mountaineering expedition of 1960-61 declined from 192 ± 6 at sea level to 159 ± 17 at a barometric pressure of 440. Earlier observations were made by Christensen (4): in maximal work his HR reached 190 at sea level, 170 at 543, 150 at 489, 135 at 429, and 132 at 401 mm Hg. Elsner, Bolstad and Forno (5) have studied $\dot{V}_{O_2}$ max and HR at 4500 m in sojourners and in Peruvian Indians native to that altitude. The latter achieved heart rates of 180 to 200, while the range for sojourners was from 125 to 160. In our party at the White Mountain Laboratories in 1962 (6) and in 1964 (7), reductions in maximal HR (HR max) from sea level values were large: they are recorded in Table I. These large decreases in HR max in men during adaptation to high altitude contrast with the small decreases we observed at the same pressures but in the altitude chamber with no acclimatization. The average HR max for the four of us was 182 at 740, 179 at 535, 177 at 485, and 174 at 455. The difference between the averages at 740 and 455 is statistically significant, but this is not true of the small differences in HR between 535 and 485, nor between 485 and 455. It seems that in maximum exercise after only a few minutes at barometric pressures from 535 to 455 a higher heart rate can be reached than after days or weeks at corresponding altitudes.

The well-established decline in HR max with age is as manifest at high altitude as at sea level. Comparison of HR max for each, and of the grand average rate for each, is as follows:

	HR max	Average HR max, all experiments
Dill, age 74	144 at 740 and 485	137
Phillips, age 35	184 at 740 and 535	180
Myhre, age 28	210 at 740	197
Brown, age 19	204 at 740	196

The experimental design provided evidence that under the conditions of our experiments six weeks' training did not affect HR max in exercise: the grand average of HR max was 177 in the first series and 178 in both the second and third series. HR max for the first series as compared with the later two series was slightly lower in one man, slightly higher in another, and the same in the other two men.

DR. HORVATH: How long do the experiments last each time?

DR. DILL: Four of us went into the chamber; two men were to be subjects. The first experiment was at decreased pressure. The man who was to be the second subject used oxygen, which we had available, so he wouldn't have any prior exposure to hypoxia. As soon as we reached altitude, which took five or ten minutes, we made resting observations. These first observations on pulse, blood pressure, and so on, required on the order of five to ten minutes anoxia; then the man started breathing air at that altitude. In my case, since my limit was very much lower than the others, I was all through in eight or nine minutes, and the others in 14, 15 minutes, so the entire exposure to hypoxia probably was of the order of half an hour.

DR. BRAUER: And there was no exposure between experiments?

DR. DILL: None, except that everybody had oxygen in there, but if a man wasn't going to be a subject that day then his pressure was 535 or 45, he probably didn't bother to use any oxygen, but it was there if he wished to use it. I'll emphasize, and this is quite important because it may have been a source of error in other experiments, that we had a liberal flow of air into the chamber, which nevertheless if anybody is using oxygen was still contaminated with oxygen to some extent; so the intake of the oxygen supply or the air supply of the man who is the subject was from this air intake, and it was a rapid enough flow so we were positive that he was breathing air of outdoor composition.

Observations of $\dot{V}_E$ in maximum exercise at altitude, notably those of Pugh (3), indicate that the respiratory bellows function is unimpaired up to 6000 m. As is clear in Figures 4 and 5, this was true of our observations within

the range of pressures studied. Even though Dill's $\dot{V}_E$ max is only about one-half that of the other three men, we are justified in averaging maximum values: there are the same number of observations on each man at each altitude. The average values for $\dot{V}_E$, BTPS, for the three series of experiments are as follows:

Barometric pressure	740	535	485	455	Average
1st series	134	129	142	133	135
2nd series	149	151	156	145	150
3rd series	147	158	155	149	152
All series	143	146	151	142	146

We conclude from our results that (a) there was a training effect resulting in greater $\dot{V}_E$ max in the second and third series than in the first, and (b) $\dot{V}_E$ max, BTPS, is independent of barometric pressure within the range covered.

COL. GOLTRA: Were those volumes corrected to sea level?

DR. DILL: VTPS. Yes. This is body temperature – –

COL. GOLTRA: You mean actual volume – –

DR. DILL: Actual volume out of the lungs, yes.

DR. GOLTRA: – –increased practically in proportion to the diminution in pressure?

DR. DILL: Yes, that's right.

DR. CHOIDI: How was an individual, considering you separately because you just diminish it a lot, how were the others, was there not also an increase in the ventilation . . .

DR. DILL: We all behaved about the same way, each of us. Mine stayed around 80 liters.

DR. CHIODI: And the others stayed, there was no change?

DR. DILL: I mentioned Brown as reaching 200, the others were around 180, 160 to 180. Phillips and Myhre were around 160 to 180, Brown was about 200 and I was about 80 liters.

DR. CHIODI: And how long was the experiment, how long did it last, this measuring of ventilation?

DR. DILL: Ventilation was going up all the time.

DR. CHIODI: But how long was the time?

DR. DILL: Oh, a maximum I think of fifteen minutes in Phillips, who reached the highest workload; but it was a stepwise increase, you see, so that each minute the ventilation was going up. The oxygen consumption usually leveled off, and sometimes reached a peak in the penultimate minute, but the ventilation was going up and the CO_2 production continued to increase.

DR. CHIODI: I wondered a little because, well, many studies have been done showing that the response to low oxygen, respiratory response to low oxygen takes some time then . . .

DR. DILL: Rest, not exercise.

DR. BLATTEIS: To come back a minute to your increase, to the better

heart rates initially, might that be that there are oxygen stores initially that therefore in effect are not operating at the altitude where you are?

DR. DILL: For the first minute or two.

DR. BLATTEIS: Only for the first minutes?

DR. DILL: Oh, yes, I was using at the end 1.9 liters of oxygen a minute and they were using 3.6, 3.4 or 3.6 liters a minute, at the end, so that would be only the very first minute or two.

Tidal volume, V_T, throughout the Balke test proved to be independent of atmospheric pressure within the range studied. There were individual patterns. In Phillips' case, V_T increased steadily from about 1.1 liters at the beginning to 3.0 liters at the end. Myhre's increased from 2.4 to about 3.5, Brown's from 2.2 to 3.3. Dill's V_T increased from 0.9 to 2.0 in the sixth minute and ended at 2.2 in the ninth minute. It is interesting to note that the breathing pattern in the basal state shows greater idiosyncrasies than in the last minutes of all-out work:

	Phillips	Myhre	Brown	Dill
Tidal Vol., liters				
Basal state	0.54	1.62	1.13	0.45
At V_E max	3.0	3.5	3.3	2.2
Respiratory rate				
Basal state	12	3	6	15
At V_E max	60	48	58	36

DR. HORVATH: Just as a sidelight, a comment on Myhre's very low basal respiratory rate . . . Dr. Dill once told one of our sons that he ought to count the heartrate of a cat and the boy–after two years of prodding–finally did it, and the resting heartrate of a cat turns out to be about 40 per minute. A cat that's accustomed to being held by children and so forth goes down to about 40 per minute, and the usual heartrate is certainly way up in the 120's, something like that. I think it's very interesting that if you can get individuals at a purely basal resting rate, you might find differences which are quite a way off from what we generally assume them to be.

DR. DILL: Right.

Of great current interest in view of the forthcoming Olympics at Mexico City is the question: To what degree is the capacity for oxygen consumption, $\dot{V}_{O_2}$ max, reduced at altitude? The plan was to measure $\dot{V}_{O_2}$ during each of the last minutes of exercise. If the man could not complete the full minute, we were prepared to measure $\dot{V}_{O_2}$ in the last half-minute. In about three-fourths of the experiments the highest values were reached in the last minute or half-minute. In about one-fourth the penultimate value was highest, but in only two cases was the difference greater than 0.10 l/min. Hence, in comparing performance as related to altitude, we used the highest value whether it was last or next to last. The highest $\dot{V}_O$ in each test at 740 was taken as 100%. Performance in each test at each other altitude was calculated in % of performance at 740. Thus in the three series of experiments we obtained the following average percentages:

	1st series			2nd series			3rd series		
	535	485	455	535	485	455	535	485	455
Phillips	86	77	73	86	81	75	88	79	74
Myhre	92	91	84	87	86	79	93	91	82
Brown	86	88	84	94	90	86	89	84	83
Dill	87	86	78	91	89	81	104	92	88
Average	88	85	80	89	86	80	93	87	82

The grand average indicates a reduction in percentage to 90 at 535, 86 at 485, and 81 at 455. There is indication of individual differences, Phillips showing the greatest drop in nearly every case.

These performances are equal to or better than those of Dill in 1962 (6), and of Dill, Klausen and Dawson in 1964 (7) at White Mountain Laboratories. In 1962, after two days at 535, Dill reached 89% of his sea level performance. At 485 he improved from 70% after 9 days, to 78% on days 10 and 20, and 88% on day 34. During a visit to the summit laboratory, 455, on day 28 he reached 75%. In 1964 (7) in four Balke ergometer tests, during the first 8 days at 485 his percentages dropped from 80 on day 2, to 73 on day 3, and then increased to 75 on day 5 and 79 on day 8. Phillips showed a greater drop: 68% on day 3, 77 on day 5, and 73 on day 8. Balke in 1962 reached 79% of his sea level performance at 485 after 16 days at altitude, chiefly at 535. This is one of the few instances in which a man

performed as well after a few weeks at altitude as he did without acclimatization. Among others who have studied this question some find performance improves within a few days, while others find no improvement. Consolazio et al. (8) found in soldiers taken to 3475 m that there was no clear-cut improvement in 19 days. The percent of sea level performance was highest, 82, on day 1 and lowest, 75, on day 17. Two groups were studied on Pikes Peak, 4300 m, about 460 mm Hg. Those ascending gradually reached 82% of their sea level performance; those ascending rapidly reached only 73%.

In another study, Balke (9) measured the maximum oxygen intake in five men at sea level and at 2300 m, first on arrival and again after 10 days. Two were superior athletes, two were non-athletic, and one had done cross-country running; all trained regularly during their 10 days at altitude. There was a loss in performance on their first day and subsequent gains as shown below:

Percent of original sea level performance		
At 2300 m		Back at sea level
1st day	10th day	
91	95	99
98	99	103
93	105	109
95	108	119
95	100	109

It is not possible to say in this case whether improvement in performance at altitude was anything other than a training effect.

While we have found no record of a systematic study such as ours, there have been three similar studies of limited scope. In one, Åstrand (10) measured on himself $\dot{V}_{O_2}$ max in an acute exposure to 526 mm Hg. He reached $\dot{V}_E$ max of 190 l/min and a lactate of 17.7 mM/l; his $\dot{V}_{O_2}$ max was 4.2 l/min or 91% of his sea level value. He recorded a ventilation of 135 l/min and an oxygen consumption of 3.1 l/min at 464, but this seems to have been sub-maximal. In acute exposure to 462 in the same laboratory (11), five young men had a $\dot{V}_{O_2}$ max about 72% of their average sea level value. The reduction to 91% at 526 is within the range of our measurements, but the reported reduction to 72% at 462

is below the range of our measurements and well below our averages of 86% at 485 and 81% at 455. A study by Balke, Wells and Ellis has been reported only in an abstract (12). The oxygen consumption is not given but it is stated that there was a 27% reduction in work capacity in an acute exposure to 4300 m (approximately 460 mm Hg). During six weeks at that altitude there was no perceptible increase in work performance.

The oxygen pulse, the oxygen used per heart beat, has been calculated for the last minute of work in each experiment. There appeared to be a training effect from the first to second series in Phillips, Myhre and Brown, the average increase being 10%. There were no further increase in the third series; there was no training effect in Dill. The decrease in oxygen pulse with increasing altitude was as follows:

	740	535	485	455
Phillips	20.2	17.6	16.6	15.2
Myhre	16.7	15.9	15.2	14.6
Brown	17.3	15.7	15.4	15.1
Dill	13.0	12.7	11.7	11.3
Average	16.8	15.5	14.7	14.1

The average overall value at 455 is 84% of the 740 value. However, in Myhre, Brown and Dill the drop is to 87%, while in Phillips it is about twice as great, to 75%.

The ratio of CO_2 output to oxygen intake, R, increases almost without exception to a maximum in the last minute of work. This reflects an increase in lactic acid and is associated with an increase in ventilatory volume out of proportion to the rate of increase in oxygen consumption. Hyperventilation and high levels of lactic acid are characteristic of the last minutes of the Balke test. However, there is no correlation between R and lactate except possibly in the case of Dill, who did not reach as high levels of lactate as did the others. It appears that the demand for oxygen provides a stimulus to the respiratory center superimposed on the need for balancing the accumulation of acid. However, one must bear in mind that the R values reflect the pattern of breathing in the last minutes of exercise, while venous blood for lactate was obtained in the sixth minute of recovery. We do not know how reliably lactate concentration in such samples reflects the state of affairs in arterial blood during the last minutes of work. Further studies of this problem are warranted.

There are individual variations in the pattern of R values. The overall averages for R in the last minute for Phillips, Brown and Dill are about 1.3 while that for Myhre is about 1.4. Then there appears to be a slight training effect: the average of all values in the first series is 1.27, while it is 1.34 in series 2 and 3. Mean values of R in the last minute of work at each altitude are as follows:

	740	535	485	455
Phillips	1.23	1.33	1.31	1.34
Myhre	1.44	1.40	1.44	1.37
Brown	1.18	1.27	1.32	1.30
Dill	1.26	1.25	1.30	1.33
Average	1.28	1.31	1.34	1.33

The slight upward trend with altitude probably is not significant.

Values for True O_2 give a picture of acceleration in $\dot{V}_E$ in the last minutes of work. This supplements the curves for minute-by-minute ventilation in Figures 4 and 5. All four subjects show acceleration in $\dot{V}_E$ from the beginning, i.e., the rate of increase is greater proportionally than the rate of increase in the work load, this being directly related to time. The curve is steepest two or three minutes before the end of work; in the last minute it may flatten out as the limiting capacity for $\dot{V}_E$ is approached. The meaning of increasing R and decreasing True O_2 is this: the capacity for utilization of oxygen is nearly reached by the penultimate minute while the rate of CO_2 output continues to increase. The average increases for all experiments at each altitude are as follows:

	$\dot{V}_{O_2}$ (l/min)		$\dot{V}_{O_2}$ (%)	$\dot{V}_{CO_2}$ (l/min)		$\dot{V}_{CO_2}$ (%)
	Penultimate minute	Last minute		Penultimate minute	Last minute	
740	2.97	3.09	+ 4	3.59	3.96	+10
535	2.69	2.78	+ 3	3.39	3.70	+ 9
485	2.57	2.63	+ 2	3.24	3.52	+ 9
455	2.39	2.47	+ 3	3.06	3.29	+ 9

The relations between $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ are interdependent. The high rate of CO_2 output lessens the effect of accumulating lactic acid on hydrogen ion concentration in the blood and reduces the shift to the right of the oxygen dissociation curve, facilitating the uptake of oxygen in the lungs. At the same time, conditions within active cells may favor the uptake of oxygen. It has been shown that lactate diffuses rather slowly from plasma to red cells (13). If it also diffuses slowly from muscle cells to interstitial fluid, conditions in the cells would be favorable for release of CO_2 and uptake of oxygen. Further studies are required to explain the small increase generally seen in $\dot{V}_{O_2}$ in the last minute of work, as well as the occasional decrease under similar conditions.

The record of maximum work rates has been reduced arbitrarily to relative values to facilitate comparison. Phillips' performance in the first experiment at 740, 2100 kpm/min for 60 seconds, has been taken as 100. For other loads continued for 60 seconds, the percentage is $\frac{100(\text{kpm/min})}{2100}$. When the man stops at 30 seconds, the percentage is $\frac{100\ (\text{kmp/min} - 75)}{2100}$, i.e., it is assumed that he could have maintained a load increment of 75 kpm/min for a full minute. Finally, since Phillips rode on two occasions for 90 seconds at the load limit, 2100 kpm/min, this is rated at 2175 for 60 seconds or 103%. Table II has been prepared on the basis of these assumptions. The averages show the decrease in work performance with altitude and also give an assessment of training gain. If Phillips' initial performance is taken as 100, the averages for all experiments at the four altitudes are 85, 81, 77 and 73. Relative to 85 the performances at 535, 485, and 455 are, respectively, 95, 91 and 86. The training gain is proved by the relative performance in the first, second, and third series. As shown in Table II the averages are 74, 80 and 82, respectively. This amounts to a gain of 8% in the second series and a further gain of 3% in the third. It is noteworthy that all subjects improved in their performance at all altitudes. While the average gain in all subjects was 11%, one subject (the youngest) gained 20%.

The Balke test calls for maximum energy expenditure, aerobic and anaerobic. An incomplete measure of expenditure of energy anaerobically is the concentration of lactate in blood. Movement from tissues to blood probably is slow, and equilibrium between red cells and plasma certainly is slow (13). However, distribution within the body and equilibrium in the blood is nearly complete about five minutes after work stops. Hence our values for lactate in blood from an arm vein in the sixth minute of recovery give a useful though imperfect measure of anaerobic expenditure. The average values for lactates in mM/liter are as follows:

Barometer Pressure	Phillips	Myhre	Brown	Dill	Average
740	100	90	71	57	85
	103	97	86	61	
	103	100	90	61	
	102	96	82	60	
535	93	90	71	50	81
	100	93	83	54	
	97	90	86	54	
	97	91	82	53	
485	86	86	71	50	77
	90	86	79	54	
	93	90	83	54	
	90	87	78	53	
455	79	79	71	43	73
	86	83	75	50	
	90	86	79	54	
	85	83	75	49	
Ave., 1st series	90	86	71	50	74
Ave., 2nd series	95	90	81	55	80
Ave., 3rd series	96	92	85	56	82

TABLE II

Relative work capacity in the Balke test.
With an rpm of 50, the load on the brake starts at zero and is increased 150 kpm/min at the end of each minute. Two men completed one minute at 2100 kpm/min; this is taken as 100. See text for further details.

	Phillips	Myhre	Brown	Dill	Ave.
740	16.0	16.7	12.8	8.1	13.4
535	14.5	15.5	12.0	7.4	12.4
485	13.6	16.2	13.6	7.8	12.8
455	11.9	15.0	12.2	7.9	11.9
Ave., 1st series	11.6	14.4	9.6	6.3	10.5
Ave., 2nd series	14.4	16.2	14.3	8.6	13.4
Ave., 3rd series	16.1	17.1	14.1	8.6	14.0

A statistical analysis of the lactate results indicates that there was no significant correlation between lactate level and altitude. Under the conditions of our experiments, man in all-out work on the bicycle ergometer attains about the same lactate levels regardless of altitude. So far as training is concerned, the lactate levels attained in the second and third series were significantly higher than in the first. Also, there is evidence supporting the opinion that age limits the capacity for anaerobic work: Dill at age 74 could reach only one-half the level reached by the young men.

	Phillips	Myhre	Brown	Dill	65 men (14)	42 men (15)	35 men (16)
$\dot{V}_{O_2}$ l/min	3.76	3.56	3.58	1.90	2.40	4.11	3.91
$\dot{V}_{O_2}$ ml/min·kg	41.8	45.8	40.9	26.5	32.0	58.6	56.5
$\dot{V}_{O_2}$ ml/min·kg LBM	52.5	51.9	52.4	34.2	37.1		63.4

$\dot{V}_{O_2}$ max per unit of body weight is highest in Myhre. However, when referred to lean body mass it is virtually identical in Phillips, Myhre and Brown—52. In Dill it is two-thirds as great—34. These calculations are based on the estimates of lean body mass made early in July. Body fat was estimated again in mid-August at the end of the six-week training period. Body weight changes were small; estimated LBM in kg was slightly increased in Brown and Dill, slightly less in Phillips and Myhre. It is tentatively concluded that improvement in performance

at 740 as well as at altitude did not involve a measurable increase in LBM. It is quite possible that muscles that limited performance gained in mass without significantly affecting the estimate of total LBM.

It is of interest to compare the performance of these four men with reports of similar published studies. Luft and associates (14) studied 65 men, 27 to 44 years of age, who were candidate pilots for the U.S. Space Program. Their average $\dot{V}_{O_2}$ max and derived values are given for comparison in the fifth column of the preceding table. Records in Scandinavia are at the other end of the scale. Thus Åstrand (15) found that for males from 7 to 33 years of age $\dot{V}_{O_2}$ max was from 56 to 59 ml/min·kg. Subjects in the age range of 7 to 18 were representative of boys in Stockholm schools. Those from 20 to 33 were students in the College of Physical Education, Stockholm; all members of three consecutive classes took part; the observation on 42 men in this group are shown in the sixth column. In a later study, von Döbeln (17) estimated $\dot{V}_{O_2}$ max from sub-maximal work performance, extrapolating by the nomogram of Åstrand and Ryhming (18). He estimated LBM by the Keys-Brožek formula and determined total hemoglobin. In his 35 men $\dot{V}_{O_2}$ max was a linear function of LBM 0.71; there was equally good correlation with total hemoglobin. Parenthetically this was not true of our findings. All four of us had about the same amount of hemoglobin, especially when referred to lean body mass. However, Dill had only about one-half the $\dot{V}_{O_2}$ max of the other three. There is no major change in blood volume nor in hemoglobin concentration with age although $\dot{V}_{O_2}$ max declines steadily with age. Hence von Döbeln's finding cannot be applied to men ranging widely in age: Its applicability was assessed only in a group that was within a narrow age range.

Von Döbeln's mean value for $\dot{V}_O$ max in liters per minute was 3.91 ± 0.09 as shown in the last column above. The range was from 2.85 to 5.45. His least fit subject surpasses 80% of the Americans studied by Luft. In the 35 Swedish men the mean percent of body fat was 10.6; only five men were outside the range of 5 to 15. Average values for $\dot{V}_{O_2}$ max per kg of body weight and per kg of LBM were above ours. The superiority of the Swedish men in this respect is extraordinary. Their $\dot{V}_{O_2}$ max per unit of LBM was 20% above that of the three men in our study of the same age range, and 70% above the mean value for the 65 men studied by Luft.

The foregoing comparison proves that the three young men of our study were far superior to the group of Americans studied by Luft, and significantly inferior to Swedish men studied by Astrand and by von Döbeln. Some may object to deductions about the handicaps imposed by acute hypoxia with only four men studied and with such a wide range in age. While some advantage

statistically is gained by numbers, there may be disadvantages, in that care and precision in observations may decline as the numbers increase. Essentially we have four case histories of acute exposures of man to all-out exercise in a suddenly-imposed deficiency of oxygen. As it turned out, all showed above the same pattern of response. Accordingly, we present the following summary of average relative responses, taking the response at 740 as 100:

	535	485	455
Work Capacity	95	91	86
$\dot{V}_{O_2}$ max	90	86	81
Lactate	93	96	89
$\dot{V}_E$ max	102	106	99
Heart rate	98	97	96
O_2 pulse	92	88	84

The first two responses can be interpreted in the light of the others. The fact that there was less loss in work capacity than in $\dot{V}_{O_2}$ max may depend in part on a smaller decrease in lactate (i.e., anaerobic work) than in aerobic capacity–$\dot{V}_{O_2}$ max. Success in attaining the same limiting $\dot{V}_E$ max means that within this range of pressures the bellows function of the respiratory system is unimpaired. Not only is this true in acute exposures; Pugh (3) found this to be true in chronic exposures. Maximum heart rate was nearly, but not quite, as high as at sea level. This contrasts greatly with experience at altitude. The decline in O_2 pulse is nearly parallel to the decline in $\dot{V}_{O_2}$ max, but this merely reflects the near constancy of HR max.

These observations and the many at altitude, some of which we have mentioned, lead to the tentative conclusion that man is more handicapped during the first days or weeks of chronic exposure than by acute exposure. This first stage of acclimatization brings him up to the level of performance attainable in acute exposures. The next stage, requiring months or years, involving increase in total red cell and blood volumes, can enable him to match his sea level capacity at 3000, possibly 4000 meters.

Summary

Four men ranging in age from 19 to 74 were subjects in three Balke tests on the von Dobeln ergometer at each of four pressures, 740, 535, 485 and 455 mm Hg, the last three pressures being in the altitude chamber without prior

acclimatization. Temperature ranged from 14° to 20° C. The effects of training on altitude performance were balanced out and, at the same time, training effects were assessed. Observations made included work capacity, V_E max, $\dot{V}_{O_2}$max, P, the time course of heart rate, blood pressure, and $\dot{V}_E$; in recovery, heart rate and blood pressure were observed for five minutes. Blood was obtained for lactate in the sixth minute of recovery. Taking $\dot{V}_{O_2}$ max at 740 as 100, the relative values were 90 at 535, 86 at 485, and 81 at 455. $\dot{V}_E$ max was independent of altitude, as was maximum blood pressure. Maximum heart rate was slightly but significantly less at 455 than at 740. Lactate was not significantly less at 455 than at 740. It appears that in the first stage of acclimatization in chronic exposures to altitude, performance is inferior to that in acute exposures.

DISCUSSION

DR. CHIODI: You said that at high altitude the older men have an increase of plasma volume. Did you measure the water intake and diuresis of the men?

DR. DILL: No, we didn't but we have body weight and it didn't change much. I think we'll hear more about that–in women at least–later on. We should have taken body weights every day but we took them irregularly, and they didn't change much, they dropped a pound or two perhaps, with some fluctuation up and down.

DR. CHIODI: You mean there was no difference between – –

DR. DILL: Phillips and I were about the same as far as change in body weight was concerned, but we can't explain it that way, there's a real redistribution of body fluids. It's different in an old man than it is in a younger man and why is a mystery. I hope somebody here can give me the information.

DR. GROVER: Dr. Saltin was telling me that the depression in maximum heart rate at altitude occurs much more slowly than I had realized, and it is a process covering several weeks. I wonder if you or anyone else knows of any study where this has been investigated systematically. It's certainly in keeping with what you found, a very little depression on immediate exposure.

DR. DILL: We have observations in work experiments particularly on Will Forbes and myself, Forbes three weeks and myself five weeks, but I can't say how long it took for the minimum to be reached.

DR. BUSKIRK: In our experiments on the track athletes, taking them to altitude, we were unable to detect any drop in maximal heart rate. One boy ran a very high heart rate at sea level, it was continued at altitude, and he was at altitude for sixty some days. It was the same the day when he last finished at altitude as it was the day he went up, so I think this is highly individual.

DR. SALTIN: I think there are two different problems with maximum heart rate. One is the altitude, you have to be I think higher than 4,000 meters or something like that to see a decrease in maximum heart rate. And then it is a question of time and the only study I know about this is Vogel's; he took 60 subjects from sea level up to Pike's Peak. After four days they had just a couple of beats lower maximum heart rate. After four weeks it's down 25 beats and at even higher altitude and longer stay, there's a decrease of 30, 40 beats. So it's a question of time and altitude above 4,000 meters.

DR. HORVATH: Is it also a question of the amount of work that is being done, namely, how frequently these tests are repeated, if they're done let's say every day?

DR. SALTIN: In Vogel's study--I plan to take up this question in my talk later, but in Vogel's study half of the group performed some regular exercise and the rest no exercise at all, and there was no difference, no.

DR. HANNON: Half of these were on a physical training program, and it didn't seem to make much difference. Each of these groups were by themselves with respect to improvement.

DR. HORVATH: There's so much difference in our so-called physical conditioning programs in terms of what they expect of an individual and what they really cost the individual, but unless these programs are very definitely spelled out so that you know precisely how much work the individual is doing, at what level is he performing and for how long, I think it will have little meaning to say he is exercising. I think it is sort of a misuse of this conditioning term. So often we really don't know how much work the individual is actually doing, and we can't really tell whether he's actually being conditioned or whether he's maintaining a level of conditioning which he had beforehand, so you get improvements in some and you get deterioration in others, depending on the program that's set up.

DR. HANNON: I don't know the details of the training program, but it was monitored fairly closely to ascertain whether there was an improvement in performance due to training. There was a variety of activities, various calisthenics, running, and this sort of thing. There were measurements made periodically to see that there was improvement in the work capacity, this being the only criterion, and there was improvement.

DR. DILL: There is the fact that individuals differ a great deal in their experience with mountain sickness, and some get quite sick, nauseated, vomiting, and others don't at all. I have a feeling that the deterioration which occurs during the first two or three days, of course, varying with individuals, may be related in some way or other to the factors responsible for mountain sickness. You just don't seem to feel up to working very hard when you have a headache and haven't slept much the night before and are maybe nauseated some, or have had no breakfast. We had absolutely no symptoms of discomfort during these short exposures and aside from some breathlessness on exertion, we were completely unaware of any unpleasantness.

DR. CHIODI: Wasn't the stroke volume changing at the same time the heart rate changed?

DR. SALTIN: There is one point I want to comment on, and that is what happens during acute exposure and then during prolonged stay, and I mean prolonged stay, hours, the first two or three days. I have no experience with higher altitude, but in my group of top athletes at Mexico City, we can compare acute exposure in a low pressure chamber with experiments performed in Stockholm after three days stay, and after six weeks stay in Mexico City, and they had exactly the same decrease in maximum oxygen uptake.

DR. DILL: Well, of course if it is directly related to mountain sickness or related to the same common factor responsible for mountain sickness, you rarely get mountain sickness below 3,000 meters and not always until you get to 4,000 meters.

DR. BUSKIRK: Perhaps you will be thinking a little about why we should expect a decrease in the maximum heart rate at altitude. What reasons can we suggest for this, if venous return is fairly normal? There is one situation, perhaps, when the heart rate is measured in recovery, it may fall down or it may decrease, because here we have observed some leg cramping. Have you seen this in your chronic experiments at all?

DR. GROVER: In these athletes there was a decided tendency for this, after a maximum workload at altitude with perhaps a modest amount of sinus arrhythmia during this period with an abnormality in the conventional cardiac pattern. I don't know whether others have seen this or not.

DR. HORVATH: Yes, this has been reported. In fact some of the people whom we have run suggest that the reason they quit is simply that they just can't use their muscles–their legs any more. The muscles are cramped up so tightly that they are unable to move the bicycle pedals, or they think they can go further but of course they have no power to exert and therefore they stop.

DR. BUSKIRK: Well, venous return must be altered.

DR. HORVATH: The venous return from the exercising muscles at that time must be practically nil because there must be complete interference with the circulation from the extremities.

DR. BRAUER: The reason I am interested is because in the diving mammals you have maximum work output with practically complete peripheral ischemia for periods of twenty or thirty minutes, and I have been very curious for some time as to what factors are involved in tolerance to this. Whether these represent CNS tolerance to pain or special biochemical mechanisms that allow for more effective anaerobic metabolism or lactic acid tolerances is unknown.

DR. DILL: Speaking of leg cramps, we learned from Clausen in Denmark what we hadn't been so careful about before, and that is to raise your seat to the level where your legs are fully extended. We had no trouble with cramps in any of these experiments. I didn't mention lactate levels, but I reached a lactate level of between about eight and nine millimols and the others reached levels of around 13 to 16. It was all-out work, no question about that.

DR. BUSKIRK: We had one boy who was our best two-miler, who at the altitude of a little over 13,000 feet could ride eight minutes or a little more under the conditions that we were using. Now this boy on at least four different occasions had to be supported when he finished his work, and we went very carefully to the adjustment that you suggested, each one had his own seat position, this was changed every day just for him, but then this cramping would last for a period of five or six minutes. He could not stand and once you see it, you don't forget it.

DR. HORVATH: But it does not answer the question that Dr. Brauer brought up: why is it some mammals can operate so efficiently with no circulation to the extremities, and yet the human organism under these circumstances quits?

DR. EVONUK: Is this peculiar to the bicycle erometer or did you experience this on the treadmill?

DR.BUSKIRK: He had never experienced this before in his life, under any other circumstances.

DR. BRAUER: You don't see it in the swimmers, in the underwater swimmers, even in the fairly severe cold exposure. Once they have been trained to use the big flippers, cramps are not an accompaniment of fatigue, of total fatigue. Of course these men are supine, which may be a pertinent point.

DR. EVONUK: Had the subject performed the same workload on a treadmill, do you think he would have gotten the cramping?

DR. BUSKIRK: This is a funny cramping, because if you felt his muscles they weren't particularly tight. The feeling was of a sudden vascular occlusion, with a feeling of deadness in the extremities, proprioceptive kinesthesis was lost.

DR. HORVATH: It's like a severe case of intermittent claudication. They take another step and they're flat on their face, they just simply can't do it. We've seen this on the treadmill, too.

DR. BUSKIRK: I think it's seen more frequently on the bicycle because of the position.

DR. BLATTEIS: In the study that we ran last summer on four Peruvian soldiers, on the treadmill at much milder workloads, but which turned out to be exhausting during the first four weeks at 14,900 feet at Morococha, there were three things that caused them to quit: either they had leg cramps, they had extreme dryness of throat and just couldn't seem to be able to breathe any more, or else they became dizzy.

DR. BUSKIRK: They became dizzy on the bicycle?

DR. BLATTEIS: No, on the treadmill. Those were the three things that caused them to stop.

DR. WEIHE: But did not Elsner do studies, compared natives in Morococha with newcomers and he found that natives could stand it much longer than the newcomers, and the cramps appeared much later in the natives?

DR. BLATTEIS: Well, we also ran natives, but our time of exercise was arbitrarily set for ten minutes, and in ten minutes it was not maximal for the natives.

DR. REYNAFARJE: The endurance of the natives is much longer, it's almost doubled for the same type of work.

I am not an expert in this, but I want to ask Dr. Dill: the criteria used for maximal oxygen uptake is to make an exercise hard enough to exhaust the subject in a period not longer than eight minutes but not shorter than two minutes, running at 14 kilometers per hour on a 14 percent slope. Do you feel that criteria applies for all our altitude subjects? If the speed is increased to 16 kilometers per hour, the oxygen uptake also increases. Ventilation increases as well. What should the criteria for maximal oxygen uptake be in these cases?

DR. DILL: Well, I think that this is still open to some debate, I don't know. We used to attempt to do maximum oxygen consumption by having a man run on the treadmill at a fixed rate for five minutes and adjusted the rate to produce exhaustion within that time. Sometimes we failed because he was so fit that he hadn't reached his maximum in five minutes, and in this case if we had time, we would have him wait, rest and run at a higher speed. However, we have pretty well given up that type of procedure and now we attempt to do some type of Balke test which can be varied to suit the individual, and which I think should be aimed towards reaching exhaustion within 12 to 15 minutes. The first minute is essentially a warmup, and we start with work that is easy for him. At this rate of work increase here, our best man was Phillips, who reached about 3.6

or 7 liters of oxygen a minute. He was exhausted in 15 minutes. However, the first ten minutes of the exercise was easy for him so that it was only during the last five minutes that he was really being pushed. Another illustration: we had Edelund as a subject a year ago: he had won the marathon tryout in New York City just a week or two earlier by a distance of about two miles over all the other competitors. It wasn't an extraordinary time because it was a very hot day, about 92 degrees Fahrenheit and high humidity. We did a Balke test on him, and as I remember it we started him on a 15 percent grade running at seven miles an hour, which was pretty easy for him, but he kept on running until he got up to about a 25 percent grade. I think his maximum oxygen consumption wasn't a record, it was 75 milliliters per kg per minute, something like that, so I think that the Balke-type test is best, but that you need to adapt it to some extent to the capabilities of the individuals.

DR. REYNAFARJE: There are variations I think we must take into account for evaluating the maximum oxygen consumption. Two subjects, for example, when the gradient was increased to 16 percent, they increased oxygen consumption but they also increased ventilation. When they were given 36 percent oxygen at high altitude—these subjects were natives of high altitude-one of them increased oxygen consumption but didn't increase the ventilation, at the same ventilation he had an increased oxygen consumption; the other increased ventilation and oxygen consumption.

DR. DILL: Did you do any lactate determinations? Do you have a measure of the extent to which the two men pushed themselves? Did the man who didn't increase his ventilation perhaps not work as hard as the other?

DR. REYNAFARJE: We didn't measure.

DR. DILL: In all these experiments, virtually without exception, the CO_2 production rose steadily in the last minute, even though in about a third of the cases the oxygen consumption was no higher or lower during the last minute or half minute then it had been in the previous minute. In other words, the oxygen consumption would go up and as Dr. Horvath pictures it, can drop off during the last minute, but the CO_2 production continues on up. This is associated with a

continuous increase in lactic acid production, and the ventilation was rising in most instances.

DR. REYNAFARJE: We measured CO_2 production around nine kilometers per hour. In high altitude natives, the CO_2 tends to increase after a few minutes of exercise and then at the end of ten minutes of exercise, it decreases. In the sea level native for the same work the increase is much higher and tends to stay at that level.

DR. DILL: This is sub-maximal work, is it?

DR. REYNAFARJE: This is maximal, 12 kilometers per hour on a six percent grade. Some of them will suffer this for ten minutes.

DR. GROVER: Is that CO_2 concentration or CO_2 production?

DR. REYNAFARJE: CO_2 production.

DR. BUSKIRK: What is your feeling now, Dr. Dill, about the maximum lactates? Do you think there is a basic difference in the anaerobic mechanism and that lactates are reduced slightly at altitude, and if so, why should one expect that they be reduced? What is the general feeling about this now?

DR. DILL: Well, I think we will know more about that after next summer because threee of us, Brown, Myhre, and myself, are going through this again at altitude next summer. It will be three weeks in the desert and then three weeks at altitude, with as quick a transition as we can make, about 8-10 hours. Then we continue to make observations over the three weeks period, so I will know better at the end of the summer, I think, the answer to that question.

DR. HORVATH: At the present time it's certainly a confusing picture.

DR. BUSKIRK: Is there a reason for thinking that it might be reduced?

DR. DILL: Yes, I think our own evidence indicates that it is reduced, it was reduced in ourselves in 1962.

DR. BUSKIRK: How do you explain this? Why?

DR. DILL: I don't know why.

DR. HORVATH: Dr. Dill, I wonder if you would care to make a brief statement as to what you think are the problems relating to the older individual in altitude against those of the younger individual? I realize we don't have much data as yet, we need a lot more, but what about projecting it a little bit for us?

DR. DILL: I think that the relatively unexplored field is body composition and fluid in various body compartments. Obviously this is very different in old men than it is in young men. Careful measurements of body weight and urine volume, and so on, water intake, together with observations on work performance, I think would be pretty interesting. Of course with older subjects, motivation is of major importance, and we worked in these studies only with dedicated investigators who certainly pushed themselves to the limit. If you have volunteer subjects, they may not be doing this more than once or twice. However, studies of body composition can be done without any particular stress, and I think that correlating this measurement with mountain sickness and other evidences of failure to adapt would be interesting. There's another point that is worth following up. Hall and I both experienced evidence of poor adjustments of the circulation to change of posture, getting up quickly out of bed. In our case, our ages made us feel as though we were about to faint. I know in my own case if I walked upstairs rapidly I would be on the verge of fainting when I got to the top, and this was after a few days at 12,500 feet. There are circulatory inadequacies in older people which I think need to be studied.

DR. WEIHE: I notice your residual volume was pretty high.

DR. DILL: It's quite high, but I have some asthma, and some emphysema.

DR. WEIHE: It's a medical problem involved there, because they say exposure to hypoxia will increase respiratory disease or improve it. Did you notice whether there was a change at the end of your study, did you measure at the end again?

DR. DILL: It is a fact that my asthma has cleared up completely both at White Mountain at high altitude and in the desert, which is one reason for my moving to the desert, but I doubt if my residual volume really changed much.

DR. EVONUK: I think Dr. Eagan has some information that bears out what you say about older people. Last summer a group of about twelve older subjects seemed to tolerate altitude, 13,800 feet, and also those who had the greatest responsibility seemed to tolerate it more.

DR. EAGAN: I would concur with what Dr. Dill says about motivation, and of course the older ones of the party seemed to be the ones with the greater responsibility. Indeed there seemed to be less mountain sickness and an easier time of it in general with the older subjects. Another thing is with respect to weight changes; the older ones in the party seemed to find it easier to maintain weight, whereas the younger ones didn't. Now whether that is correlated with the mountain sickness I couldn't say.

DR. BRAUER: This is what happened at 4200?

DR. EAGAN: Yes.

DR. BLATTEIS: The only case really of acute mountain sickness that we saw this past summer was in Dr. Favoyr, and this was after he had gone down from Mt. Evans, spent a day in Denver and then came back up, and this incapacitated him for about 24 hours. He was the sickest man I've seen under these conditions for a long time.

DR. HORVATH: This is a real problem. Those people who made the trip back and forth have more of a problem with mountain sickness than the others who are observing.

DR. SALTIN: Yes, we had studied the well trained, old, still active cross country skiers and cross country runners. In this table they are compared with younger, well trained, and also untrained subjects. If you have a look at heart volumes, you can see that it is increased with training and that both well trained groups are about the same. With that big heart, they are able to maintain very high stroke volume even though they are 51 years old. However, the maximum oxygen uptake is reduced compared with this other younger well trained group, and this of course is the same finding as if you study sedentary people. You can't say that the heart fails, but the oxygen difference is much lower and we have no way of possibly explaining why it is so much, much lower. These subjects train every day and they have done so since they were 15, 20 years old, and now they have this change. Why is this difference?

DR. BUSKIRK: Is that heart volume from x-ray?

DR. SALTIN: X-ray, yes. I think there are many problems still unsolved regarding circulation during exercise in older people.

DR. WEIHE: Well, we have the problem of age at our Jungfrauhoch observation station at 3,800 meters altitude. These people have worked there for many years and they go up and down, our electricians and technicians, and other workers. It's not a question of maximum working capacity but more of a question of altitude tolerance, and we found that the age of 40 is a critical one. After 40 these people, though their motivation is excellent, they want to work there, they get higher pay, they like it, and yet after 40 they deteriorate, they can't sleep, they have headaches, they don't concentrate as well as they did before. This is an observation among people who are exposed to cold and altitude repeatedly.

DR. CHIODI: How many years do they stay at high altitude?

DR. WEIHE: Some of them have been working there for 11 years.

DR. CHIODI: Were those worse than the others?

DR. WEIHE: They are now passing the age of 40 and they find that they are deteriorating.

DR. HORVATH: They go up for a short period of time only?

DR. WEIHE: For 10 to 14 days.

DR. HORVATH: And then they come down?

DR. WEIHE: Then they come down and stay down for four weeks, that's the regular schedule. This is repeated for years.

DR. BAUER: So that is the measure of ability to acclimate rather than of tolerance to altitude?

DR. WEIHE: Yes.

DR. BUSKIRK: Would you care to comment at all, Dr. Dill, about your friend's article, Dr. Ross McFarland, in which he compared the effects of aging to hypoxia in general. Did you read this at all?

DR. DILL: I'm afraid I'll have to say that I read it only sketchilly.

DR. HORVATH: It's where he postulated that aging is essentially due to a relative hypoxia.

DR. DILL: Of the central nervous system?

DR. HORVATH: Of the central nervous system predominantly, based on Flicker Fusion Frequency tests, on some other psychological tests, visual acuity. It's been a potential theory for a long time; it doesn't explain what happens but it does offer another suggestion.

DR. DILL: Well, my friend Harold Himwich, who has published a book on metabolism of the brain, is fond of saying that a person is born with a maximum number of cells and aging begins from then on; he has fewer and fewer cells year by year, but the rate of disappearance or breakdown of cells varies a lot from one individual to another and from one organ to another. I daresay that, well, there's certainly some truth in this, and certainly we see wide differences in the aging of the central nervous system, but this is tied up with the breakdown of other organ systems, including I suppose the cardiovascular system, blood supply, oxygen supply and so on.

DR. GROVER: Dr. Dill, didn't you report that the A-V gradient widens with age, so that the older man is more hypoxic than the younger man at a given altitude?

DR. DILL: Yes, I think this is true. Something else that deserves mention is the finding of Ralph Miller, which strikes me as highly significant, and that is that he did arterial oxygen saturations with the oximeter which is good for relative purposes, in sleep and wakefulness or resting state, at the White Mountain laboratory. His way of expressing his findings was that there is an increase in altitude of about 1500 feet at night. We had an observation that can be, I think, reasonably interpreted in the light of that observation. Ancel Keys and John Talbot constituted a pair of our subjects who came and stayed a week at the different stations last summer, and Ancel had been one of the most resistant subjects to altitude in 1935 and Talbot one of the most susceptible. In

1935 Talbot was quite ill at the summit and we did an arterial puncture on him and he had an arterial oxygen saturation, resting, of about 55 percent, with severe headaches. It was a little disturbing to us, whereas Ancel got along quite well with a much higher oxygen saturation. In 1962 Ancel had a bad time and John, who expected to have a bad time, actually got along pretty well. In fact he took his editorial work with him and enjoyed the sunshine at the summit while he was reading papers and what not. I don't know how well the job was done. Talbot was very pleased with himself while Ancel was having a bad time. He hadn't slept well, he had headaches every day, he complained about food and so on, but he was feeling however somewhat better when we went to the summit where he spent only one night and had to leave early. Talbot stayed over a second night. We got a sample of arterial blood from Ancel early in the moring. We didn't have to wake him, he said he had been awake, this was five o'clock and he said he had been awake since four. We found his arterial blood was about 80 percent saturated at the time we made the arterial puncture, whereas John's the next day was approximately 70 per cent saturated. And the way I interpret this finding was that Ancel was exhausted by loss of sleep and finally on this last night at the summit he slept very soundly, his ventilation went way down and he had a period of maybe five or six hours sleep when his saturation was down to perhaps 50 or 55 percent and the cumulative effect of this–this cerebral injury–was this very severe headache. When we made the arterial puncture his ventilation was back up again and his saturation point up to 80 percent.

DR. CHIODI: That agrees with my own experience with chronic mountain sickness; the worst part of the day for the chronic mountain sickness subject is in the morning, when you wake up. That was the worst part of the day; when I had edema in my eye was just the beginning of the morning when I woke up. I feel that's one factor, and the other perhaps is the hydrostatic change in the circulation to the brain, because when you are just supine there is not much draining and the return of the venous blood is in some way involved.

DR. DILL: We had good evidence of the variation in the wakefulness of our party, particularly of Ancel who on the first days would wake up in the morning unhappy and not only complaining of headaches but he also complained of all the noise that had been evident all night long, the breathing of some of the others. The rest of us slept through it, but he was awake listening to it.

DR. HORVATH: I would like to point out something that came out of all of Dr. Dill's observations, namely the importance of looking at individual responses. I recall very vividly the description of his first notice of this differnce in the concentration of hemoglobin or the number of red cells in older people. When Dr. Dill went back to look at Barcroft's data the mean showed the typical increase, but when he looked at the individual data, the older members of the party, especially Haldane, showed the typical decreases which Dr. Dill also observed this time. This information has been lost ir the lite.ature because we thought about average effects and we forgot that there are these variations and the average isn't enough. The older individuals on the average expedition show up the same sort of pattern as Dr. Dill is now finding. It behooves us to keep in mind again the tremendous importance of having available, for purposes of re-evaluation, individual data and that somehow or other we must devise ways of retrieval of this individual data so that we can identify some of these characteristically different changes which we have tended to ignore.

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THE REACTIONS OF THE NEWBORN TO COLD AND ALTITUDE

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Exposure of newborn animals to a cold environment can lead to a large increase in their rate of oxygen consumption, an increase largely achieved without shivering. Upon the induction of hypoxia, this thermogenic response to cold is immediately suppressed.

This paper will attempt to examine the dependency of the oxygen consumption of newborn animals on the inspired oxygen tension at low environmental temperatures. This will involve an account of the thermoregulatory responses and their control in the neonate exposed to cold under normoxic and hypoxic conditions, in comparison with those in the adult. In this presentation, altitude and hypoxia will be used interchangeably, except where otherwise specified, and will signify hypoxic hypoxia; air indicates sea-level conditions.

Heat Loss during the Prenatal Period

In air. Under cool conditions, heat is dissipated from newborn animals essentially as from adult ones, i.e., as sensible heat by way of conduction, convection and radiation (1). However, because of its relatively smaller size, the newly born has a surface-to-volume ratio larger than that of the adult. Moreover, the newborns of many species lack subcutaneous white fat and a coat of hair so that the absolute thickness of the body shell is generally less in the newborn than in the adult. Thus, axiomatically, the thermal conductance coefficient of the shell is large in the newborn, as compared to his adult counterpart (or in the small as compared to the large animal), i.e., the thermal insulation of the core is poor. As a result, the flow of heat from core to shell, and from shell to ambient air, is large in the newborn relative to the adult.

Indeed, this is illustrated most dramatically at birth when the newborn, emerging quite suddenly from a warm wet environment into a usually dry, cool and sometimes breezy environment, exhibits a tremendous susceptibility to the

thermal effects of the environment. Unless special precautions are taken to minimize the shell to ambient air temperature gradient, a precipitous fall in body temperature is invariably recorded at birth (2). It is because of this apparent thermal instability that newborns were for so long considered to be imperfect homeotherms.

At the neutral temperature, in order to minimize heat loss after birth and maintain body temperature at the optimal level (38°-39° C), euthermic newborns maintain higher skin temperatures than do adult animals (3). In a cool environment, the normal, full-term neonate can invoke postural and behavioral responses (flexion in monotocous, and nesting and huddling in polytocous species), as well as pilo-erection and peripheral vasoconstrictor reactions (which are operative in most species at birth), to adjust further heat loss (4), i.e., to increase insulation (Figure 1). Mount (5) calculated the thermal insulation in

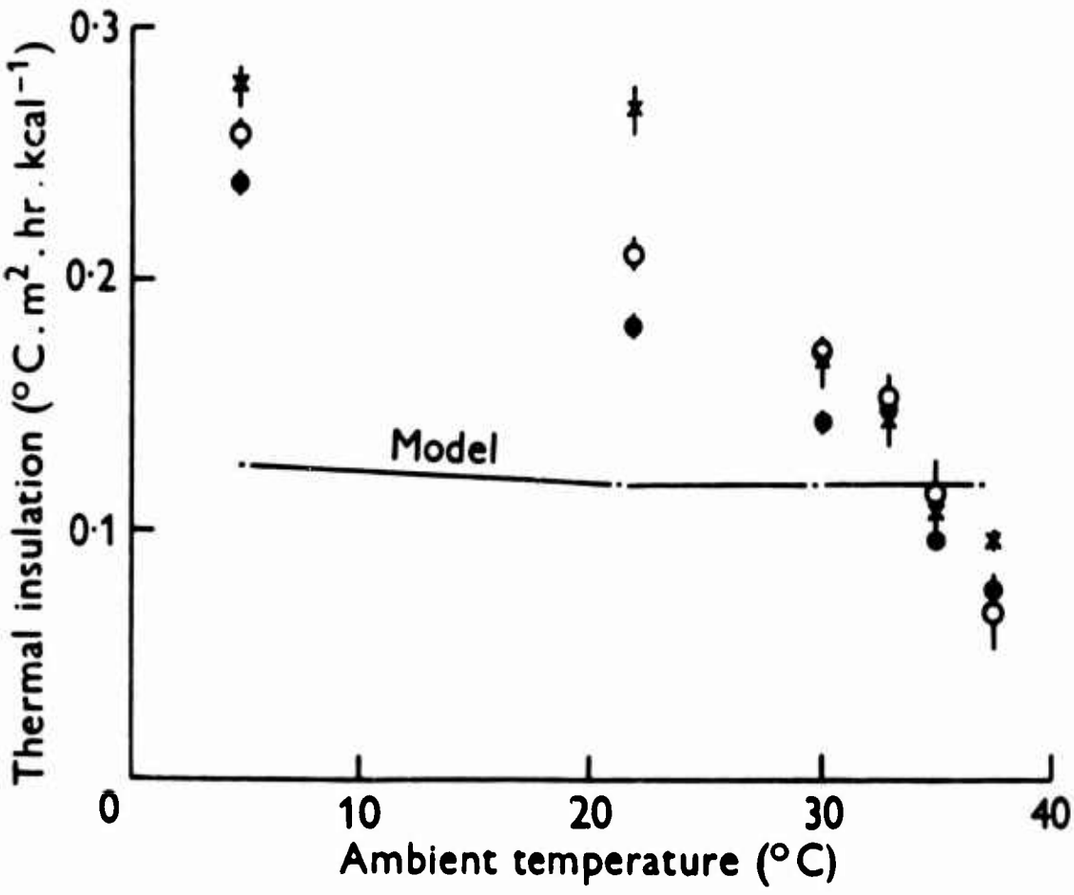


Figure 1
The thermal insulation related to ambient temperature for pigs 0 to 37 days of age. Insulation increased as the temperature decreased at all ages, but the increase was smallest in the youngest animals (0 = 1 day, ● = 1-7 days, x = 8-37 days). From Mount (4).

piglets exposed to 20° C to be about two-thirds of what it would have been without these reductions. The decrease in mean skin temperature had approximately twice the effect of the associated decrease in effective surface area in reducing heat loss. In newborn infants, Bruck and his associates (6, 7) found thermoregulatory changes in skin circulation similar to those in adults. In newborn rats, on the other hand, Hahn et al. (8) and Taylor (9) did not observe pilomotor reactions or vascular changes until the rats were two weeks of age. The suggestion is that the peripheral control of body temperature is well developed in the newborns of most species from birth, but, because of their small size and relative lack of insulation, neonatal heat conservation is inadequate to maintain body temperature in a cold environment.

Thermal insulation changes with age (Figure 1). Mount (4) found a fall in insulation in piglets during the first eight days after birth, which he attributed to a progressive postural relaxation, since his measurements were made below the critical temperature when vasoconstriction was maximal. Subsequently, thermal insulation increased again, probably in relation to the deposition of subcutaneous white fat and the growth of fur. In rats 10 days of age, white fat is present in considerable amounts.

In hypoxia. There are no systematic studies on the effects of altitude on the thermal insulation of newborn animals; nor have skin temperatures of newborns breathing low O_2 mixtures in neutral and cold environments been reported. Presumptive consideration would suggest that, due to the lowered air density, radiant heat exchange would be increased (if the humidity were low) while convective and conductive losses would be decreased. Indeed, there is some suggestion that in altitude environments with high humidity heat conservation is improved due to decreased evaporative and respiratory heat losses (12-15). However, newborn rabbits (16) and kittens (17) breathing 7-15% O_2 commonly are seen to become flushed and to grow somewhat more agitated. Even cooling under these conditions does not induce blanching, all of which might be expected to increase their rate of heat loss. Kottke et al. (18) found that the skin temperatures of adult human subjects breathing 10% O_2 while sitting in a cool room rose above those of controls. They concluded that hypoxia induces a greater dissipation of heat from the skin in a cold environment. Similar results were obtained by Wezler and Frank (19), Frank and Wezler (20), Poppen (14), Brown et al. (21), Elsner (22) and Davis (23). Jouck (24), Huhnhagen (25), and Lim and Luft (26), on the other hand, found that skin temperatures of men in a cool environment were not different during air- and hypoxic-breathing. Blatteis (11) also found no differences in mean skin temperatures between adult dogs breathing air and those breathing 12% O_2 at 6°

C, although some surfaces tended to cool more slowly (particularly the inguinal region). In sea-level men acutely exposed to 10° C at various altitudes, on the other hand, average skin temperature fell less than at sea level. Six weeks' stay at 13,800 ft. further reduced the fall in skin temperature in the cold.

The altitude newborn is usually smaller and leaner than his sea-level counterpart, and his environment is usually cooler, so that unless special precautions are taken he may be expected to lose more heat in the perinatal period.

Heat Production in the Neonate

At the neutral temperature: The minimal O_2 consumption.

1. In air: As a consequence of their meager thermal insulation, newborn animals, for optimal temperature control at minimal energy cost, are limited to a neutral thermal environment which is maintained within narrow limits (35°-37° C) near the core temperature (37°-39° C) and thus which is much higher than that of adults (25°-30° C, depending on the species and other conditions). It follows that the critical temperature of newborns is high, so that temperature which is comfortable to the adult will induce a marked thermoregulatory response in the newborn (e.g., 26° C).

The basal metabolic rate of newborn animals at parturition is only slightly higher than that of the adult if expressed on a weight basis, and considerably lower if expressed on the basis of surface area (27). However, in the days after birth, an increase in minimal O_2 consumption to levels much in excess of adult metabolic rate per kilogram of body weight, but about the same if related to surface area, has been recorded in most species studied. Thus, in human infants (28-30), there is a 75% rise over 2 days; in puppies (31,32) a threefold increase over 3-4 days; in lambs (27), a two- to threefold increase over 6 to 48 hours; in rhesus monkeys (33), a nearly twofold increase over 6-10 days; in rats (9), a 50% rise over 2 days; in kittens (34), a 50% rise over 6 days; in piglets (35), 40% over 48 hours; in guinea pigs (28), 50% over 2 days; and in rabbits (36), 50% over 4-6 days.

This increase in metabolic rate is normally accomplished by the restoration of the rectal temperature (following its acute fall immediately after birth) in most, though not in all, species. Some very small neonates (e.g., rats [2], mice [37]) remain hypothermic despite the postnatal rise in metabolic rate until one

to two weeks of age. In piglets (35), the increase in minimal O_2 consumption occurs coincidentally with the decrease of thermal insulation mentioned earlier, indicating that the rise in metabolic rate is proportionately larger than the rise in body temperature. In infants (30), the rise occurs when the body weight is decreasing, so it cannot be ascribed to an increase in body weight. It does not seem to be due, at least in monkeys and lambs (38), to a direct adaptive response to the thermal demands of the cooler extra-uterine environment, since the increase of metabolic rate is observed to the same extent at 35° and at 30° C. It is also likely that the change is not due to the increase in arterial O_2 tension at birth, since it is not observed in lambs delivered by Caesarean section and artificially ventilated with air or oxygen (27). Other possibilities which have been suggested (38) but not tested are the extra work of breathing, an increase in gastrointestinal activity, the specific dynamic action of protein, an increase in the work of postural muscles, and an increase in skeletal muscle tone associated with wakefulness. A Q_{10} effect has also been proposed, but the results of studies on the correlation between rectal temperature and minimal O_2 consumption have been contradictory (2).

The postnatal rise in minimum O_2 consumption occurs in the human baby without any concomitant increase in CO_2 production (29). Some workers (39, 40) however, have reported a decrease in CO_2 production during the infant's first few days of life.

2. In hypoxia: In adults there is little change in O_2 consumption when the O_2 content of the inspired air is progressively reduced until 6% O_2 or less is breathed. At altitude, it is generally accepted that basal metabolism is unchanged (41), although Cook (42), and Berg and Cook (43) reported a decrease in O_2 consumption due to decreased barometric pressure, and recent evidence in acclimatized subjects suggests that, on the contrary, it may be increased (44, 45).

The minimal O_2 consumption of young kittens (46), newborn rabbits (16), and monkeys (33), is not reduced until the inspired O_2 content is lowered to about 10%. The O_2 consumption of the newborn rat, however, is decreased in 18-15% O_2 at the neutral temperature (9). It is maintained, though, in rats 3.5 days or more old, probably because the ventilatory response to hypoxia increases over this time (47).

The decrease in minimal O_2 consumption of newborn rats breathing low O_2 mixtures could be due to either inadequate O_2 uptake or a decreased blood flow in certain vascular beds of the body. Certainly the animals are hypoxemic, as evidenced by general cyanosis and increased blood lactate, and possibly

reduction of blood flow to certain regions further aggravates the metabolic depression.

A fall in O_2 consumption occurs in lightly anesthetized newborn lambs at the neutral temperature when the O_2 level in the inspired air fell below 12% (48) (Figure 2). It was found also that under the conditions of these experiments the O_2 consumption of the hindquarters fell proportionately more than that of the whole lamb during hypoxia, suggesting that the reduction of O_2 consumption may be associated with regional changes in O_2 uptake. The magnitude of the fall in O_2 consumption varied with age from birth. Thus, the O_2 consumption at the neutral temperature of lambs less than one day old which had not achieved the postnatal increase in minimum O_2 consumption was very little reduced by a degree of hypoxia that reduced considerably the O_2 consumption of slightly older lambs (48). It would seem, therefore, that in the lamb the newly acquired increase of O_2 consumption appears particularly susceptible to hypoxia.

Rectal temperature is not maintained during hypoxic breathing in the newborn rabbit even when the O_2 consumption does not change (16).

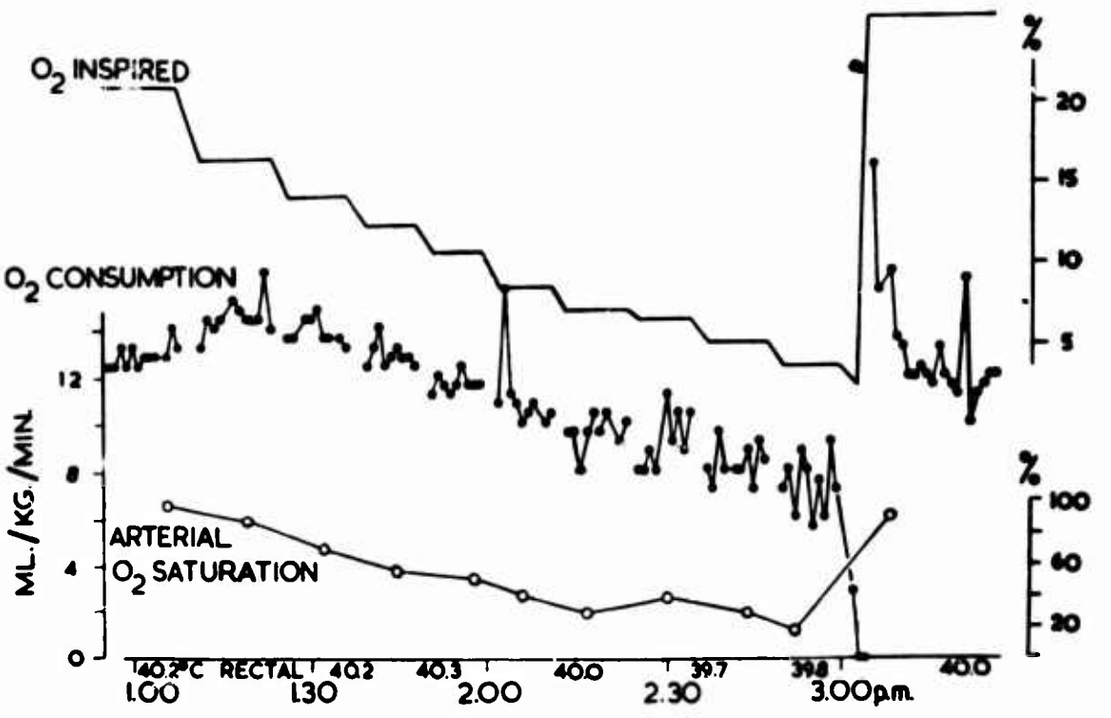


Figure 2

Effect of reducing the inspired O_2 content on the O_2 consumption and arterial O_2 saturation of a newborn lamb at the neutral temperature. The decrease in minimal O_2 consumption became evident near 15% O_2. From Cross, Dawes and Mott (48).

Below the neutral temperature: The metabolic response to cold

1. In air: Contrary to the age-related, more slowly developing increase in minimal O_2 consumption discussed above, an increase in O_2 consumption in response to cold can be elicited at birth in most species; e.g., infants (2, 7, 30), puppies (31, 46), kittens (34, 46), lambs (27), rabbits (16, 36), monkeys (33), piglets (35), rats (9), and guinea pigs (49). However, the magnitude of the response and the rate of its development differ from species to species and even between littermates.

Physiologically "mature" newborns (e.g., guinea pigs) show a larger calorigenic response than do "immature" ones (e.g., rabbits), and very small newborns (e.g., rats, mice) are least able to elicit a large metabolic rise at birth and for some days thereafter (50). Prior feeding appears to be a prerequisite to cold-induced thermogenesis at birth in rats (9). Other things being equal, however, the maximum amount of heat that a newborn can produce appears to be limited by its weight rather than its age (51), and at a given temperature during the first 17 to 20 days of life, it is generally less than the heat lost at this temperature (30). Furthermore, the metabolic rise cannot be maintained indefinitely, although this improves with age. Under these conditions, even mild cold exposure almost invariably leads to a fall in body temperature of the animal.

With advancing age, as the animal increases in size, deposits subcutaneous white fat, and grows fur, the thermoneutral range gradually widens and shifts downward. The critical temperature consequently falls, and the metabolic response evoked at a given temperature (e.g., 26° C) grows smaller and smaller. The maximum O_2 consumption in the cold, on the other hand, increases with age as the temperature at which this occurs decreases, particularly where this is feeble initially, as in the rat (10).

When exposed to environments below the critical temperature, newborn animals usually become agitated, writhe, cry, and generally grow restless. The resulting increase in O_2 consumption, however, is of itself insufficient to account for the entire metabolic rise in the cold, since the same degree of activity in the warmth yields lower metabolic rates (52). Rarely does this active behavior continue for a long time, although heat production rises two- to threefold basal levels. Indeed, Dawes and Mestyan (49) found that newborn rabbits could still double their rate of O_2 consumption on cold exposure during curariform-induced muscular paralysis (provided there was no fall in blood pressure). Electromyographic studies by Bruck and Wunnenberg (53) in unanesthetized guinea pigs have shown that during the animals' first days of life, muscle action potential discharge is negligible in animals exposed to cold, despite

a 200-300% increase in O_2 consumption (Figure 3). Variations in O_2 consumption are not correlated with electromyographic activity under these conditions (7). Thus, the elevation of heat production in a cool environment

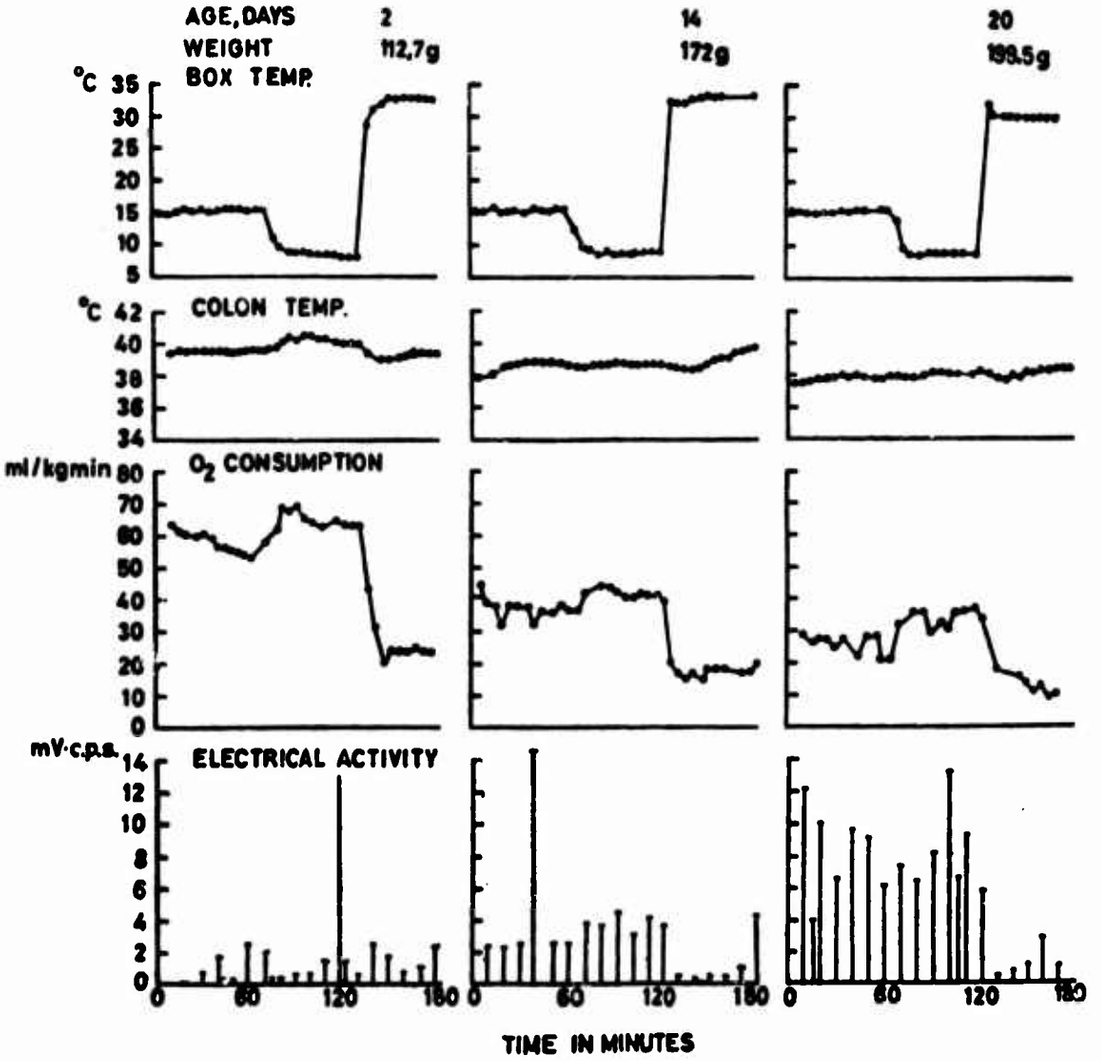


Figure 3
Colonic temperature, O_2 consumption and shivering activity of a guinea pig exposed to a cold environment 2, 14, and 30 days after birth. The rise in O_2 consumption became less with advancing age, while the shivering activity increased. From Bruck (7).

appears during the perinatal period to be due primarily to chemical thermogenesis. In this respect, newborns, of course, are completely different from normal adults, although they resemble the cold-adapted adults of some species (54). In the course of postnatal development of the animal, however, nonshivering thermogenesis is more or less, depending on the environmental conditions, replaced by shivering thermogenesis. From the second week onward

in guinea pigs (28), rhythmic discharges were occurring on cooling, and shivering became evident; a positive correlation was found between O_2 consumption, shivering, and electrical activity. The occurrence of shivering, however, did not further increase the O_2 consumption. On the contrary, it was less at this age when shivering occurred than in the early newborn without shivering.

Thus, with advancing age and the appearance of shivering, the nonshivering component diminishes. Apparently, the development of shivering thermogenesis occurs fastest in the absence of cold stimulation and can be retarded in neonates reared in cold environments (7). The adult without previous cold experience, of course, displays vigorous shivering on cold exposure (55). Shivering, however, can be induced in the early newborn when the body temperature falls below some threshold value, even when the cold-induced nonshivering thermogenesis has already increased to high levels (28). Under these conditions, shivering, when it occurs, is unaccompanied by a much further increase in metabolic rate. The threshold temperature for shivering which can be set in function under hypothermic conditions is thus lower than the core temperature normally maintained by nonshivering thermogenesis.

The metabolic rise in the cold is surprisingly prompt, occurring before there is a drop in rectal temperature (7). Day (56) and Adamsons et al. (57) found that the difference between skin and environmental temperatures showed the highest correlation of several variables tested with the magnitude of the metabolic response of the infant to cold. Mestyan et al. (50) and Scopes (2) also observed this relation, and Adamsons (58) further showed that when newborn rabbits, rhesus monkeys, and infants with low core temperatures in a cool environment were suddenly subjected to external radiant heat, their elevated O_2 consumption immediately fell to a resting level. Bruck (7) found that a plot of the metabolic rate against the average skin temperature of newborn infants fell to the right of and was steeper than the adult curve; he suggested that the thermogenic response to cold is produced in the newborn infant by stimulation of cutaneous cold receptors which are more cold-sensitive in the newborn than in the adult.

2. In hypoxia: In 1955, Cross, Tizard and Trythall (59) observed that the breathing of 15% O_2 caused a reduction in the O_2 consumption of unanesthetized newborn babies. The environmental temperature was not indicated, but it probably was below the neutral zone of the newborn human infant. This observation was confirmed in the newborn infant at 26.2° C (60), the lamb at 19° C (48), the puppy at 30° C (61), the kitten at 30° C (62), and the rat at 32° C (9), i.e., well below the thermoneutral environment for the neonates studied. In 1959, Dawes and Mott (47) and Adamsons (63) showed

that the ventilatory response of newborn rabbits to hypoxia varies with the environmental temperatures below the neutral zone, and Hill (17) presented evidence that, in response to a given degree of hypoxia, the O_2 consumption of newborn kittens may be either unchanged or greatly reduced, depending entirely on whether the animal was originally consuming O_2 at its basal rate or faster than this. In these experiments the animals' original metabolic rate was varied by changing the thermal environment.

It has since been amply confirmed that it is the "extra" metabolism of the cold-exposed newborn which declines when the ambient O_2 tension is suddenly reduced in a cool environment. This is illustrated in Figure 4.

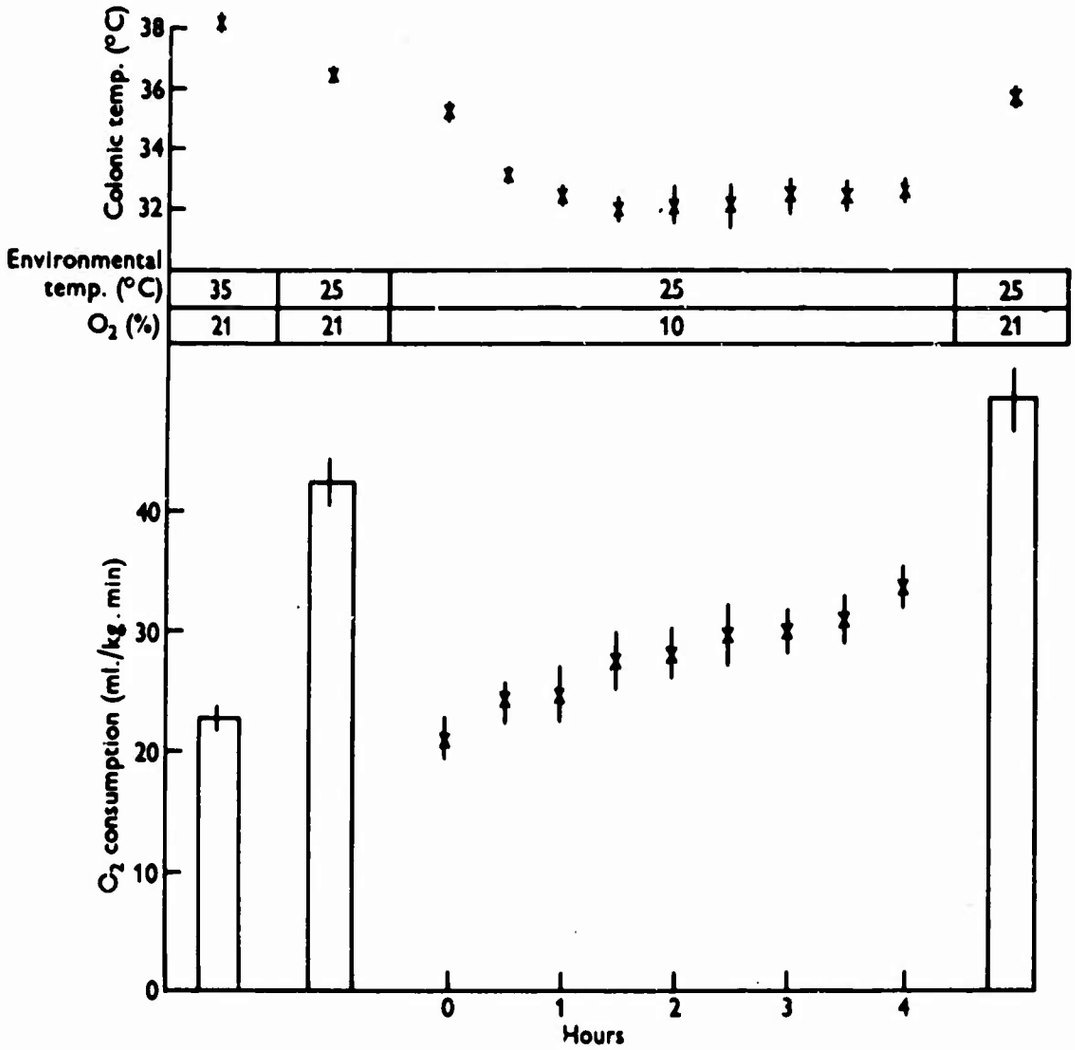


Figure 4

The colonic temperature and O_2 consumption of newborn rabbits at the neutral temperature and in a cold environment (breathing air and 10% O_2). Hypoxia initially abolished the rise in O_2 consumption caused by cold exposure. However in the subsequent four hours, O_2 consumption gradually recovered. Shivering developed after one hour and persisted into the post-hypoxial period. From Blatteis (16).

The metabolic response to cold is at once and precipitously reduced by acute hypoxia in newborn rabbits (16), kittens (17), rats (9), mice (64), monkeys (33), puppies (46), lambs (48), and infants (29, 59). The extent of the O_2 consumption fall depends on the degree of hypoxia (16, 46). Rectal temperature falls rapidly under these conditions, proportionally to the degree of hypoxia and the depression of O_2 consumption.

The hypoxic reduction of the metabolic response to cold is not uniform with time. In newborn rabbits exposed to 10% O_2 at 25° C for four hours, after an initial large fall, there was a gradual recovery of the O_2 consumption (16) (Figure 4) to approximately 50% of its pre-hypoxial level. This was accompanied by increasingly vigorous shivering which developed after an hour of the hypoxic exposure. Previous exposure to 10% O_2 at 35° C or to 25° C in air did not modify the immediate reduction of the O_2 consumption by 10% O_2 (at 25° C) subsequently (16).

On reoxygenation, the depression of the cold-induced increase in O_2 consumption is reversed, the metabolic rate rising rapidly to values frequently higher than those obtained before exposure to hypoxia (16). The rectal temperature, lower at this point than before hypoxia, also increases very rapidly, but following the rise in O_2 consumption, not leading it. Shivering does not normally accompany this recovery.

The hypoxic depression of the metabolic response to cold is not confined to neonatal animals alone. Adult animals are equally susceptible, although it appears that the smaller species are the more sensitive (17). Lintzel (65) has shown that the O_2 consumption of adult rats at low atmospheric pressure is much reduced at environmental temperatures below the neutral zone. This response has been confirmed in the human (18), rabbit (66), dog (18, 67, 68), rat (69), cat (70), and mouse (18, 64). There is, however, disagreement as to whether shivering is abolished under these conditions (70, 71). The partial recovery of this hypoxic depression has been documented in the adult dog breathing 12% O_2 during three hours at 6° C (67) (Table I).

The mechanism of the depressing action of hypoxia on the O_2 consumption increase in the cold is uncertain. Mott (66) showed that stimulation of systemic arterial chemoreceptors inhibits shivering in the adult cold-exposed rabbit and suggested that hypoxic excitation of these receptors may be the means whereby the metabolic response to cold is abolished by hypoxia. However, Blatteis (16) showed in the newborn rabbit that when the carotid sinus nerves and the vagi are cut, the hypoxic-induced fall in the increase in O_2 consumption in the cold is not prevented (Fig. 5). Adamsons (63) observed that the increased respiratory frequency and minute volume induced in

	Air 26°C	Air 6°C	Air or 12% O_2 6°C				Significance (air vs. hypox)
O_2 Consumption (ml/Kg/min.)	Controls						
Air (n=4)	8.21 ±.43	11.98^{0} ±1.30	13.67^{0} ±1.58	13.72^{2} ±.82	14.13^{2} ±.92	13.09^{2} ±.52	13.92^{2} ±1.09	
Hypoxia (n=8)	7.52 ±.54	11.57^{2} ±.95	8.29^{4} ±.87	$9.94^{0.1'}$ ±1.06	10.41^{0} ±1.39	10.39^{1} ±1.09	11.09^{1} ±1.47	
n=12	7.75 ±.38	11.71^{2} ±.73						
Rectal Temp. (°C)								
Air (n=4)	38.78 ±.15	39.08^{2} ±.19	39.10^{2} ±.20	39.12^{2} ±.20	39.25^{2} ±.25	39.22^{2} ±.25	39.20^{2} ±.23	F = 5.15
Hypoxia (n=8)	38.80 ±.11	39.02^{2} ±.12	38.48 ±.17	38.44 ±.18	38.39 ±.19	38.12 ±.18	38.11 ±.15	P<.025
n=12	38.79 ±.08	39.04^{2} ±.09						

Significant differences between air and hypoxia determined by analysis of variance are indicated by F ratios. Comparisons significant by paired t-test are indicated by superscripts as follows:

from 26°C, 0 = p<.05, 1 = p<.02, 2 = p<.01

from 6°C, 1' = p<.05, 2' = p<.02 3' = p<.01, 4' = p<.005

TABLE I

The effect of exposure to 6° C for 3½ hours either in air or in 12% O_2 on the O_2 consumption and rectal temperature of unanesthetized dogs. The values represent means ±S.E. From Blatteis (67).

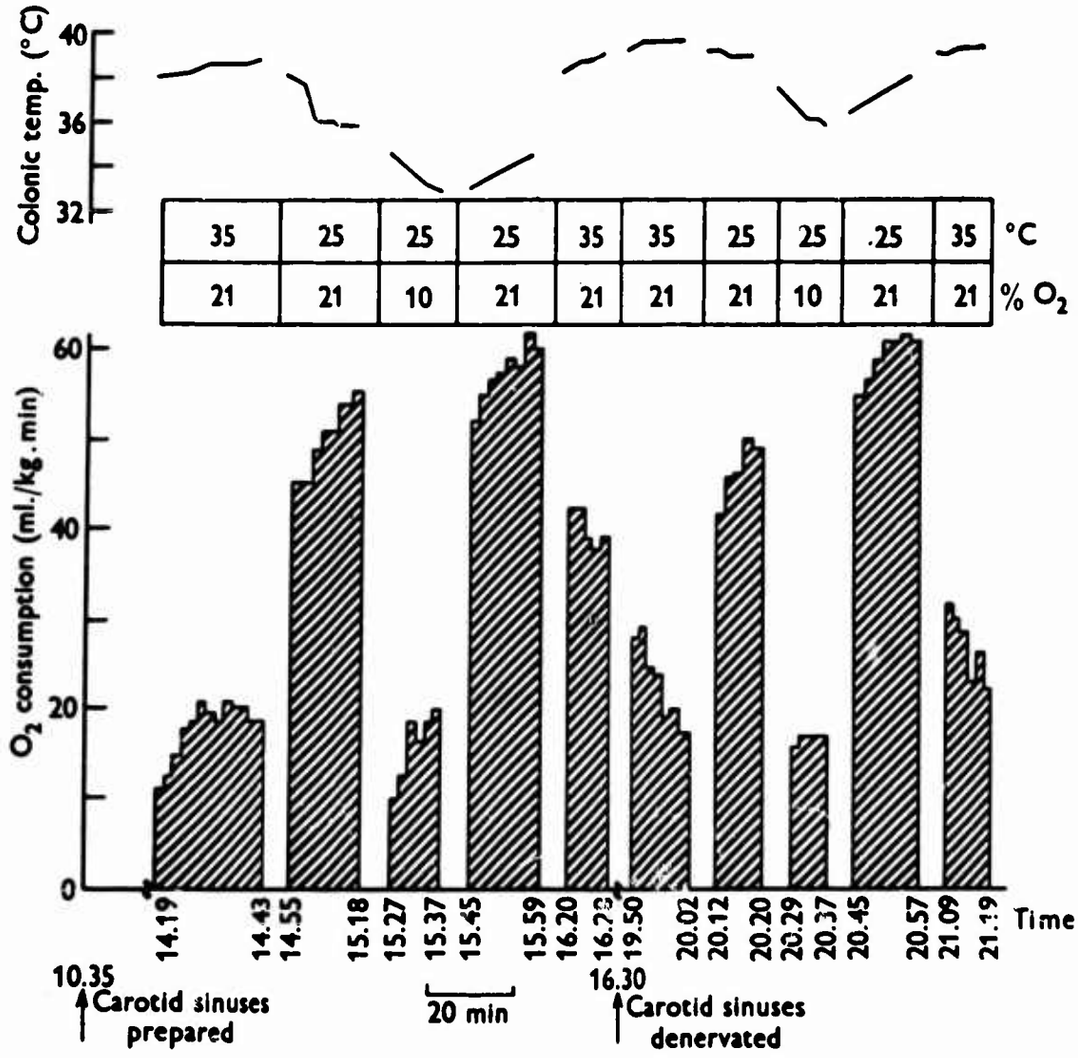


Figure 5

Effect of carotid sinus nerves section on the hypoxic depression of the metabolic response of newborn rabbits to cold. Carotid sinus denervation had no effect on this response. From Blattels (16).

newborn rabbits by breathing 10% O_2 in the thermoneutral environment was less in a cool environment. He suggested that the reduction in O_2 consumption caused by hypoxia in the cold may be due, in part, to the decrease in the work of breathing. However, administration of pictrotoxin to newborn rabbits during cold exposure in hypoxia did not reverse the fall in O_2 consumption, although it increased the respiratory rate markedly (11). Examining the possibility that vascular shunting mechanisms consequent to the hypoxia may be involved in the hypoxic depression of the metabolic response to cold, Moore and Underwood (46) noted that adrenergic blockage with hexamethonium modified

quantitatively but not qualitatively the response in newborn kittens, suggesting that this was probably not the mechanism involved. In the adult cold-exposed rat, Jarai and Lundvay (72) found that the hypermetabolism of ∝-DNP was not abolished by hypoxia, although the fall in body temperature was not diminished and Donhoffer et al. (69) found that epithalamic lesions abolished the fall in O_2 consumption caused by hypoxia in the cold, but not the fall in rectal temperature.

Hence, the nature of the hypoxic depression of the metabolic response to cold in both newborn and adult animals remains controversial, but it would seem that the nonshivering component is the more hypoxia-sensitive.

The Probable Mediator of the Metabolic Response to Cold During Early Postnatal Life: Noradrenaline

The effect of catecholamines on O_2 consumption at sea level. It is well known that the administration of adrenaline to adult mammals causes a large rise in O_2 consumption; noradrenaline and other sympathomimetic amines have a similar but less powerful action.

In the newborn human (39), kitten (17), rat (9), and rabbit (16, 49), however, it has been shown that, at an environmental temperature of 35° C, noradrenaline has the larger calorigenic action (73) (Figures 6 & 7). Isoprenaline shares this potency, but adrenaline is less effective. In newborn rabbits, adrenaline causes an immediate fall in O_2 consumption, and the delayed rise reaches a maximum which is only 25% of the response to noradrenaline (16, 49, 74). In a cool environment (25° C), noradrenaline has little effect on O_2 consumption when it is already high, and adrenaline reduces it, but not so if it is low. Dawes and Mestyan (49) suggested that this might simply be due to an inability of the tissues and the circulation to respond any further, since an increase in the infusion rate in thermo-neutrality does not lead to a further proportionate increase in O_2 uptake, but rather can cause respiratory distress and even pulmonary edema.

The dependence of both newborn animals and cold-adapted adults on nonshivering thermogensis in a cool environment, plus the greater potency of noradrenaline to exert a calorigenic effect, have suggested to Moore and Underwood (73) that noradrenaline might be the "regulator" of heat production in the newborn animal in a cool environment. There is considerable evidence that in adults the sympathetic nervous system influences the metabolic response to cold (54).

The observation that the increase in O_2 consumption on cold exposure is

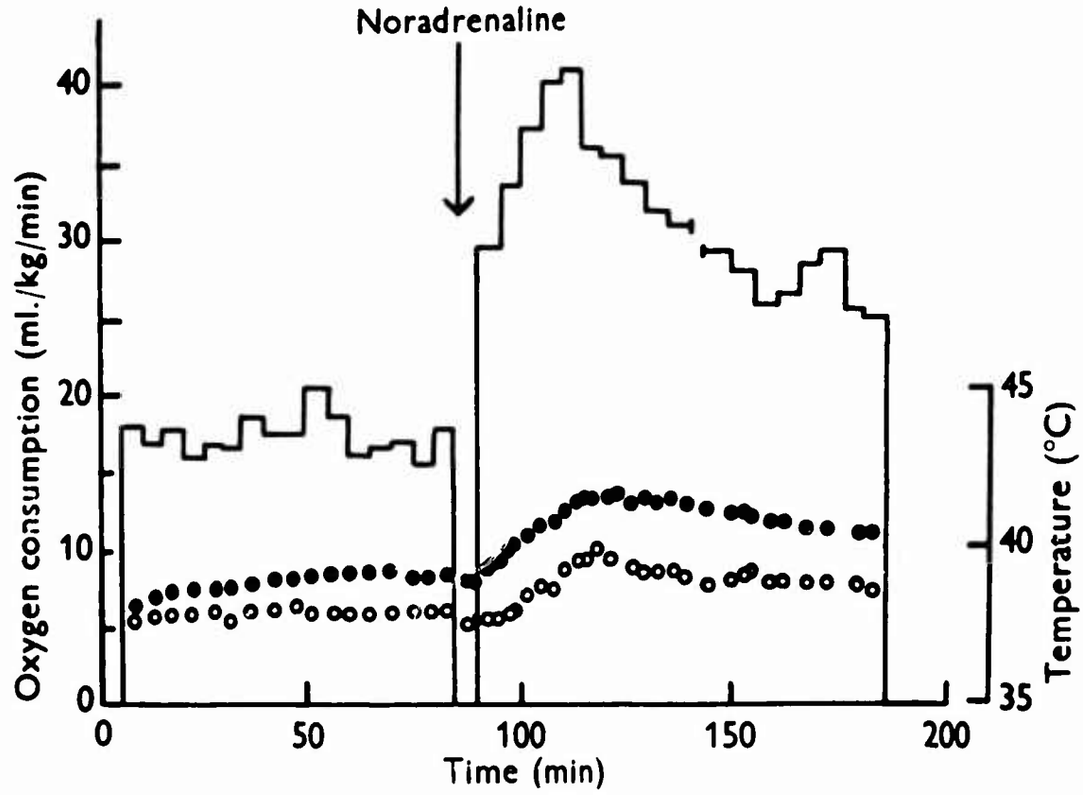


Figure 6

Effect of noradrenaline, 400 µg/kg. s.c., on O_2 consumption and body temperatures (0 = rectal; ● = clipped lumbar skin) in a 3-day old kitten at 35° C environmental temperature. From Moore and Underwood (73).

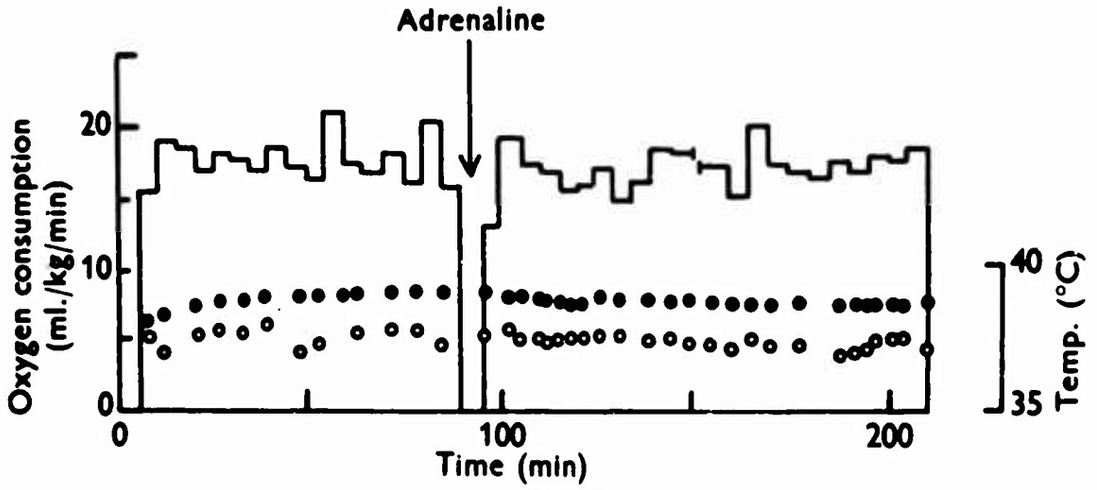


Figure 7

Effect of adrenaline, 400 µg/kg. s.c., on O_2 consumption and body temperatures (symbols as in Figure 6) in a 5-day old kitten at 35° C environmental temperature. From Moore and Underwood (73).

greatly reduced or abolished by administration of various catecholamine antagonists in newborn kittens (17, 46), puppies (46), guinea pigs (53), and rabbits (49), gave some support to the hypothesis that the catecholamines also might be operative in the cold-exposed newborn. Also, a 25% increase in urinary excretion rate of the catecholamine metabolite, VMA, was demonstrated in babies 4-9 days of age at an environmental temperature of 75° F as compared with 85° F (39). Bruck and Wunnenberg (53) found that when the cold-induced rise in O_2 consumption was blocked by adrenolytic agents, very young guinea pigs began to shiver even while O_2 consumption and rectal temperatures were falling, indicating a selective action by these agents on nonshivering thermogenesis (Fig. 8). Under these conditions, the elicitation of shivering prevented the O_2 consumption from being reduced all the way to the basal level. However, even those animals who displayed vigorous shivering were unable to maintain or restore the level of O_2 consumption that was observed prior to the administration of the drug.

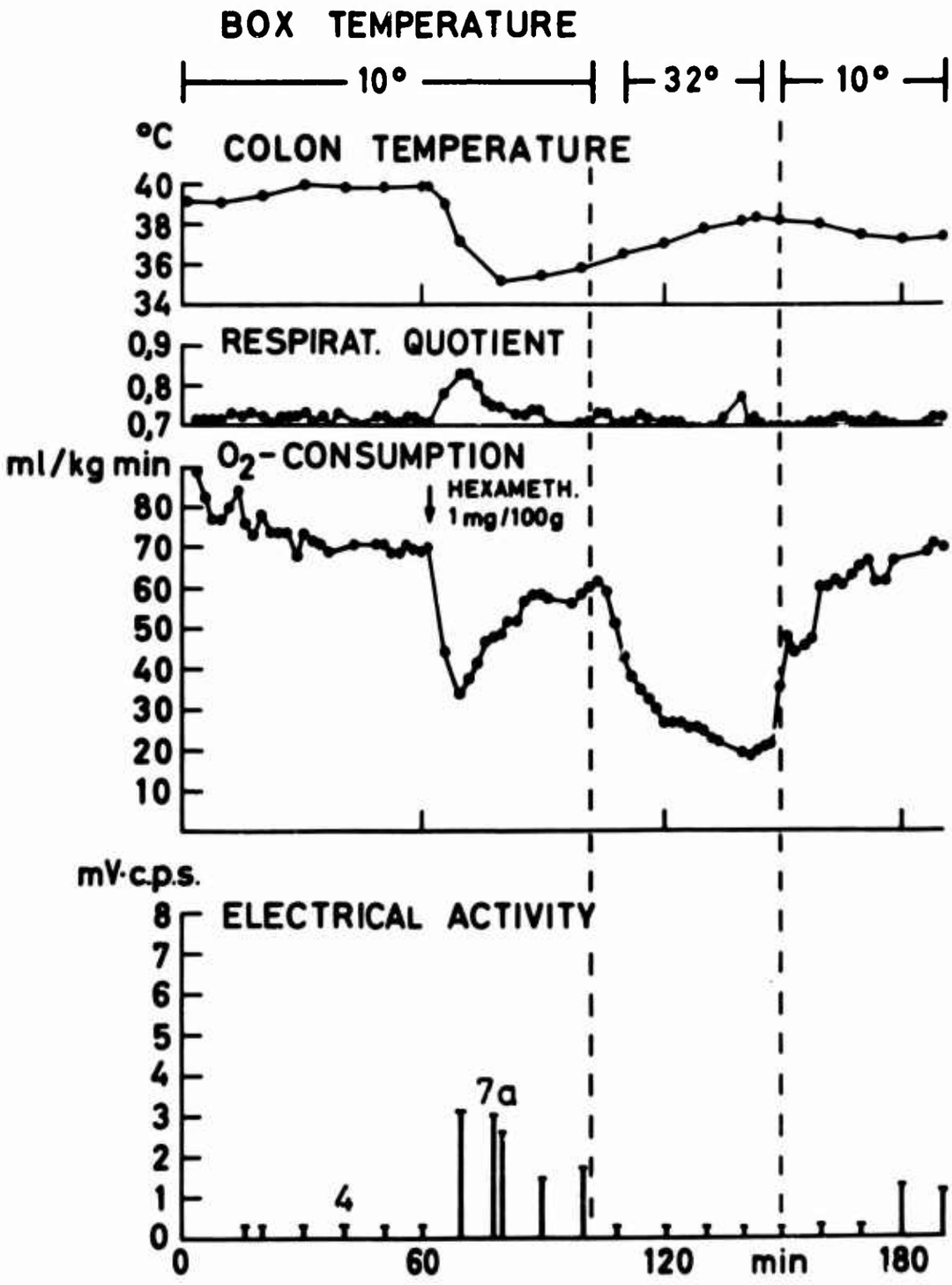


Figure 8

The effect of hexamethonium on the metabolic response of a newborn guinea pig to cold. Injection of this agent induced an immediate fall in O_2 consumption and colonic temperature. Shivering, which was insignificant before the drug, developed during the depression of the O_2 consumption. The RQ increased. From Bruck and Wunnenberg (53).

Evidence in support of a primary role for noradrenaline is not conclusive, however. The results of Moore and Underwood (73) were obtained with hexamethonium and have been challenged (49) because this drug causes a fall in cardiac output and in blood pressure. Bruck (53) also used hexamethonium and DCI and pronethalol in newborn rabbits. It has been shown that selectively-induced hypotension also causes cold-induced thermogenesis to fall (49). In rabbits (74), pronethalol prevents the increase of O_2 consumption during a 10-minute infusion of noradrenaline, but does not alter the rise in cold-induced metabolic rate, suggesting that circulating noradrenaline is probably not essential to the metabolic response to cold (Fig. 9). DCI, on the other hand, causes a rise in O_2 uptake and rectal temperature (53).

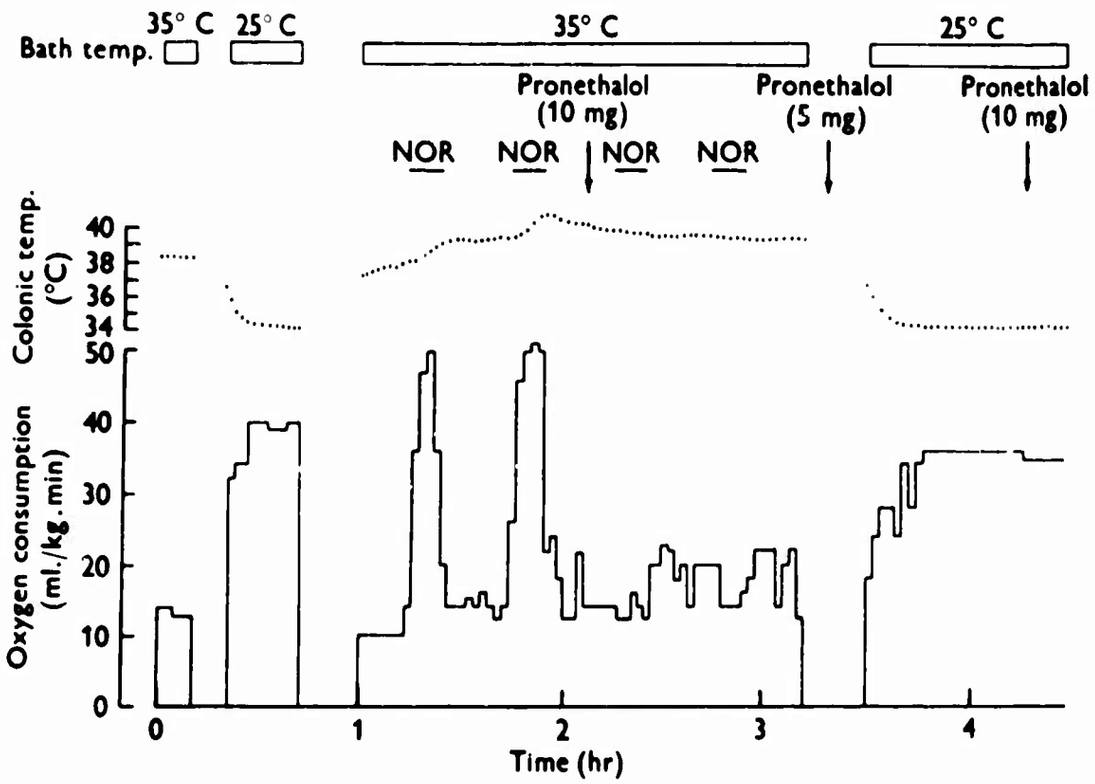


Figure 9

Pronethalol, noradrenaline and the metabolic response to cold in a newborn rabbit. Pronethalol abolished the rise in O_2 consumption caused by noradrenaline infusion but not that due to cold. From Hull (74).

Moreover, the relative calorigenic potency of noradrenaline and adrenaline is different in different species and probably related to maturity at birth. After treatment with dibenzyline, kittens become thermogenically responsive to adrenaline, while newborn untreated guinea pigs respond to both catecholamines almost equally (49). Thus, the role of noradrenaline in the metabolic response of neonates to cold is not fully clear, although a generalized sympathetic discharge on cold exposure cannot be ruled out.

As animals grow older, the stimulation of their metabolism by catecholamines varies both in character and in degree (73). By 25 days of age, the thermogenic potency of noradrenaline has progressively declined. By the same token, the inhibitory action of the adrenergic blocking agents on the metabolic response to cold gradually lessens (7, 75) (Figure 10). When shivering is already present, as in older animals, it remains uninfluenced by the adrenolytic agents, further suggesting that these agents may block nonshivering thermogenesis selectively under these conditions.

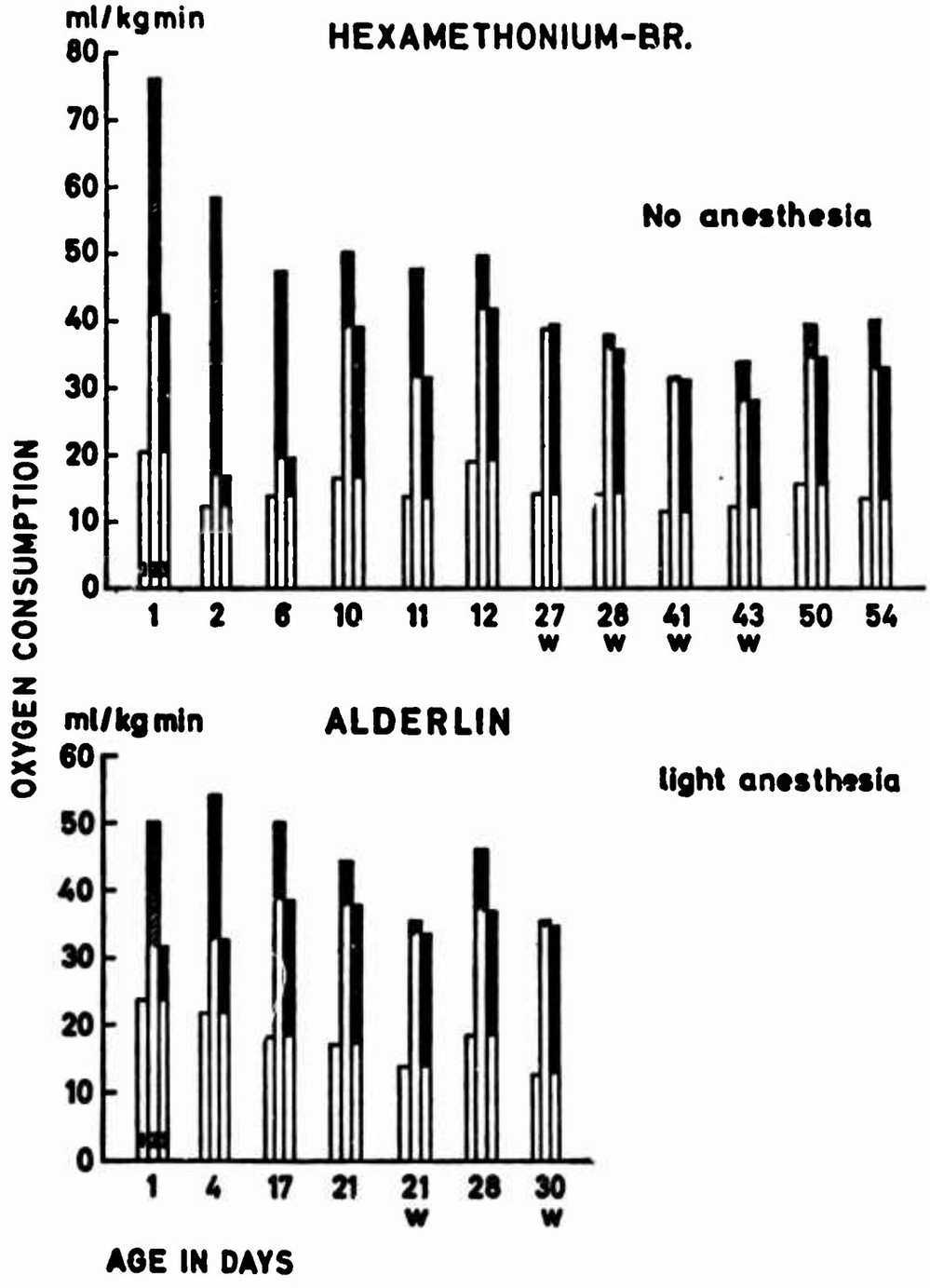


Figure 10

Effect of adrenergic blockade on the metabolic response to cold of guinea pigs of different ages (1 = minimal O_2 consumption; 2 = O_2 consumption in the cold; 3 = O_2 consumption in the cold during adrenergic blockade. Striped area = nonshivering heat production; shaded area = shivering heat production). Hexamethonium and alderlin reduced the increase in O_2 consumption caused by cold exposure, but did not abolish it. Shivering developed during the adrenergic blockade, and probably prevented the total suppression of the O_2 consumption. With increasing age, as shivering supplanted nonshivering means of heat production, hexamethonium and pronethalol were progressively less effective in inhibiting the O_2 consumption response to cold. From Bruck (7).

The influence of hypoxia on the catecholamine-induced increase in O_2 consumption. The increase in O_2 consumption caused by noradrenaline is significantly reduced by hypoxia in the newborn rabbit (16, 76), kitten (46), and puppy (46). The inhibition occurs at both neutral and cold temperatures (16) (Table II). The rise in body temperature normally caused by noradrenaline administration is reduced or abolished under these conditions.

Environmental temperature (°C) ...	35	35	25	25
O_2 content of gas breathed (%) ...	21	10	21	10
Controls (55/6)	22·9 ± 1·4	20·2 ± 1·0	43·2 ± 2·7	25·8 ± 2·0
Noradrenaline	52·0 ± 2·3	29·9 ± 1·9	56·8 ± 4·1	36·0 ± 2·5
	+127%	+48%	+31%	+40%
Controls (38/4)	20·7 ± 1·8	19·3 ± 1·4	30·2 ± 2·3	23·7 ± 1·0
Isoprenaline	40·4 ± 5·2	29·4 ± 2·2	40·0 ± 2·6	29·8 ± 1·5
	+95%	+52%	+32%	+26%
Controls (36/4)	22·4 ± 1·7	18·4 ± 0·5	43·6 ± 5·8	30·8 ± 3·9
Adrenaline	29·6 ± 2·1	26·4 ± 2·8	44·9 ± 4·5	31·2 ± 1·9
	+32%	+43%	+3%	+1%

TABLE II

Effect of hypoxia on the O_2 consumption increase caused by noradrenaline, isoprenaline, and adrenaline in newborn rabbits. Hypoxia significantly reduced the metabolic actions of noradrenaline and isoprenaline, but not of adrenaline, in both a thermoneutral and a cool environment. From Blatteis (16).

The hypoxic suppression of noradrenaline thermogenesis is similar in many respects to the depression of the cold-induced increase in O_2 consumption by hypoxia. The degree of reduction varies with the degree of hypoxia (46). The suppression during an infusion is not transient, but lasts as long as hypoxia is allowed to persist. It occurs irrespective of the stage of the metabolic action of the amine at which hypoxia is induced (46). If this is during the course of a noradrenaline response, then there is an immediate fall in O_2 consumption; if before, then either no response or a smaller response is observed. If the animal is held in hypoxia until the metabolic action of the injected hormone is over, re-oxygenation produces no increase in O_2 consumption. Re-oxygenation before this restores the level of O_2 consumption to a level comparable with that of an animal in air at the same time after injection of noradrenaline. Hence, it would appear that hypoxia does not delay the O_2 consumption response to noradrenaline, but suppresses it.

The calorigenic action of isoprenaline is similarly reduced by hypoxia in the newborn rabbit (16). But hypoxia does not alter the metabolic response to adrenaline either at 35° or 25° C (16), probably because of the smaller overall rise in O_2 consumption caused by this catecholamine in neonates.

Hypoxia is still able to reduce the noradrenaline-induced increase in O_2 consumption in the hexamethonium-treated newborn kitten and puppy (46), i.e., hypoxia alone is as potent a depressant of O_2 consumption as the combination of hypoxia and hexamethonium. This suggests, then, that hexamethonium does not block all the O_2 consumption which can be affected by hypoxia, but does not clarify whether hypoxia and hexamethonium are both acting on a common mechanism.

Blatteis (67) recently showed that in the adult dog the metabolic action of adrenaline, which is the larger in adult animals, is significantly reduced (or delayed) by hypoxia. On the other hand, the O_2 consumption rise caused by noradrenaline, which is small, is little affected by moderate hypoxia (Table III).

Hence, the inhibition by hypoxia of the metabolic action of the catecholamines is consistent at all ages of the animal, although the amine so affected depends on whether its thermogenic action is the more potent at the given age. Beyond this, it is still not clear why hypoxia inhibits this response.

Sites of Heat Production in the Neonate

The possible role of brown adipose tissue in neonatal thermogenesis. On the basis of findings in adult animals exposed to cold, possible major sites of heat production in the newborn might be skeletal muscle, liver, and brown fat. Newborn animals do not shiver readily, as we have seen. Dawkins and Hull (77) studied newborn rabbits exposed to 20° C and found that even when they did shiver, the subcutaneous temperature close to the lumbar muscles was always much lower than the deep colonic temperature, suggesting a minor calorigenic importance of muscle. Scopes and Tizard (76) investigated heat production in the liver and found that in functionally eviscerated kittens there was a 51% decrease in the minimal O_2 consumption, while the increase of O_2 uptake on infusion of noradrenaline was 50% of that before evisceration. Dawkins and Hull (77) found liver temperature to be always lower than deep colonic temperature in newborn rabbits. Thus, neonatal thermoregulatory heat production does not appear to be confined to the liver, although it may contribute to it.

Silverman et al. (79) and Dawkins and Scopes (79) noted that the temperature of the nape of the neck of cold-exposed newborn infants remained relatively warmer as compared with other surfaces, and Dawkins and Hull (77) observed that the subcutaneous temperature over the interscapular brown fat

	AIR			HYPOXIA		
	Oxygen Consumption (ml/Kg/min.)	FFA (mEq/L)	Glucose (mg%)	Oxygen Consumption (ml/Kg/min.)	FFA (mEq/L)	Glucose (mg%)
Controls	$9.39^{\dagger}.96$	$0.85^{\dagger}.11$	$108^{\dagger}4.8$	$7.86^{\dagger}.60$	$0.73^{\dagger}.19$	$101^{\dagger}8.2$
Epinephrine	$11.68^{\dagger}.80^{3}$	$1.55^{\dagger}.26^{1}$	$170^{\dagger}18.6^{1}$	$9:40^{\dagger}.86^{0}$	$1.72^{\dagger}.16^{1}$	$162^{\dagger}22.1^{1}$
Recovery (n=12/7)	$12.05^{\dagger}.82^{3}$			$8.28^{\dagger}1.08$ (F=4.49) (p<.05		
Controls	$7.20^{\dagger}.80$	$0.71^{\dagger}.03$	$109^{\dagger}6.7$	$6.77^{\dagger}.93$	$0.71^{\dagger}.09$	$110^{\dagger}2.7$
Norepinephrine	$9.11^{\dagger}1.23^{2}$	$2.70^{\dagger}.44^{1}$	$143^{\dagger}3.7^{1}$	$7.49^{\dagger}.79$	$2.21^{\dagger}.49^{1}$	$143^{\dagger}12.4^{1}$
Recovery (n=9/5)	$8.96^{\dagger}1.19$			$8.33^{\dagger}.81$ (F=1.04) (p>.20)		

†Indicates significant differences between air and hypoxia, by analysis of variance.

The numerical superscripts indicate significant differences from control by paired t-test as follows: 0=p<.05, 1=p<.02, 2=p<.01, 3=p<.005.

TABLE III

The effect of intravenous infusion of catecholamines (2μg/Kg./min. for 10 min) on the O_2 consumption, the plasma free fatty acid (FFA) and glucose concentrations of unanesthetized dogs exposed to 26° C in air or 12% O_2. The figures indicate the means ±S.E. (n-infusions/dogs). From Blattels (67).

pad of newborn rabbits fell less (by 2° C) during exposure to cold than did the colonic temperature (Figure 11). This was confirmed by Donhoffer and Szelenyi (80) in the newborn rabbit, and by Bruck and Wunnenberg (81) in the newborn

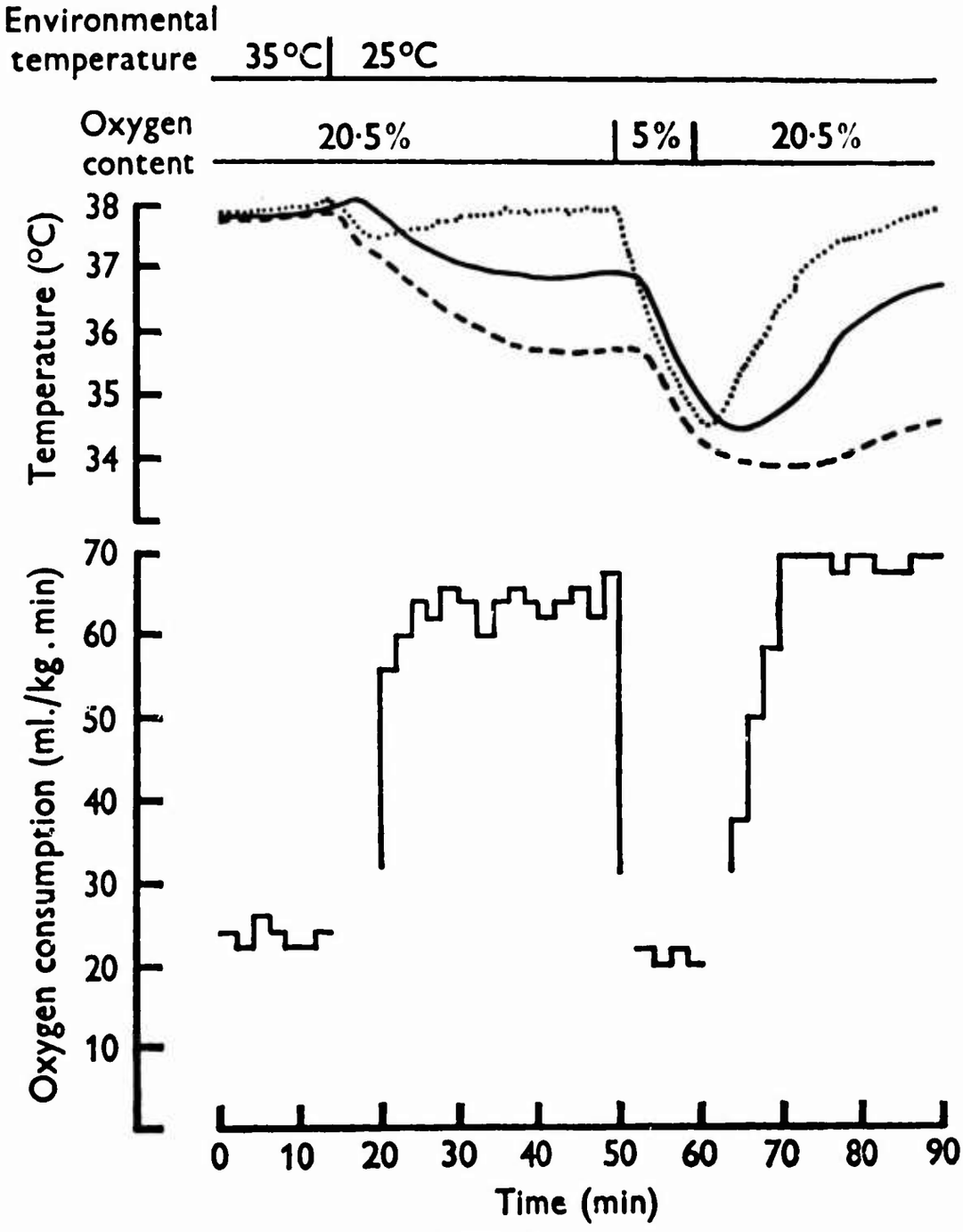


Figure 11

O_2 consumption, subcutaneous interscapular (···), subcutaneous lumbar (---), and colonic (——) temperatures of a 12-hour old rabbit at thermoneutrality and in the cold (breathing air and 5% O_2). The temperature over the interscapular brown fat pad was consistently higher than the others. It fell first during hypoxia and rose first during reoxygenation, simultaneously with the changes in O_2 consumption. From Dawkins and Hull (77).

guinea pig. Hull and Segall (82) found, furthermore, that the removal of brown fat reduced the increase in O_2 consumption on exposure to cold (82%) or infusion of noradrenaline (80%) in the newborn rabbit (Figure 12). Bruck and Wunnenburg (81) demonstrated that blood flow measured indirectly in the interscapular brown fat pad of newborn guinea pigs increased simultaneously with the metabolic rate following both administration of catecholamines and exposure to a cool environment. Heim and Hull (83) confirmed the increase in blood flow in the newborn rabbit by direct measurement of the venous outflow from a portion of the cervical and interscapular brown fat pads.

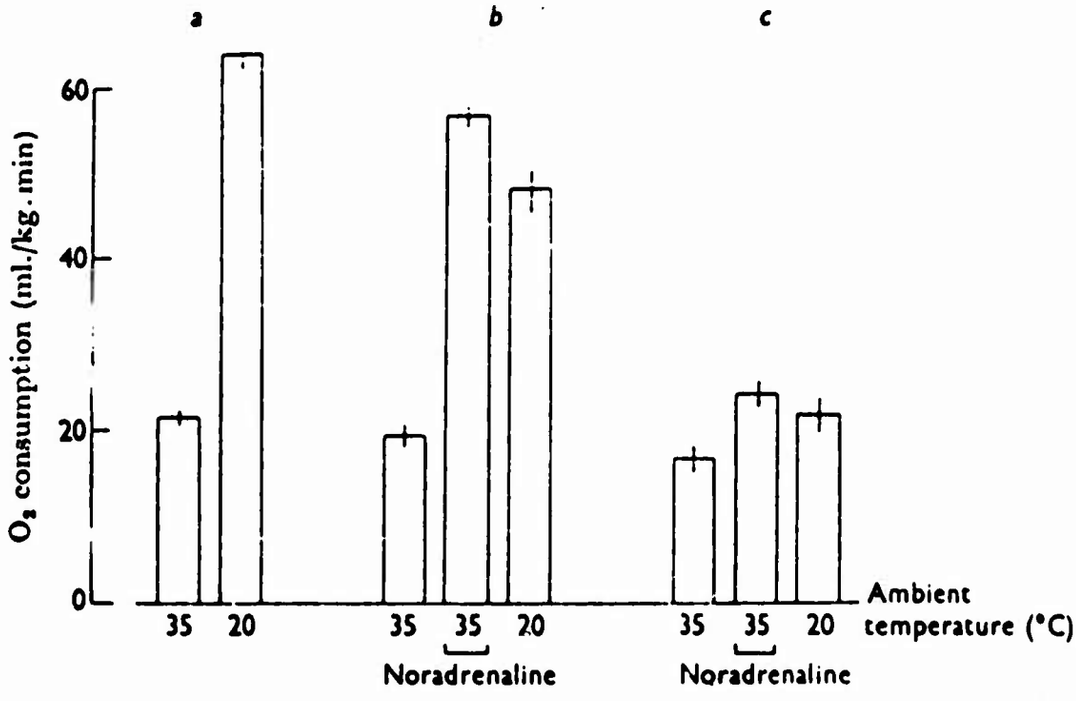


Figure 12
Contribution of the interscapular brown fat pad to the O_2 consumption response to noradrenaline and cold in newborn rabbits. Removal of this pad abolished the rise in O_2 consumption produced by noradrenaline and cold. From Hull and Segall (82).

Both the noradrenaline and cold-induced increases in brown fat blood flow could be reduced or abolished by pronethalol (83). This often caused the onset of shivering. These results inferred that the sympathetic nervous system participates in the control of heat production in brown fat, probably by the local release of noradrenaline (83). Indeed, brown fat has a rich nerve supply and contains comparatively large amounts of noradrenaline (84). When the sympathetic nerves to brown fat are cut, the fat depletion which normally occurs during prolonged exposure to cold is prevented (85). Denervated brown fat appears to be unable to utilize its stored fat for heat production, while, on the other hand, stimulation of the cervical sympathetic nerve of the newborn rabbit causes a rise in the temperature of the anterior cervical lobe of brown fat (26).

The role of brown fat in thermogenesis, where it has been demonstrated, diminishes rapidly with increasing age. Bruck and Wunnenberg (81) observed in guinea pigs 25-42 days old that the temperature difference between brown fat tissue and colon remained low and showed that the decline of the thermogenic capacity of brown fat occurred simultaneously with its replacement by white fat and coincidentally with the disappearance of nonshivering thermogenesis and its replacement by shivering.

The effect of hypoxia on brown adipose tissue thermogenesis. Dawkins and Hull (77) observed that the rectal, subcutaneous lumbar, and subcutaneous interscapular temperatures of newborn rabbits fell simultaneously with the O_2 consumption where the inspired O_2 was abruptly reduced to 5% at 25° C (Figure 11). The subcutaneous temperature over the brown adipose tissue approached that in the lumbar region, indicating that the insulation over the two sites was similar. On re-oxygenation, the temperature over the interscapular fat pad immediately increased, while the lumbar subcutaneous and rectal temperatures continued to fall. Later, the rectal temperature started to rise before the subcutaneous lumbar temperature. Heim and Hull (83) found that in newborn rabbits the increase in blood flow though the interscapular brown fat pad caused by infusion of noradrenaline or exposure to 25° C was only slightly reduced when these animals were exposed to hypoxia, although the increase in O_2 consumption or rectal temperature was absent under these conditions. They concluded that heat production in brown adipose tissue is dependent on an immediate and generous supply of oxygen.

Different means, however, must exist whereby hypoxia reduced the O_2 consumption increase caused by cold and catecholamines in other neonates and in adults in whom the thermogenic role of brown fat is less clear. Indeed,

hypoxia may even be a stimulus to "brown" fatty tissue development in the adult rat (86). Hence, the exact mechanisms by which the effects of exposure to hypoxia on O_2 consumption are mediated remain obscure.

Chemical Basis of Heat Production in Newborn Animals

In air. In the adult of most species, both exposure to cold and administration of catecholamines induce an increase in the plasma levels of glucose, free fatty acids (FFA) and glycerol.

In contrast, the changes in blood FFA and glucose during cold exposure and after infusion of catecholamines are small in infants (79), newborn rabbits (76, 77) (Figures 13-14), and rats (87,88). Their blood lactate and ketone levels also do not rise much under these conditions (76).

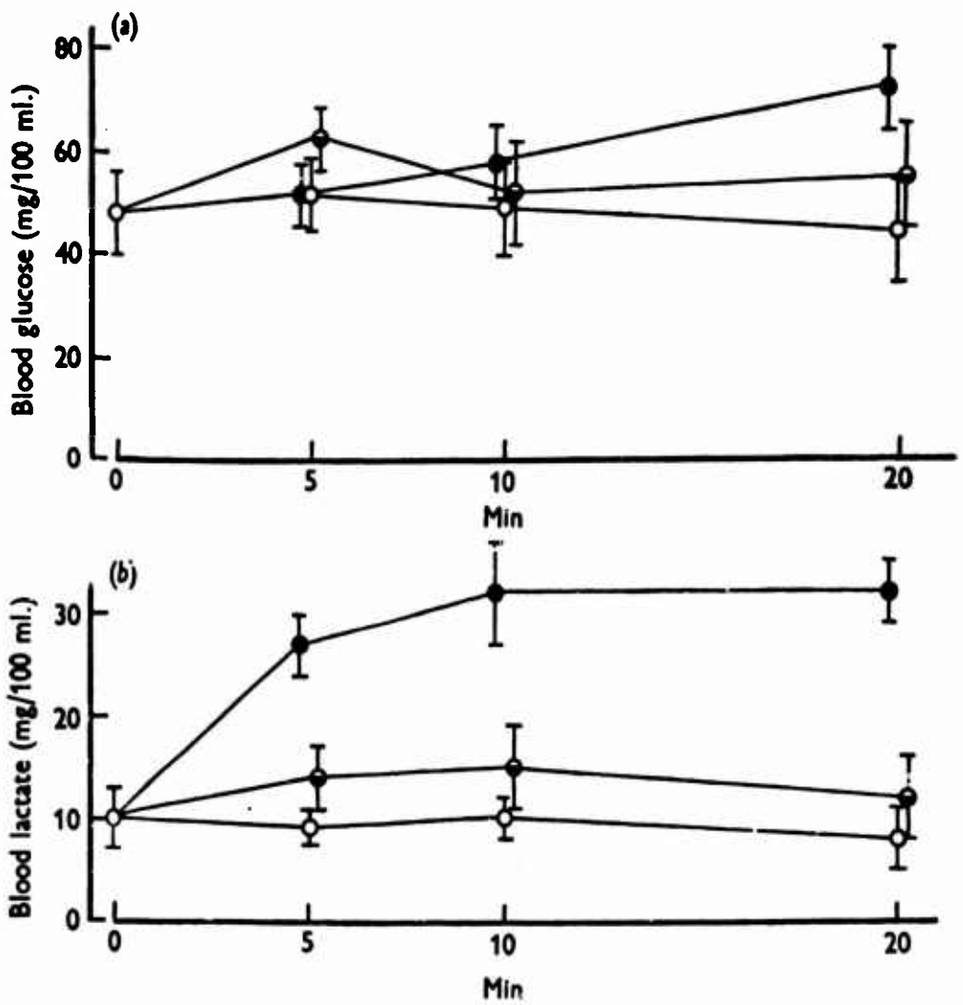


Figure 13
Blood glucose and lactate changes before (0) and after noradrenaline infusion (θ) and cold exposure (θ) in newborn rabbits. Lactate increased threefold during cold exposure, but blood glucose was little changed. From Dawkins and Hull (77).

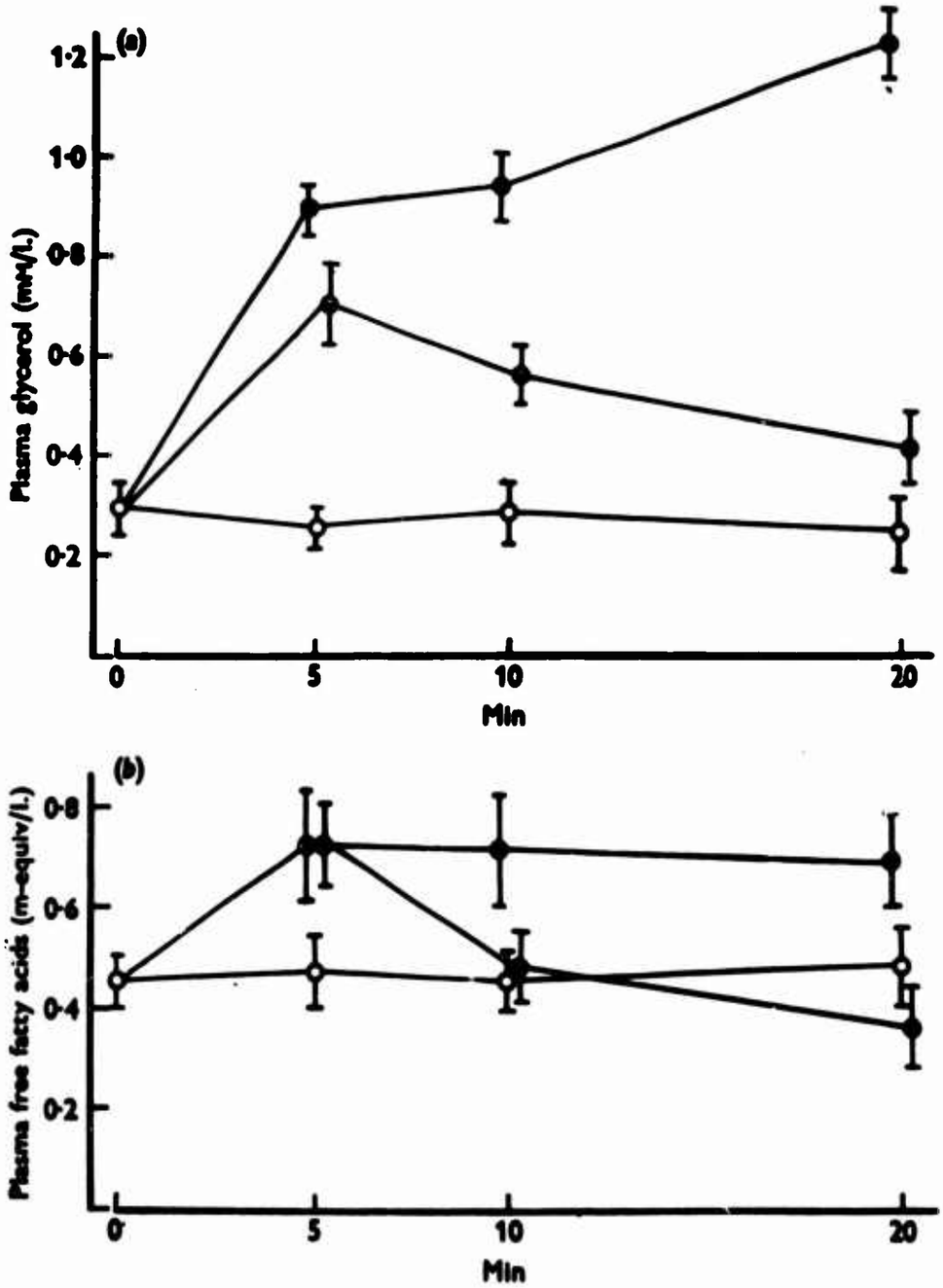


Figure 14

Blood glycerol and free fatty acids before (0) and after noradrenaline infusion (9) and cold exposure (8) in newborn rabbits. Free fatty acids were increased only slightly, but glycerol rose greatly during cold exposure. The vertical bars represent the mean values which are plotted. From Dawkins and Hull (77).

Infusions of glucose and lactate had no effect on the O_2 consumption of newborn kittens and rabbits (76). However, Shelley (89) found that liver glycogen and blood glucose fell more rapidly at 30° C than at 35° C in fasting newborn rabbits, and Blatteis (11) noted that rabbits from large litters, who are semi-starved and have smaller glycogen reserves than do members of small litters (90), generally failed to exhibit a metabolic response to cold upon the initial exposure, although an increase in O_2 consumption occurred eventually and was usually accompanied by shivering. Piglets maintained for the first 24 hours of their lives at 14° C, as compared to 35° C, show reduced blood glucose and liver, heart, muscle, and diaphragm glycogen (91, 92) (Table IV). Starved newborn piglets who slowly lose their carbohydrate reserves at 31° C, die within 24 hours at 12° C. with very low tissue glycogen and blood glucose (92). Newborn rats, on the other hand, maintain their glycogen stores under similar conditions, but perhaps this is because their body temperature falls so low so rapidly, slowing metabolic rate (10,93). Thus, these results would suggest a role of glycogen in thermoregulatory heat production.

	No exposure n = 8	At 14° C n = 20	At 35° C n = 16	Comparisons between treatments 14° v. 35°
Serum glucose (mg/100 ml)	68.68±13.8	7.18	60.52	***
Glycogen (gm/100 gm)				
Liver	3.36±2.54	0.30	1.56	*
Heart	0.34±0.14	0.13	0.35	*
Muscle	6.06±1.25	0.34	5.77	***
Diaphragm	3.63±0.23	0.43	2.93	*

* = significant at 5% level
*** = significant at 0.1% level
n = number of observations.

TABLE IV

Concentrations of serum glucose and liver, heart, skeletal muscle, and diaphragm glycogen before the after exposure to three environmental temperatures. Serum glucose and glycogen stores were much reduced after 24 hours at 14° C. From Elneil and McCance (91).

Both cold exposure and noradrenaline infusion, however, cause a four-fold rise in plasma glycerol in newborn rabbits (79) (Figure 14), thus indicating that hydrolysis of triglycerides is occurring in adipose tissue; however, the small rise in plasma FFA suggests that these are not released into the circulation but are metabolized within the fatty tissue. Dawkins and Hull (77) have offered the hypothesis that the energy for heat production in this species is provided by the oxidation of fat stored in brown fat. They observed that the fat content of brown fat fell at a rate which was dependent on the environmental temperature, and Hull and Segall (94) demonstrated that the ability of the newborn rabbit to consume O_2 maximally was related to the amount of fat in the brown adipose tissue. The maximal metabolic response to 20° C and 2 µg/kg/min of intravenously infused noradrenaline were both highest on the day of birth, when the brown fat constituted 4.3% and its fat content 1.8% of the body weight. The tissue contained 42% by weight of fat. In subsequent days, the weight of brown fat and its fat content decreased but the concentration of fat in brown fat remained high, and the cold-induced and/or noradrenaline-induced rise in O_2 consumption also was large. In unfed animals, on the other hand, the tissue was practically depleted of fat and these animals showed poor O_2 consumption responses to cold and to noradrenaline. Correlating their in vivo results with in vitro studies, Dawkins and Hull (77) further showed that the release of glycerol proceeded faster and the release of FFA proceeded more slowly from brown than from white adipose tissue; they postulated, therefore, that re-esterification of FFA to triglycerides was occurring within brown fat. The resynthesis of the ATP utilized in the formation of the CoA-FA complex, they suggested, would be accomplished by oxidative phosphorylation during the oxidation of fatty acids or glucose. Since adipose tissue is unable to phosphorylate the glycerol liberated from triglycerides, glucose would supply the α-glycerophosphate required for the re-esterification of the CoA-FA complex.

However tempting the suggestion appears, this is probably not the universal process of thermoregulatory heat production. Thus, piglets who have virtually no adipose tissue depots, either brown or white, would need to rely on some other mechanism. In newborn rats, Hahn et al. (10) found that the activity of the noradrenaline-sensitive lipase in adipose tissue was identical in brown and white fat and minimal in both until 18 days of age, when it increased. Adrenaline and noradrenaline increased the lipolytic activity of white fat at all ages but were without effect in brown fat.

Furthermore, these data have to be reconciled with evidence from other sources (95) indicating the preferential utilization of fat instead of carbohydrate as the main source of energy in most neonatal species immediately after birth.

Possible effects of hypoxia. Blatteis (67) recently found that the increase in circulating plasma levels of FFA and glucose following catecholamine infusion in adult dogs was not changed by their breathing 12% O_2 at the neutral temperature (Table III). The rise of these metabolites during exposure to 6 C for three hours (in air) was not altered by hypoxia, although the rise in FFA appeared to occur earlier in 12% than in 20% O_2 (Table V). The RQ was consistently higher during cold in hypoxia (.92) than during cold in air (.76). No definitive conclusions could be drawn from these results alone, but they indirectly suggested the possibility that both the mobilization and utilization of FFA and glucose during catecholamine administration and cold exposure could be reduced by moderate hypoxia. The earlier accumulation of FFA during cold in hypoxia, without a concomitant earlier rise in blood glucose but with an elevated RQ, could reflect a greater inhibitory effect of hypoxia on FFA utilization than on glucose utilization when the energy demands are large. This might account for the decreased O_2 consumption. However, these inferences are speculative and further studies are indicated.

There are no comparable biochemical data in newborns exposed to cold or during noradrenaline administration and hypoxia.

In the adult, moderate hypoxia of short duration in a thermoneutral environment does not appear to induce demonstrable changes in plasma FFA and glucose levels (13), although there is some disagreement regarding this. The controversial release of endogeneous catecholamines under these conditions may be implicated in this discrepancy.

	Air		Air or 12% O_2				
	26°C	6°C	6°C				
Free Fatty Acids (mEq/L)	**Controls**						
Air (n=4)	0.76 ±.18	0.71 ±.11	0.67 ±.12	0.61 ±.10	0.74 ±.12	0.94 ±.13	$0.98^{3'}$ ±.10
Hypoxia (n=8)	0.66 ±.07	0.70 ±.09	0.72 ±.09	0.82 ±.11	$1.04^{1'}$ ±.15	1.01 ±.16	$1.04^{2'}$ ±.12
n=12	0.69 ±.07	0.70 ±.06					
Glucose (mg%)							
Air (n=4)	104 ±3.9	111^{2} ±3.3	110^{2} ±2.4	107^{2} ±4.6	114^{2} ±2.3	114^{2} ±1.5	115^{2} ±1.8
Hypoxia (n=8)	118 ±3.0	127^{2} ±3.7	128^{2} ±3.0	128^{2} ±3.5	128^{2} ±4.8	131^{2} ±4.5	135^{2} ±4.6
n=12	113 ±3.1	121^{2} ±3.4					

Significant differences between air and hypoxia determined by analysis of variance are indicated by F ratios. Comparisons significant by paired t-test are indicated by superscripts as follows:
from 26°C, 0 = $p<.05$, 1 = $p<.02$, 2 = $p<.01$
from 6°C, 1' = $p<.05$, 2' = $p<.02$, 3' = $p<.01$, 4' = $p<.005$

TABLE V

The effect of exposure to 6° C for 3½ hours either in air or in 12% O_2 on the plasma FFA and glucose concentrations of unanesthetized dogs. The values represent means of ±S.E. From Blatteis (67).

SUMMARY

Thermal stability in a newborn subject exposed to a cold environment depends, as in the adult, on the efficiency of his heat conservation and heat production mechanisms. The neonate is somewhat limited in regard to the first, because of inadequate thermal insulation and small body size; however, he is well capable of inducing a large increase in O_2 consumption when below the neutral temperature. In contrast to the adult, the neonate achieves this increase largely without shivering. As in the cold-adapted rat, the increased O_2 consumption in the cold is not diminished by neuro-muscular blockade (provided there is no fall in blood pressure), but is reduced or abolished on administration of adrenergic blocking agents. There is some evidence that the sympathetic nervous system may be involved in the metabolic response to low ambient temperatures. In the early newborn human, rabbit and guinea pig, there also is presumptive evidence that the principal site of thermoregulatory heat production may be the interscapular brown fat pad. However, it is by no means established that this is the source of heat in all neonates. The increased combustion of both fat and glycogen would seem to be contributing, in the newborn as in the adult, to nonshivering thermogenesis, but the precise mechanisms have not yet been worked out.

Exposure of newborn animals to altitude (or hypoxia) probably increases their rate of heat loss in a cold environment. It further causes an immediate fall in their metabolic response to cold, resulting in a large fall of body temperature. However, on their continued exposure to both cold and hypoxia, the initially depressed O_2 consumption gradually returns toward its pre-hypoxial level. This recovery is usually accompanied by the development of vigorous shivering, suggesting that nonshivering thermogenesis is more readily sensitive to hypoxic blockage. Hypoxia similarly inhibits both the increase in O_2 consumption produced by the administration of catecholamines, and the increased thermogenic activity of brown adipose tissue caused by cold exposure and noradrenaline. The mechanisms underlying the hypoxic depression of the increased metabolism in the cold and after catecholamine administration are not yet fully clarified.

DISCUSSION

DR. DILL: How completely can you separate the brown fat from the other tissues?

DR. BLATTEIS: Well, it comes off fairly easily in the newborn, it's teased off, the intrascapular brown fat that is, is teased off rather simply in the newborn once one lifts up the overlying tissue. It's more difficult when the pads are very small, for example in the sub-axillary area where it's imbedded and encrusted into the subdermis, and in the muscle it's more difficult because one tends to pick up muscle as well.

DR. HORVATH: Is it primarily sub-scapular fat or all average brown fat you can get?

DR. BLATTEIS: No, primarily intra-scapular fat because it's the easiest to remove.

DR. WEIHE: Concerning the second to last slide which you showed on the change of the brown fat within 45 days, I think it's important that the animals live for 21 days on milk, then you put them on dry diet. Usually a rabbit is not fully developed at the age of 21 days.

DR. BLATTEIS: Rat.

DR. WEIHE: This is the rat?

DR. BLATTEIS: Right.

DR. MORRISON: You said you removed the intra-scapular brown fat to reduce oxygen consumption, is this the primary- -

DR. BLATTEIS: Well, in the other study, in the study in which the oxygen consumption following nor-epinephrine and cold was shown, the primary purpose there was to show that just by removing the intrascapular brown fat in this area you can show this decrease.

DR. MORRISON: What percentage of total brown fat would be found as intrascapular brown fat?

DR. BLATTEIS: Well, this is work of Holtz, and the values which he gives are as follows: 5.5 percent is the total amount of brown fat in the newborn rabbit relative to body weight, and the intrascapular brown fat pad constituted approximately 3.9 percent of the total relative to body weight. So it's about 80 percent of the brown fat as removed.

DR. BRAUER: What is involved in this transformation of the white fat to brown fat, are we laying down new cells, are we changing the fat composition or what are we doing?

DR. BLATTEIS: Well, we're laying down new cells, we're transforming cells.

DR. BRAUER: Transforming or adding?

DR. BLATTEIS: Transforming.

DR. BRAUER: This expressed itself in terms of what, more endoplasm being laid down or what?

DR. BLATTEIS: Well, actually in more cells, more nuclei.

DR. BRAUER: So we do have more cells?

DR. BLATTEIS: Yes. I don't know about fat composition, fat content, and so forth. That's the next step.

DR. CHIODI: You said at the beginning that the newborn don't maintain temperature even if they have a decrease of oxygen consumption. At what time do they start to keep their temperature high, exactly when they start to shiver, or is there no relation to that?

DR. BLATTEIS: No, the relation is not to that but actually they don't maintain their body temperature because of their large rate of heat loss, which is what I was going to show last, but I think time doesn't allow. The newborn animal because of its relatively small size has a high rate of heat loss, and it has a tremendously low thermo-insulation because it has no fur and it has no subcutaneous fat.

DR. BRAUER: But that is not true with the guinea pig; the guinea pig is born with fur.

DR. BLATTEIS: That's right, and therefore we have the species differences; so that to answer the second part of your question, the time when the temperature is maintained is a function of age in respect to species. So growth of fur and deposition of white fat in the rat, for example, is around . . . well, white fat begins to be deposited around ten days of age and yet stable temperature is not maintained until around 30, 35, 40 days of age. So again it depends on what temperature we're talking about, because as one of the slides showed, as the animal grows, the response to a given temperature drops. Consequently if the same temperature is used all the time, then the ability of the animal to maintain his body temperature improves because his thermoneutral range has shifted. But if we examine something else, the maximum oxygen consumption that the animal is capable of on cold exposure increases with age, so if we were to use that as a criterion, his rectal temperature would continue to fall until the animal gets even older.

DR. CHIODI: You said that hypoxia depressed the oxygen consumption in the guinea pig and the rabbit. But when you injected, I think, some adrenalytic agent, in one case you got a suppression of that effect and in the other no response. How would you explain that? Both are newborn, it could be different in the adult, but what about the newborn?

DR. BLATTEIS: In the first place, well, one possibility is that the catecholamines are not glycolytic in the rabbit, and in the newborn rabbit the brown fat is an important site, but in the guinea pig it may not be such an important site. I pointed out that the administration of pronethalol in the guinea pig blocks their response to cold but did not in the rabbit, so there are species differences which are very peculiar, but which are erased when the animal grows older, so that when we make our studies in adult animals we often find things to be the same, very much the same, but when we go to the newborn of the same species they are the same no longer.

DR. CHOIDI: You said the lactates increased. Would that be due to shivering at that time?

DR. BLATTEIS: Not shivering, no.

DR. CHOIDI: How do you explain that?

DR. BLATTEIS: Well, glucose has to be utilized, whatever glucose is there is utilized because it has to supply glycerol for the re-esterfication of the fatty acids to tri-glycerites. The glycerol which is broken down in the adipose tissue cannot be utilized, so this may be a by-product of that glycolosis.

DR. CHIODI: About the RQ of the men in hypoxia, at least my experience has been that I always saw the lowest side, the RQ in a man, even the native at high altitude, always on the lowest side, close to a .75 or something like that.

DR. BLATTEIS: In the cold?

DR. CHIODI: Not in cold, no.

DR. BLATTEIS: This is in the cold. But I am not really sure that this represents something which is, let's say, endemic to the individual, but may be an indication rather of his exogenous diet, because the altitude natives and the people at altitude in Peru, as you well know, have a very high intake of carbohydrates, whereas the same soldiers at sea level had a more balanced diet furnished to them by the hospital at which we were working. Therefore this change may be due to the diet and preferential utilization because of the high carbohydrate inta e rather than something else, so I – –

DR. MORRISON: You speak of the differences between the different species as representing species differences. Certainly there are going to be true species differences, but I think that you should perhaps introduce the concept of different physiological age of these animals, because birth is an incidental process -- –

DR. BLATTEIS: Right, very important.

DR. MORRISON: – – in growth and development at different places. We have a spectrum of ages–physiological ages–at birth in the different species.

DR. BLATTEIS: Right, that's very important, that so-called maturity, if you like, at birth. We find the guinea pig a more mature animal than the rat and there are differences also in glycogen stores; the mature animal has lower glycogen stores than the immature animals.

DR. MORRISON: This is a very hard thing to be exact about, and yet it's still an important phenomenon, so I think we must try to make some approximation of physiological age.

DR. BRAUER: I might point out–from one of your introductory statements–that the premature rabbit, rat, guinea pig, and infant also have a metabolic response to cold, and that that is depressed by hypoxia.

DR. BUSKIRK: What do we know about the human infant?

DR. BLATTEIS: It has been demonstrated that infants one or two days old have a decrease in oxygen consumption when they breathe 17 percent oxygen, and it was later found out that those infants were probably not at their thermoneutral environment but in a less than thermoneutral environment. This report is a result of this type of study because one of the slides I have simply illustrates this: the effects of hypoxia on oxygen consumption is practically negative, it is not significant until about 8 percent, very much like in the adult, whereas in the cold it's very, very pronounced. I mean as soon as the ambient oxygen drops, then the oxygen consumption temperature drops.

DR. HORVATH: In the lamb, isn't it true that the ability to mobilize free fatty acids is a determinant factor of success? Lambs have extraordinarily low levels of glycogen reserves, and therefore the circulating carbohydrate levels are very often below 50 milligrams percent. If the animal is able to mobilize his free fatty acids, he survives, and if he isn't, then, of course, that means disaster.

DR. BLATTEIS: Well, it depends on when this is measured, because actually at birth the glycogen stores, depending on the species and the physiological age, in general are fairly high, but they drop rapidly within hours. You see, it depends on when you measure it. Now there is evidence accumulating from the workers in Czechoslovakia, Hahn in particular, that as soon as the animals are born they are laying down fat, and the measurement of resting RQ indicates that they are burning fat instead of carbohydrates, so that as soon as they are born apparently it's fat that becomes the principal substrate.

DR. HORVATH: It might be interesting to go back to Dr. Morrison's comment because in a sense what he is asking us to do, which as the moment I feel is relatively impossible, is to identify the so-called relative physiological age

of the organism. This also relates to what Dr. Dill had to say earlier this morning, namely that maybe some of the differences in the individuals that he has reported are simply due to this unknown physiological age variable, and that Dr. Dill, as a prime subject, may really be quite a bit younger than his so-called chronological age may indicate. It certainly is not feasible, I believe, to identify physiological age by the absence of certain of these overt characteristics, but there must be some better criteria made available to us to identify physiological age in order to follow along with this sort of analysis. We're almost at an impasse in our state of knowledge. There may not really be a great deal of difference, this may simply reflect the phenomena that you mention, but we must have better ways of identifying so-called physiological age than we have at the moment, or do you have any better, newer information?

DR. MORRISON: One easy way of improving the situation is to measure age from conception instead of from birth. That isn't the only factor, but it is one important factor. Then you must make qualifications in comparing animals of about the same size, but this is one thing you can define and it is an important consideration in these newborn animals.

DR. BLATTEIS: The smaller animals are much more susceptible to this hypoxic effect than the larger animals, but it is interesting also that smaller animals in general maintain a much higher oxygen consumption even in their so-called resting state, and I think the interesting thing is that it's extra oxygen consumption and the more extra there is of it, the more susceptible it is to this depression, and I am not sure how it all interrelates.

DR. BUSKIRK: Many of these slides that you showed indicate a new thermal balance is established in these animals. When we think of man and the newborn, we think of a certain amount of resistence to a cold environment; I mean, for example, babies survive when placed on doorsteps. What is the picture in the newborn animals with respect to species differentiation and tolerance to cold or survival in cold?

DR. BLATTEIS: Very poor, and the human infant included. At birth, they show a tremendous drop in rectal temperature from which it takes a long

time to recover, but this is because in nature most animals are born in an environment which is considerable cooler than the environment from which they emerge. They emerge from an environment around 38, and if they're born in nature they emerge into an environment that can be anything from . . . well, literally anything. It's usually a dry environment and they come out wet; it's usually a breezy environment, and so the amount of heat that they lose is fantastic. They do increase their oxygen consumption under these circumstances, but the aggression of the environment is so tremendous that they cannot overcome it. This was evident even in infants born in the maternity wards, because for the comfort of the mothers oftentimes these are air conditioned, and so the infact is born in an environment which is very cold. So the new practice is, and this is a very recent practice, either to keep the maternity room warm or to swathe the infant in clothing immediately to avoid this fall. If their temperature drops sufficiently, then their metabolism drops sufficiently, and they are in any case anoxic resistant. You see the newborn and the fetus are very much more anoxic resistant than the adult.

DR. DILL: What do we know about the temperature under ordinary conditions of the newborn during their first days of life? I'm not talking about children nor necessarily domestic rats, but rats or small and large mammals in nature, how much do they cool down in their nest within the first few days?

DR. MORRISON: Nest temperatures with the mother in the nest are very little below the temperature of the internal resting animal. Nest temperatures for a mouse can be 35 degrees, as opposed to 37 for body temperature. But the mother is not always there.

DR. BLATTEIS: If there are more than one in the litter, you see, then nesting and huddling is an important defense. If there is only one then curling and flexing and so on are the common defenses, that is what they do mostly to try to conserve heat, but when the rectal temperature does fall, it takes days before it recovers. The length of time varies with the species and is directly correlated with what has been described as an increase in the so-called minimal oxygen consumption of the newborn–in effect the basal metabolic rate increases with age depending on the species within various days, and I have the data here. I can give you that if you like.

DR. DILL: You're speaking of animals under laboratory conditions which you control, and I'm interested in animals under natural conditions where they have the opportunity of regulating their own environment to a considerable extent.

DR. BLATTEIS: I know in the case of sheep, for example, which I have observed in Peru, where the mothers take care of the newborn as much as possible and—it tends to be a behavioral adaptation rather than a – –

DR. DILL: They're quite mature, though, aren't they?

DR. BLATTEIS: Right, they're mature.

DR. HORVATH: It's rather strange that the veterinarians today are looking back at natural birth of the animal out in the open. They report that the incidence of death is markedly decreased, for example, if the mare is permitted to have her foal out in the field rather than in the nice confines of a barn, the same with sheep, and the same with the cow. The fatality rate is much greater in the barn than it is out in the open, though they aren't necessarily relating that to temperature, per se, but to other factors which are involved in the birth proper, namely such things as redistribution of the blood supply from the placenta. I don't know that they've done a great deal with temperatures, except that there are these experiments that are going on which seem to indicate that if you keep the temperature a little bit lower than normal you might do better with the infant but I don't know quite what – –

DR. BLATTEIS: In the latest conference on this problem the American group, Ray, Adamson, Oliver and so on, all felt that the important thing is to keep the environment of the newborn infant at its thermoneutral level because in reality – – up to now the fall has been a natural thing and everyone seems to be doing all right. We don't know enough about the physiology that ensues from this fall to be really sure.

DR. BUSKIRK: What did they set, or what did they establish as the thermoneutral level?

DR. BLATTEIS: Well, it depends on the species, but for the newborn infant, it's around 35 degrees centigrade.

DR. HORVATH: It's a pretty hot environment.

DR. WEIHE: For how many days should this be?

DR. BLATTEIS: Well, they say about seven days. As a matter of fact, they measure it.

DR. CHIODI: Then it increases progressively day by day?

DR. BLATTEIS: Right. Oliver measured the minimal oxygen consumption when the infants were kept at thermoneutrality and he did not see the increase in minimum oxygen consumption that I was mentioning before. There is a possibility that the increase in minimal oxygen consumption is a response to the environment, and yet there is enough other evidence to suggest that it is not a response to the environment, either, so there too is a big problem.

DR. EAGAN: I wonder about the role of brown fat in the human infant, is there much on that?

DR. BLATTEIS: Yes, brown fat intrascapular temperature and circulating free fatty acids and glycerol have been measured, and they found in the infant the same thing as they found in the rabbit, that is, suggesting to them that the brown fat is important. Autopsy studies by Ahern and Hall have shown a large amount of brown fat in the newborn infant.

DR. EAGAN: What percentage of weight?

DR. BLATTEIS: I can't answer that, it is very variable. In the rabbit, as I said, it was about 5.5 percent, in the guinea pig it's around 2.3 percent, in the rat it's 1.9 percent. The rate of disappearance of the fat varies in the guinea pig and disappears completely within about twelve days; in the rat and rabbit it never disappears completely.

DR. MORRISON: The caribou calf is born on the Arctic Slope at temperatures well above and below freezing, often below, and Hart's studies of the caribou in the barren grounds in Canada indicated that the calves are born quite precocious, so that it takes a pretty spry man to catch one of them after a couple of hours. They do suffer from cold and wind, and if there is precipitation, rain particularly—which is not too common, then they really do suffer. I think also there are some similar observations on the danger to newborn lambs from cold, indicating with more experimental data that their tolerance to the cold does depend on their endurance, which is more or less proportional to the degree of feeding they get. If they get fed they can take a lot of it, and it's apparently similar with the caribou. They do suffer from hypothermia but the calf comes through if it is promptly and sufficiently nourished immediately after birth.

DR. BLATTEIS: The newborn rat won't show metabolic response to cold apparently unless he has suckled first, so in some species that first suckling is important.

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A COMPARATIVE REVIEW OF CERTAIN RESPONSES OF MEN AND WOMEN TO HIGH ALTITUDE

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The physiological responses of humans and lower animals to high altitude exposure represents one of the most thoroughly investigated areas of environmental medicine. Yet, when we review the literature on this subject, particularly that concerned with human responses, we find data on females are not only scarce, but also widely scattered, and oftentimes hidden in articles which are not specifically concerned with the sex of the subjects. In fact, there would appear to be only two or three articles where the process of altitude acclimatization has been compared in men and women. Perhaps the best known of these is the report by Grollman (1) of his studies conducted on Pikes Peak in 1930. The sole female subject was his wife and, in many respects, she responded to high altitude in an atypical manner. This lack of information on the responses of women to altitude, coupled with an excellent opportunity to study a group of college girls who lived and worked on the summit of Pikes Peak during their summer vacations, engendered the experimental work reported here. It is the purpose of this report to summarize this work and to compare, where possible, the responses of these women to those observed in men.

Two studies of these women were made, one in the summer of 1964, and the other in the summer of 1965. Our subjects, as indicated above, were girls who journeyed from low altitude areas to Pikes Peak during the summer months where they were employed as waitresses and salesgirls in the tourist concession. One day per week, their day off, was usually spent at low altitude in Colorado Springs (6,000 feet) or neighboring areas of Colorado (up to 12,000 feet). Such excursions constituted their only re-exposure to low altitude during the entire summer.

The 1964 study was designed primarily to explore the feasibility of using these women for physiological studies. Consequently, few usable data were gathered, but a large amount of background information pertinent to the design of future studies was obtained. Our subjects were six girls, selected at random as

they arrived in Colorado Springs in June, on their way to Pikes Peak to work for the summer. Two were permanent residents of Colorado and four were permanent residents of the midwest. Our initial measurements were made in the Biology Department of Colorado College in space graciously provided by Dr. Mary Alice Hamilton, and subsequently at Pikes Peak in space provided by Mr. William Carle, manager of the Summit House. Without the excellent cooperation of Mr. Carle, who released the girls from their duties at the Summit House to serve as experimental subjects, neither this nor the subsequent 1965 study could have been accomplished.

Perhaps the most useful information obtained in these initial experiments was how not to conduct a high altitude study of college women. For example, we made extensive measurements of physical performance on a bicycle ergometer, only to discover an improvement in physical fitness during the course of the summer. The reason for this later became obvious; the girls came from a relatively sedentary student environment to Pikes Peak where they were engaged all summer in the physical activity necessary for their employment. We also discovered that our low altitude measurements in Colorado Springs left much to be desired since the measuring site was characteristic of neither high nor low altitude. Finally, the random selection of subjects presented a variety of problems. Girls from Colorado seemed to adjust more readily to the Pikes Peak altitude than the girls from the midwest. This was subjectively reflected by a marked difference in the severity of altitude sickness. Also, selection of girls at random led to frequent, time-consuming travel from our laboratory in Denver to Pikes Peak just to obtain data pertinent to specific days of exposure. On the more positive side, we discovered the hemopoietic response of these girls to high altitude was much less than we had anticipated.

In our subsequent 1965 study we decided to use only subjects who resided permanently near sea level, to make our initial measurements at that site, and to bring all of them to Pikes Peak at the same time. To accomplish this, Mr. Carle gave us authority to recruit eight of his summer employees; assigning such a task to a group of physiologists obviously represented real business speculation. This recruitment was undertaken at the University of Missouri (700 feet) where Dr. W.S. Platner, Professor of Physiology, volunteered his services in making announcements to his classes about the nature of the study. He also conducted the initial screening procedures and assisted in the final selection of the eight subjects who were to participate. Finally, at the time of our initial low altitude measurements he provided the needed laboratory space, various supplies we had forgotten to bring, and personal assistance in getting the project underway.

Without his wholehearted interest and assistance, the success of the entire project would have been seriously jeopardized.

The main body of experimental data contained in this report was derived from these eight girls. In February they were selected from a group of approximately fifty volunteers who were screened medically for histories of present or past cardiovascular and pulmonary difficulties. Selection was based in part upon an absence of such histories, normal electrocardiograms and chest x-rays, and no history of syncope. In addition, they were screened for past work experience and physical fitness, as determined by a bicycle ergometer, as well as general appearance and personality. These later selection criteria were pertinent to their employment where they would be working long hours and meeting the public. Subsequent to their selection, we supplemented their diet with 600 mg of $FeSO_4$ daily to obviate any iron deficiency anemia which may have been present. This supplementation was continued from March until June when they went to Colorado. Thereafter, it was reduced to 300 mg daily for the remainder of the summer. Prior to altitude exposure they were also required to engage in various sports activities, intramural and otherwise, to raise their level of physical activity to approximate that expected on Pikes Peak. Dr. Platner supervised this. Our initial physiological measurements were made during the first week of June. One week later they were flown in the evening from Columbia to Denver where they remained overnight, and a few measurements were made. The next day the entire group was taken by automobile directly to Pikes Peak. Subsequent measurements were made on the 1st (24 hrs.), 7th, 30th, and 65th day of altitude exposure. Final measurements were made in September, two weeks after their return to Columbia, Missouri. Individual subject characteristics at the time of selection are shown in Figure 1.

The data obtained from these subjects were statistically analyzed by an analysis of variance and Critical Differences at the 0.05% level of confidence were computed.

In certain instances where pertinent information is available, the data obtained from these girls are compared to data previously obtained from men. With respect to the latter, data from four separate studies of male subjects were used. One of these studies was conducted at Climax, Colorado (11,400 feet) and another at Pikes Peak by a team of investigators headed by Mr. C.F. Consolazio and Lt. Colonel J.E. Hansen (M.C.). The third investigation of males was conducted in an altitude chamber at Brooks Air Force Base by Major Wayne O. Evans and a group of coworkers, while the fourth study was conducted on Pikes Peak by Captain M.I. Surks (M.C.)

SUBJECT CHARACTERISTICS

SUBJECT	AGE	HT.	WT.	B.P.	H.R.	HCT.
PB	20	5'2"	125	120/78	74	43
MH	20	5'5"	120	120/70	85	38
BR	21	5'9"	143	128/82	68	41
GS	20	5'3"	145	114/68	82	40
SR	20	5'4"	117	110/72	67	41
CW	19	5'4"	120	127/76	78	40
SW	20	5'6"	112	109/60	62	40
SY	21	5'8"	130	120/80	88	39
AVERAGE	20	5'5"	126	118/73	75	40

Figure 1
Subject Characteristics. The physical and cardiovascular characteristics contained in this table were obtained in February 1965, three and one-half months prior to altitude exposure. The subjects were measured in a resting state after an overnight fast. The age, height, weight, systolic and diastolic pressure, heart rate and hematocrit are indicated.

Mountain Sickness

For more than 70 years, reports of clinical symptoms associated with high altitude exposure have appeared in the literature (2, 3). Except for two reports (4, 5) written prior to 1920 containing comments about Peruvian women, all clinical observations of the symptomatic responses to high altitude have been

made on men. These two early reports on women suggest the severity of altitude sickness is less in women than in men. In men, the majority of reports (5, 6, 7, 8, 9, 10, 11, 12, 13, 14) agree that the predominant symptoms of altitude sickness include headache, fatigue, breathlessness and anorexia. Nausea and vomiting are common and insomnia occurs during the first week in spite of excessive fatigue. Other frequently reported complaints include chest tightness and pain, Cheyne-Stokes respiration, sinus pain, lumbar and flank pain, leg cramps, abdominal cramps, increased sensitivity to low temperature and emotional and mental disturbances (9, 14). Changes in mood, in memory, in judgment and in the ability to perform complex mental tasks and to render decisions are examples of the latter. The onset of these difficulties is usually eight to 24 hours after arrival at altitude and generally continues for the first three or four days, but sometimes longer (9, 12).

Despite the number of reports describing mountain sickness, little effort has been directed toward quantitatively evaluating the severity of the various symptoms. This is admittedly difficult to do; however, such information would be most valuable in directing our investigative efforts toward the specific physiological or biochemical changes which precipitate the illness.

During the past three years, therefore, various members of our laboratory have contributed to the development of a semiquantitative system of grading the severity of symptoms experienced at high altitude. This system consists of a questionnaire containing a list (Table I) of the various symptoms subjects may or may not experience during high altitude exposure. Each symptom is subdivided into five degrees of severity (i.e., none, mild, moderate, moderately severe and severe). In completing the questionnaire the subject gives his own evaluation of each symptom. After completing the questionnaire, an intensive oral conference is held with the subject and his response to each question is further evaluated by a physician for accuracy and supplementation. Application of the questionnaire may be made at any time, and it has been found desirable to use it every six to twelve hours during the initial stage of high altitude exposure. Its usefulness is attested to by the fact that two recent studies have shown the overall severity of altitude sickness is statistically correlated with the degree of blood bicarbonate reduction. This questionnaire was completed twice daily over a four-day period at low altitude (Missouri) and over a three-week period after the ascent to Pikes Peak. The subjects indicated the severity of each symptom during the time interval between consecutive questionnaires. The cumulative results of this evaluation, for which each symptom was scored from one to five according to severity, are shown in Figure 2. In this figure, we see that symptoms such as headache and fatigue are significantly affected by altitude exposure, whereas

TABLE I

HIGH ALTITUDE QUESTIONNAIRE

Medical Symptoms[+]

Cardiorespiratory
- Chest tightness
- *Chest pain
- Palpitations
- *Shortness of breath (rest)
- Shortness of breath (exercise)
- Irregular breathing
- Coughing
- Runny nose
- Very dry nose or throat
- Sore throat
- Common cold (with fever)
- Cyanosis of nose or ears

Gastrointestinal
- *Nausea
- *Vomiting
- Constipation
- *Diarrhea
- *Stomach cramping
- Increased intestinal gas
- Severe indigestion

General
- *Very fatigued
- *Poor sleep
- Change in appetite
- Change in thirst

Central Nervous System
- *Headache
- Visual change
- Auditory change
- Change in smell or taste

Urinary
- Oliguria
- *Dysuria
- Nocturia
- Hesitancy

Musculoskeletal
- *Generalized muscle aches
- *Joint pain or stiffness
- Back or neck stiffness

Psychological Symptoms[+]

- Drowzy
- Happy
- Pleased
- Satisfied
- Comfortable
- Energetic
- Depressed
- Vigorous
- Refreshed
- Angry
- Anxious

*When present, these medical symptoms were considered by investigators to be most disabling in terms of daily activity performance.

[+]Rated by degree of discomfort (None – Mild – Moderate – Moderately Severe – Severe)

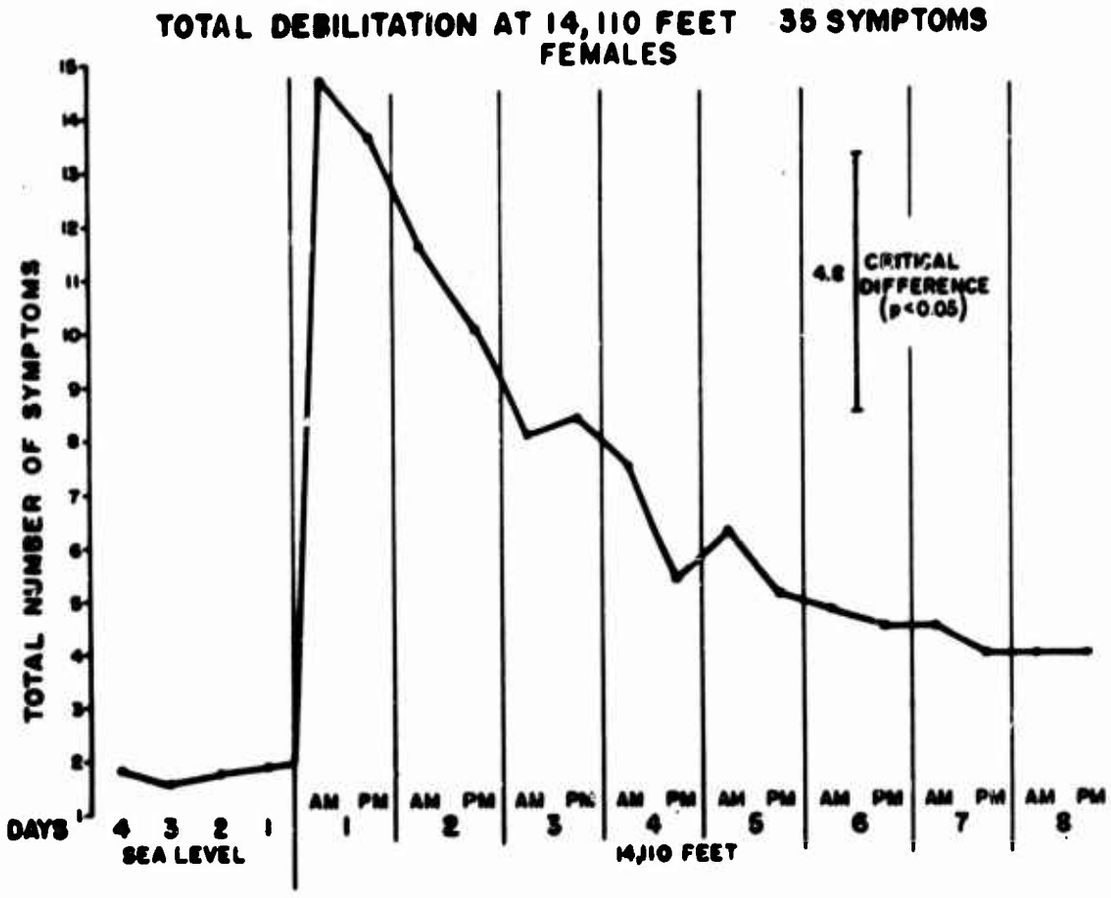


Figure 2

Total Debilitation at 14,110 feet. The scores obtained from the symptoms listed in Table 1, over a range of 1 to 5 according to severity, were summed up to arrive at the mean values contained in this figure. After the fourth day of exposure, no significant altitude sickness was observed.

others such as shortness of breath and nausea are statistically not changed at all. We also see that certain symptoms relating to subjective fatigue seem to be elevated, but not statistically, during the control period in Missouri. This may be because the subjects were engaged in final semester examinations just prior to the time of measurement.

Although this questionnaire technique for evaluating mountain sickness has been applied to men living in a decompression chamber, it has not been applied to men living at actual high altitude; consequently, a direct statistical comparison of sickness severity in the two sexes is not possible at present. It is our impression, however, that certain symptoms such as headache, nausea,

dizziness, and irritability are much more intense in men than in women. For example, in one recent study where eight men were taken directly from Boston to Pikes Peak, all of the subjects reported nausea during the first several days of exposure severe enough to cause vomiting in four of them. As can be seen in Figure 5, only one girl reported nausea and vomiting, which occurred on the second day of exposure.

A variation of this questionnaire has been used by Dr. Wayne Evans, who was highly instrumental in its development, in a study of male volunteers who were subjected to simulated altitudes of 2,000, 11,000, and 15,000 feet in a hypobaric chamber at Brooks AFB. The subjects were exposed to each altitude for a period of 40 hours with the severity of each symptom being recorded every twelve hours. The cumulative scores for each symptom over a 32-hour period is shown in Figure 7, while the changes in intensity with time of exposure for some of the more prominent symptoms is shown in Figure 8. These data show, as we might expect, that some symptoms such as headache, insomnia, depression, dizziness and fatigue are markedly more intense at 15,000 feet than at 11,000 feet. The data in Figure 8 show at least one instance, headache, where the pattern of symptom development appears to differ in men and women (Figure 6). In women, headaches were most severe during the first 24 hours at altitude and declined thereafter, while in men they became progressively more severe as exposure was extended to 34 hours.

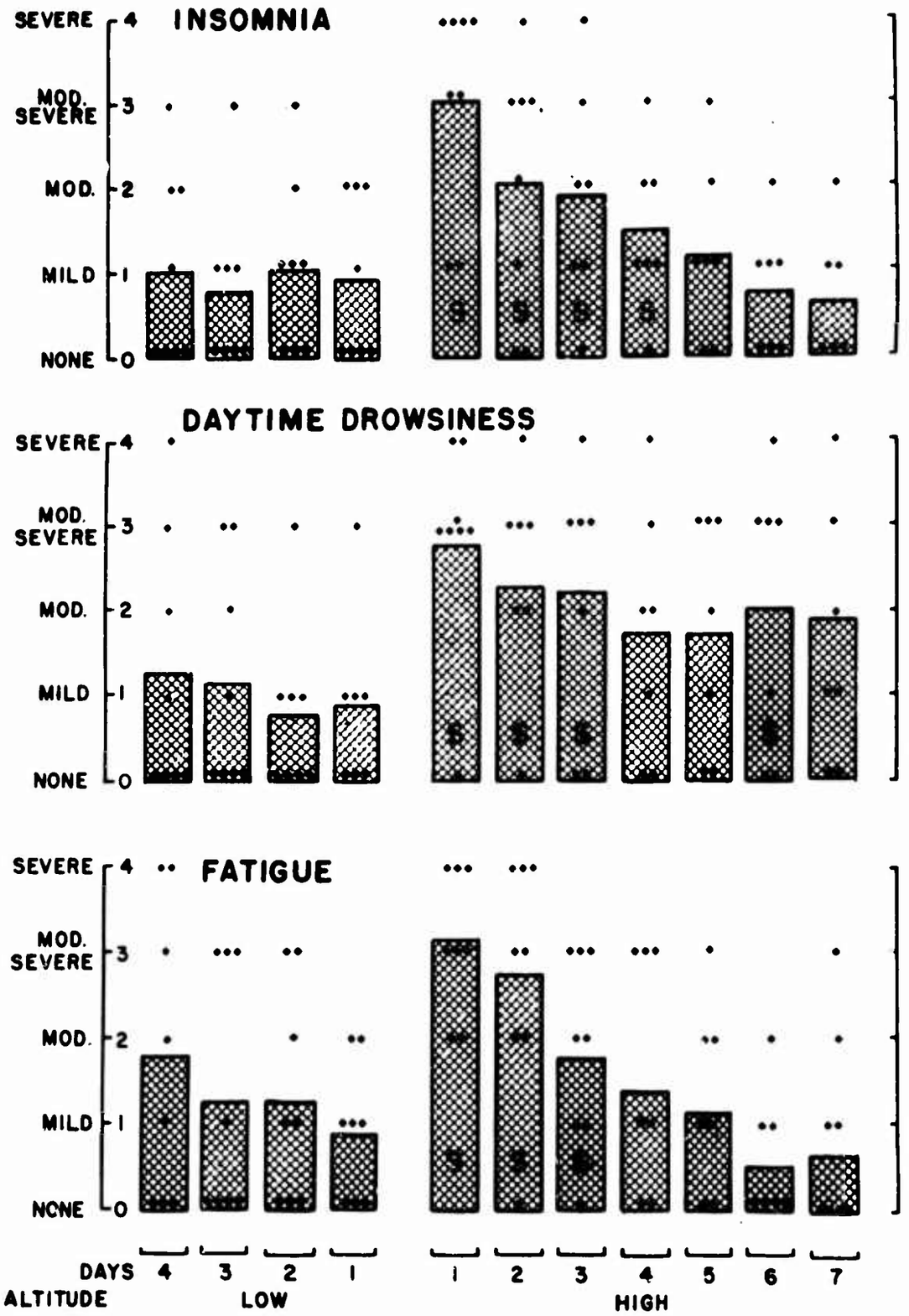


Figure 3

The individual symptoms prior to and during altitude exposure are indicated for each subject (dots) and for the group as a whole (bars). S refers to a change being statistically significant at the 5% level of confidence.

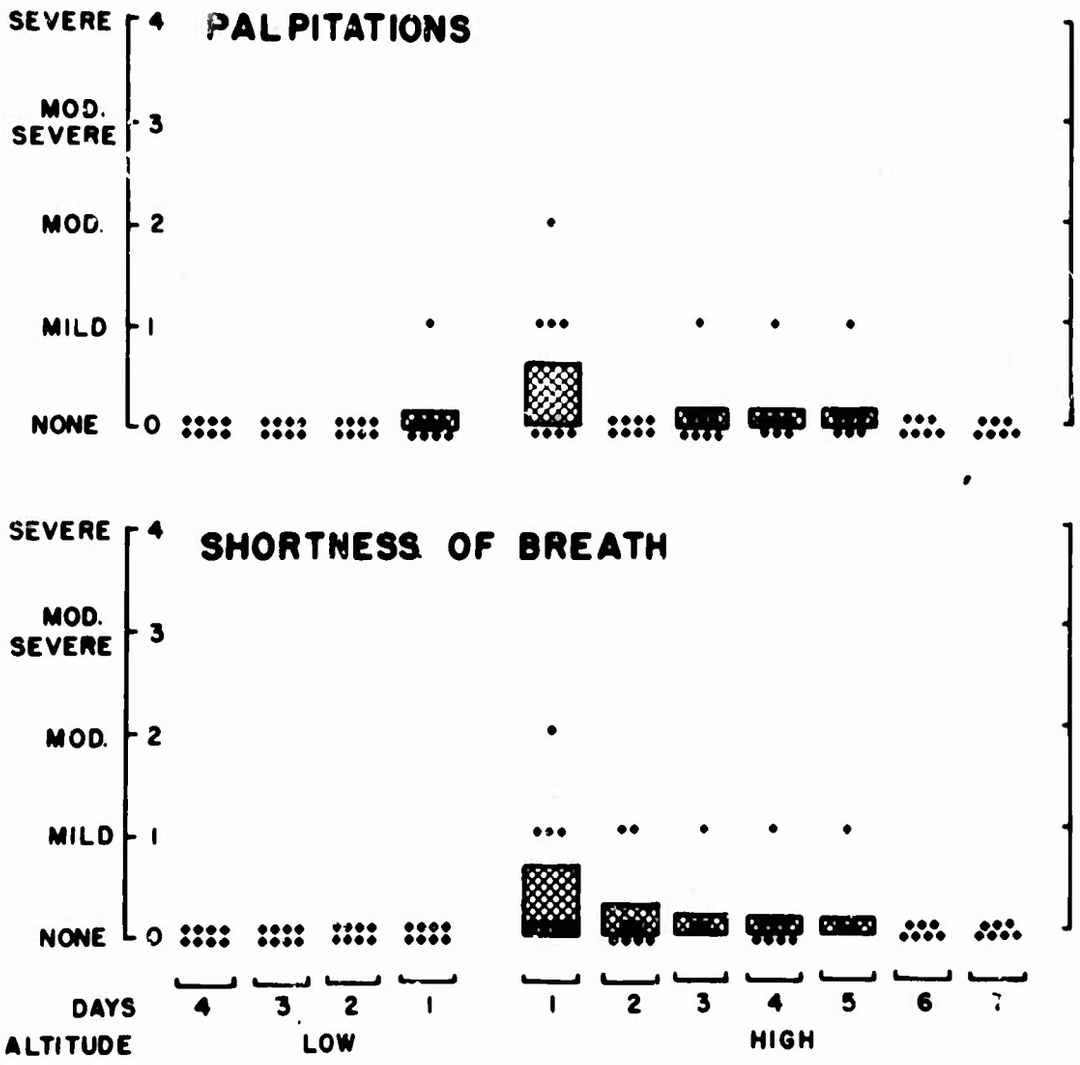


Figure 4

The individual symptoms prior to and during altitude exposure are indicated for each subject (dots) and for the group as a whole (bars). S refers to a change being statistically significant at the 5% level of confidence.

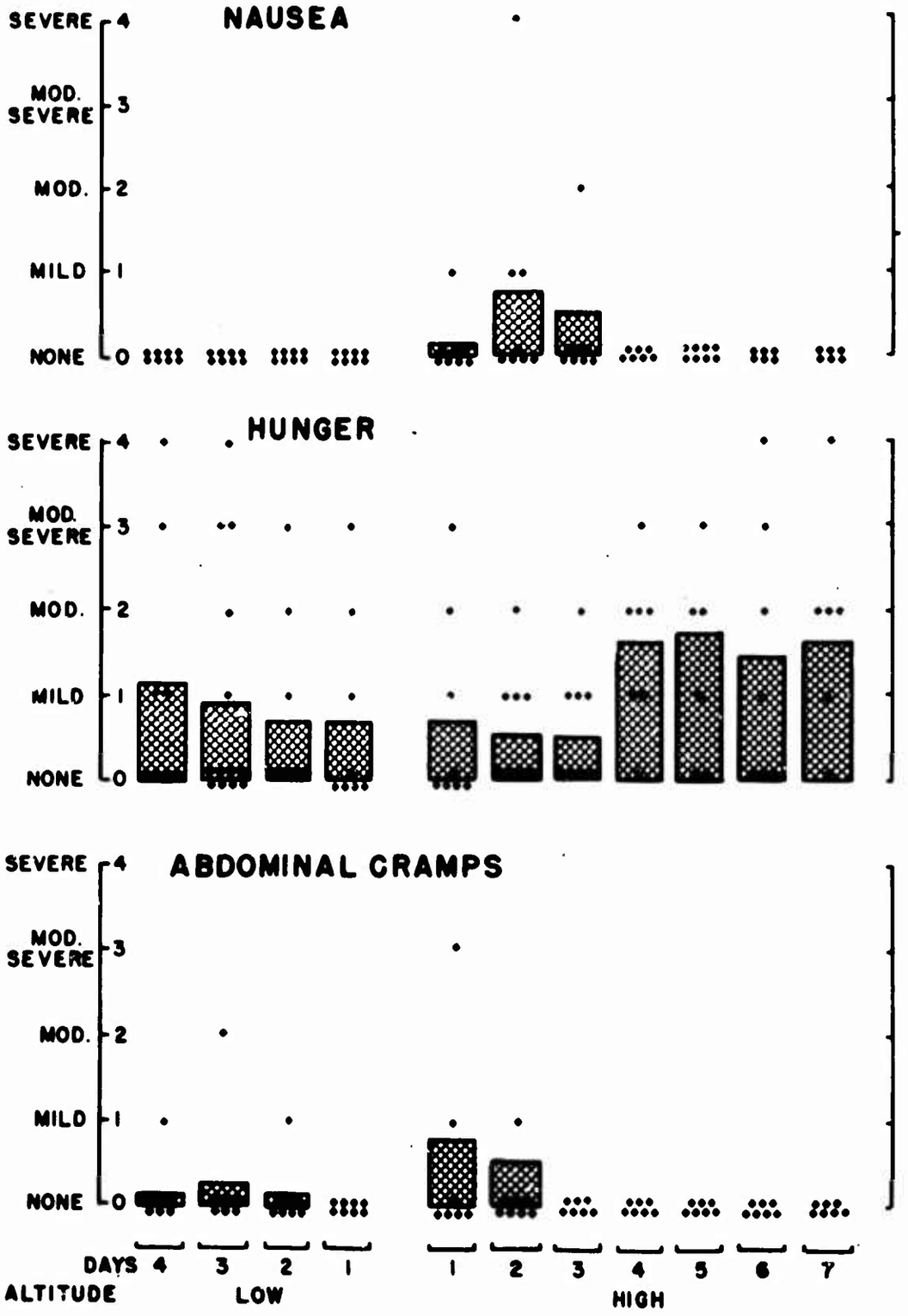


Figure 5

The individual symptoms prior to and during altitude exposure are indicated for each subject (dots) and for the group as a whole (bars). S refers to a change being statiscally significant at the 5% level of confidence.

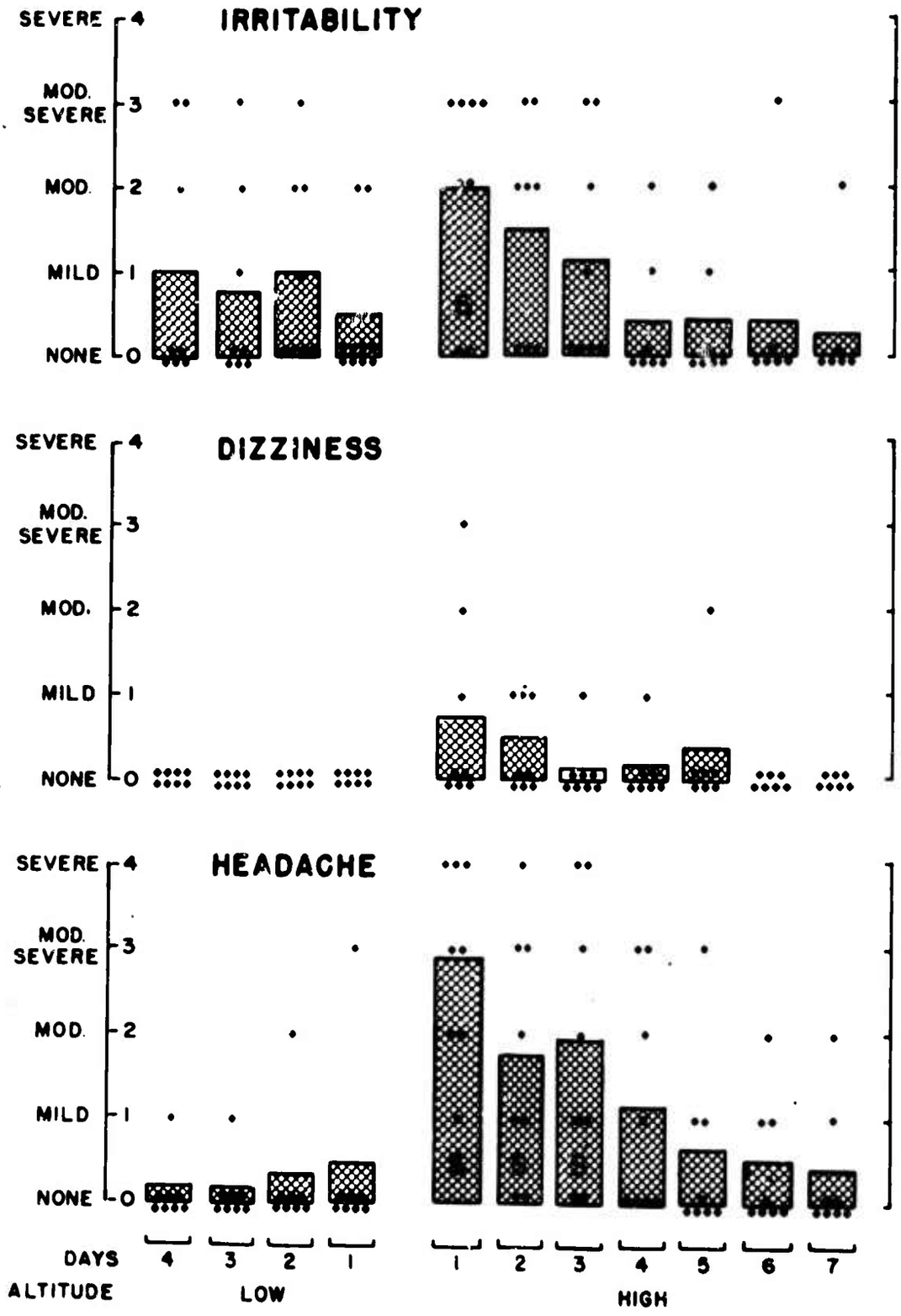


Figure 6

The individual symptoms prior to and during altitude exposure are indicated for each subject (dots) and for the group as a whole (bars). S refers to a change being statistically significant at the 5% level of confidence.

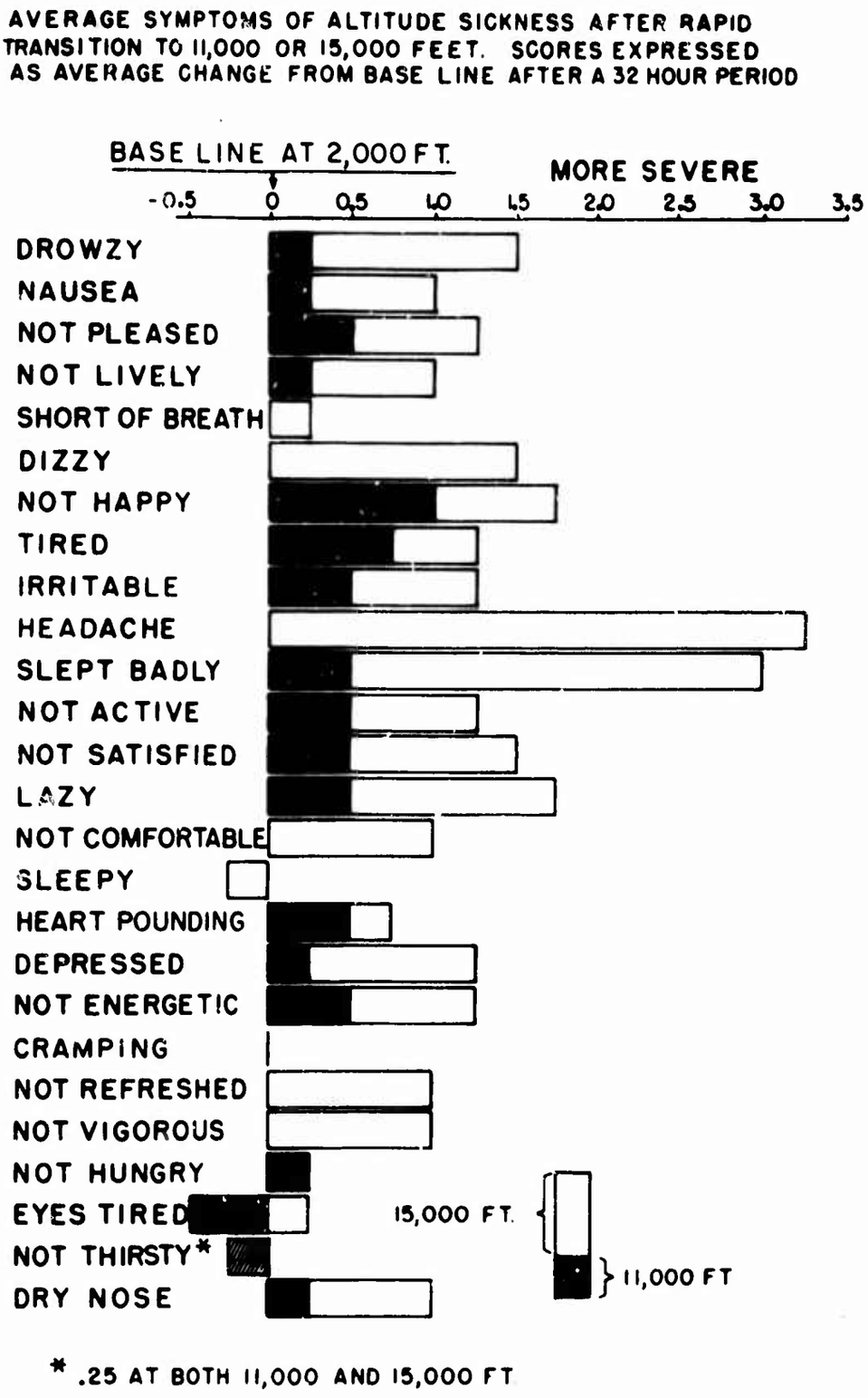


Figure 7

Comparison of the severity of various symptoms experienced at simulated altitude of 11,000 and 15,000 feet.

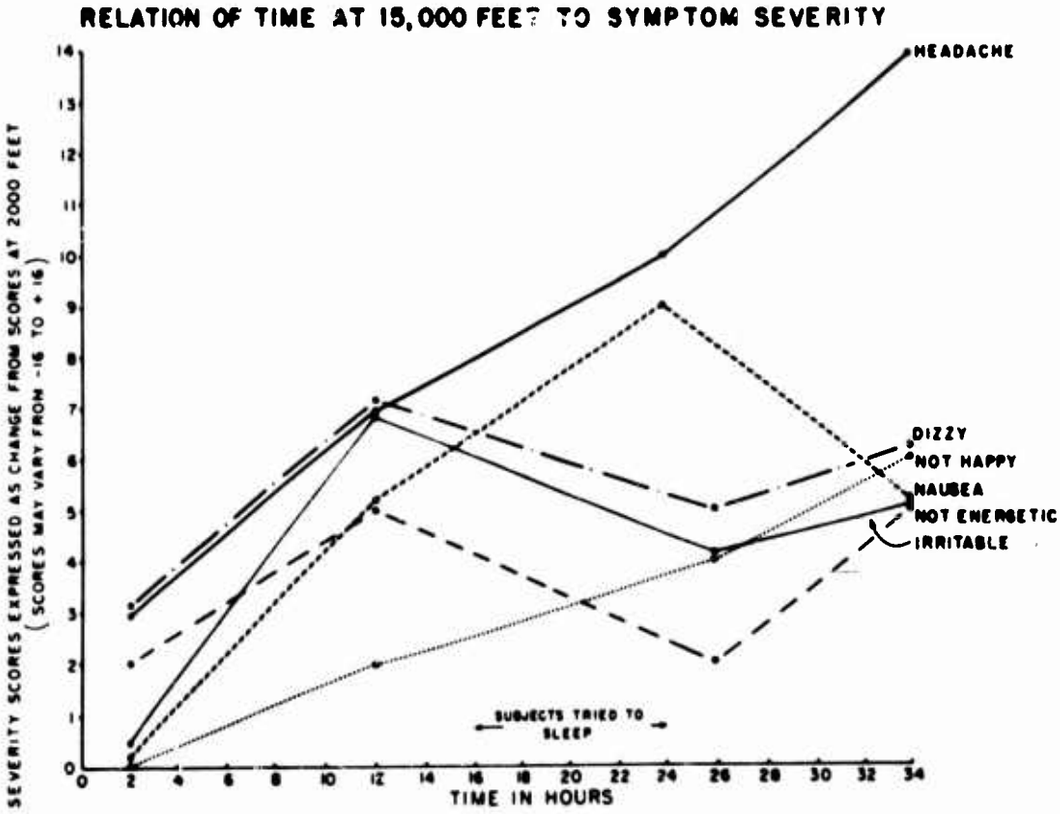


Figure 8
Changes in the intensity of altitude sickness of male subjects as a function of time. Each dot represents the mean score of 16 subjects.

DR. CHIODI: You don't see the early morning headaches in your subjects that I think most of us think of as characteristic of the 15,000 foot exposure?

DR. HANNON: The headaches we see are not much worse in the morning than in the evening, other than that they tend to be more intense when you start running around. You have them at night too.

DR. CHIODI: You don't see the morning headaches that Dr. Dill described, that others have described?

DR. HANNON: Yes, these people had a morning headache.

DR. DILL: How do you explain the 60 percent vomiting, because I have the impression that is pretty uncommon in mountain experience at 15,000 feet?

DR. HANNON: Well, I think part of it is psychological. These people are in a – –

DR. DILL: One vomits and then the odor – –

DR. HANNON: Yes, they're in a closed chamber and this I think probably was responsible for an awful lot of it.

DR. REYNAFARJE: What was the temperature?

DR. HANNON: The temperature was approximately 70 degrees Fahrenheit.

DR. BUSKIRK: This is on the males, right?

DR. HANNON: Yes.

DR. BUSKIRK: Now the females would have a different response in this, wouldn't they? If they woke up in the morning let's say, and it was their first day at altitude, their symptomatology indicated that it was greater the first day or within the first 12 hours than it was later?

DR. HANNON: Yes.

DR. BUSKIRK: Big contrast to the male.

DR. HANNON: The thing that complicates this is the difference—well, two things, one of them is being in a chamber. This in itself would influence it but there was a difference in elevation there, too, 15,000 versus 14,000. But the point is the females in terms of headaches reached their maximum in approximately 12 hours and after that there was a decline in intensity.

DR. DILL: What was the time of day when they reached the Peak, and how much time before they went to bed?

DR. HANNON: They reached the Peak at approximately noon, and then we started making our measurements the following day, day one. They went to bed I would say at approximately eight o'clock in the evening and they got very little sleep that first evening.

DR. DILL: Well, did they go to bed with a headache or wake up with a headache, or both?

DR. HANNON: They were just starting to get headaches I think when they went to bed. These seemed to get worse during the evening and then they improved on the subsequent morning.

DR. HORVATH: There is a greater tendency for female subjects to use medications for their headaches, is this true?

DR. HANNON:, We tried various medications, most of them didn't work very well, as you know. Aspirin probably was about the most effective, and even that was relatively ineffective.

DR. HORVATH: Well, what your charts don't show is what happened to individual girls where the incidence of headaches went down fairly rapidly. It's quite important to know whether different subjects did show headaches on different days or whether they are the same subject; did they all just get their headaches on the first day and have them disappear then on that day, or did maybe another one come up on the second day for one girl, and one on the third day for another girl? I don't think we have that kind of information, really.

DR. HANNON: We do have this information, but we haven't plotted it. The general tendency is for headaches to decrease, but what you say is true, one girl may have a worse headache on the second day than she did on the first day, but the overall average I guess is what we showed here.

Menstrual Cycle

Although the physiology of human reproduction at high altitudes has not been investigated to any appreciable extent, there are indications that profound changes may occur. Thus, Monge (15), in a historical review of acclimatization in the Andes, reports high altitude Indian populations (13,000 feet) reproduce normally. He also reports the invading Spanish who conquered and subsequently integrated with these people produced their first offspring 53 years later. The

functional defect, if any, which was responsible for this apparent lack of fertility has not been determined. Grover, who has studied native residents of Leadville, Colorado also feels reproduction is normal, at least at an altitude of 10 000 feet (16). On the other hand, Hecht, in comments on a paper by Chiodi on newborn animals at high altitude (17) states: "There is a high mortality in human subjects. The incidence of stillbirth is higher and congenital malformation is more frequent. Therefore, pregnant mothers move to a lower altitude level." Unfortunately, he does not document these statements.

Compared to humans, there is a wealth of information on reproductive physiology of laboratory and domestic animals. In general, it appears some aspects of fertility and reporduction may be seriously affected by altitude, whereas others remain relatively normal. Krum (18), for example, reported lactation of F_1 mothers to be reduced to one-third at the Barcroft Laboratory (12,460 feet) in California.

In this same report, however, Krum indicates that estrus cycle is interrupted for as long as 30 days when sea level rats are taken to 12,460 feet. Finally, he showed milk composition to be profoundly altered by high altitude exposure; it contained more lipid but less carbohydrate and water than sea level milk. In another study of rats, Weihe (19) also reports a reduced fertility of animals which are mated shortly after their arrival at high altitude (Jungfraujoch) but a fairly high rate of conceptions in animals mated after four weeks' exposure. He attributed the low fertility of acutely exposed animals to prolonged anestrus and not to infertility in the males. Male infertility, however, can be produced by extreme altitude exposure. Thus, Gordon et al. (20, 21) subjected rats for six hours per day to simulated altitudes of 25,000–28,000 feet. Over a three-week period, they observed a progressive deterioration of the spermatogenic cells. Since this could not be prevented by gonadotrophic hormone these investigators concluded hypoxia was acting directly on the testes. Pugh (13), on the basis of urinary ketosteroid excretion measurements at altitude, feels extreme altitude exposure (Mt. Everest) may depress both gonadal and adrenocortical function.

Our studies of college women reveal very few effects of high altitude on the menstrual cycle, and certainly nothing to suggest fertility is reduced. Data on menstrual function were collected starting in March and continuing through November. These data showed (Figure 9) cycle length and period duration to be unaffected by the transition from low altitude to high altitude. However, upon returning to low altitude both of these time periods were reduced.

When questioned about the various symptoms which may accompany menstruation only one major change was apparent (Figure 10). This was a

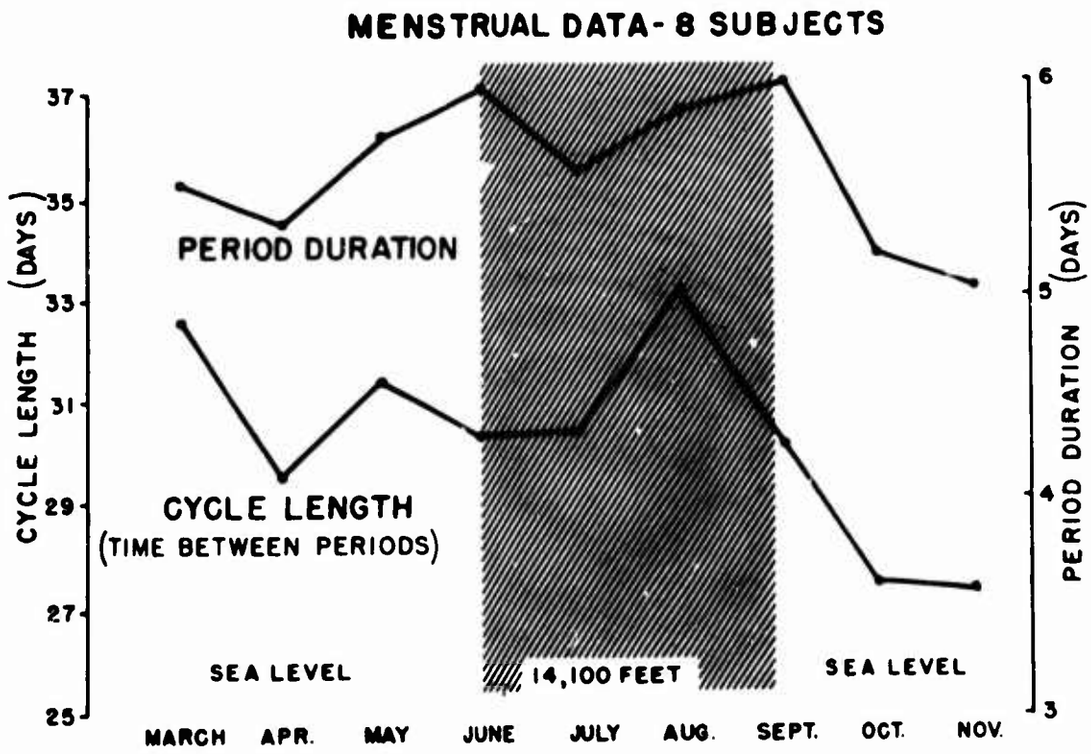


Figure 9

Effects of high altitude exposure on the duration of the menstrual cycle and the period of menstrual flow.

MENSTRUAL CHANGES AT ALTITUDE*

8 Subjects

	Type of Change (No. of girls)		
Symptom	Increased	Decreased	Unchanged
Gen. Strength	0	2	5
Flow (amount)	1	5	2
Abdominal cramps	2	1	5
Headache	1	1	6
Nausea	1	1	6
Irritability	2	1	5
Backache	1	0	7

*Change as compared to usual menstrual symptomatology

Figure 10

Effects of high altitude exposure on the clinical symptoms associated with menstruation.

reduction in the amount of menstrual flow which was reported by five of the eight girls. Two of these girls considered the reduction to be moderate; however, three girls noted minimal or absent flow in all of their periods at altitude. However, slight irregularity in the onset of menstrual periods and in the amount of flow is not uncommon in young females under normal circumstances. Whether the diminished flow noted in this study was related to high altitude exposure per se or to a generally stressful situation is not known. It may be that the reduced flow is a physiological compensation to the reduced total blood volume level present during altitude exposure, and is an attempt to conserve blood loss. This is only speculation; it will be necessary to investigate pituitary-ovarian hormonal relationships at altitudes before the observed changes can be evaluted.

DR. DILL: How long was this measured?

DR. HANNON: Just subjective impressions is all. It's almost impossible to make a quantitative measurement of this.

DR. DILL: Well, it's possible though certainly it's not good, I think, to use subjective evaluation. Girls in general tend to have a very poor concept as to what is the volume of flow they have.

DR. HANNON: Well, this is a problem, admittedly, but in the case of three of these, they reported no flow at all particularly during the first month at altitude. I think this would be a reasonably good subjective impression.

DR. CHIODI: How long had they been at high altitude before you investigated that?

DR. HANNON: Well, of course it varies with each subject.

DR. CHIODI: I know, but on the average how long had they been there?

DR. HANNON: The total exposure to altitude was nine weeks, between nine and ten weeks at altitude.

DR. CHOIDI: Then most of them had just one or two periods?

DR. HANNON: And this reflects mostly the first one here, this would be during the first month at altitude. As Dr. Horvath says, this is a very difficult thing on which to obtain accurate or quantitative results. The general impression is that this sort of change here could be due to the psychological effects of altitude as well as the hypoxia, so attaching too much physiological significance to this isn't really warranted at this time.

DR. HORVATH: We made some studies on that for another purpose one time. We collected all the napkins or the other devices they used and tried to measure the amount of hemoglobin which was present in those to give us some rough idea of the total quantity of blood produced. We found no correlation between what the girls stated, whether this was a large flow or a small flow, and the absolute amount of hemoglobin that was abstracted from the collecting devices. I am really quite curious because this might have some connotations to some of the other studies on sexual factors involved at altitude.

DR. HANNON: Well, admittedly, this does have limitations.

Body Weight

In most species, including man, acute high altitude exposure is associated with a loss of body weight by adult individuals and a reduction in growth rate by immature individuals (22, 23). The immediate cause of this weight loss is a reduced caloric intake, either voluntarily in the case of adults, or involuntarily in the case of the young (19, 24, 25, 26). With respect to the latter, a depression of milk production has been suggested as a causative factor (17, 18, 27). Until the present time, measurements of human weight changes have been limited to males and various authors have almost uniformly attributed the observed losses to anorexia. As to the magnitude of the weight reduction, Barcroft reported (23)

weight losses as high as 24 pounds in individuals sojourning in the Peruvian Andes. Hingston, in reporting on the 1924 expedition to Mount Everest (see Barcroft [29]) indicated losses ranging from 30 to 50 pounds, while Pugh and Ward (30) reported an average loss of 11 pounds in climbers exposed to 17,000 feet for a period of 26 days. In a more recent report (13) Pugh observed a weight loss rate of one to three pounds per week at 19,000. In the older literature, Douglas et al. (8), reporting on the 1911 Anglo-American expedition to Pikes Peak, noted weight losses ranging from six to eight pounds over a period of five weeks.

Body composition changes accompanying weight loss at altitude have yet to be fully resolved. It is known to be associated with a negative nitrogen balance (31, 32, 33) and we can, therefore, assume that some loss of body protein must occur. In humans this negative nitrogen balance seems to occur in spite of an adequate protein intake (33). A clue to the mechanisms involved may be found in the work of Surks (33) and Klain (34) who report, respectively, a reduced synthesis coupled with an elevated degradation rate of plasma albumin in humans and a reduced rate of incorporation of labeled amino acids into the protein of certain tissues (e.g., liver) of the rat. Both of these reports are based upon measurements made at Denver and Pikes Peak. They suggest high altitude exposure, at least during the acute stages, causes alterations in the intermediary metabolism of protein.

An elevated rate of water loss has long been thought to account for a major fraction of the weight loss observed at high altitude. Swann et al. (35, 36) found an increase in the rate of insensible water loss but no change in the losses due to feces and urine of rats exposed to a simulated altitude of 18,000 feet. During exposures lasting from 6 to 23 hours, these investigators found total water loss was increased from 50 to 100 percent. Stickney reported (37) significantly increased fecal, urine and insensible water loss, while Picon-Reategui et al. (38) calculated 94% of the total body weight change of rats subjected to a simulated altitude of 15,000 feet could be accounted for by water loss. Lawless and Van Liere (39) studied the effect of simulated altitude on tissue water content and found a significant reduction in striated muscle and skin hydration at 18,000 feet. The significance of these changes is confused by the fact that similar changes were not observed at 8,000 or 28,000 feet. In humans, Siri et al. (40) reported the total body water content was the same in Andean native populations as in sea level residents. Pugh (13), on the other hand, feels dehydration was responsible for much of the water loss observed in the 1953 expedition to Mount Everest. He suggests an increased ventilation in the dry air and a reduced thirst as the responsible factors. Our symptomatic data

on thirst (Figure 7) would tend to support this contention. In more recent investigations, an increased rate of water turnover was reported by Pugh (41), but no statistically significant change was noted in total body water as estimated by the D_2O dilution technique (42). The latter technique, at least is our experience, does not appear to predict total body water content reliably, particularly at high altitude.

In our studies of college girls on Pikes Peak, a small but significant loss of body weight was observed which seemed to progress (Fig. 11) in a relatively linear fashion after the first day of altitude exposure. Compared to men exposed at a similar location (Fig. 12) the weight loss in women was markedly lower. Accordingly, loss rate during the first few weeks at Pikes Peak was about one-fourth as great in women as it was in male residents from sea level (Boston) or Denver.

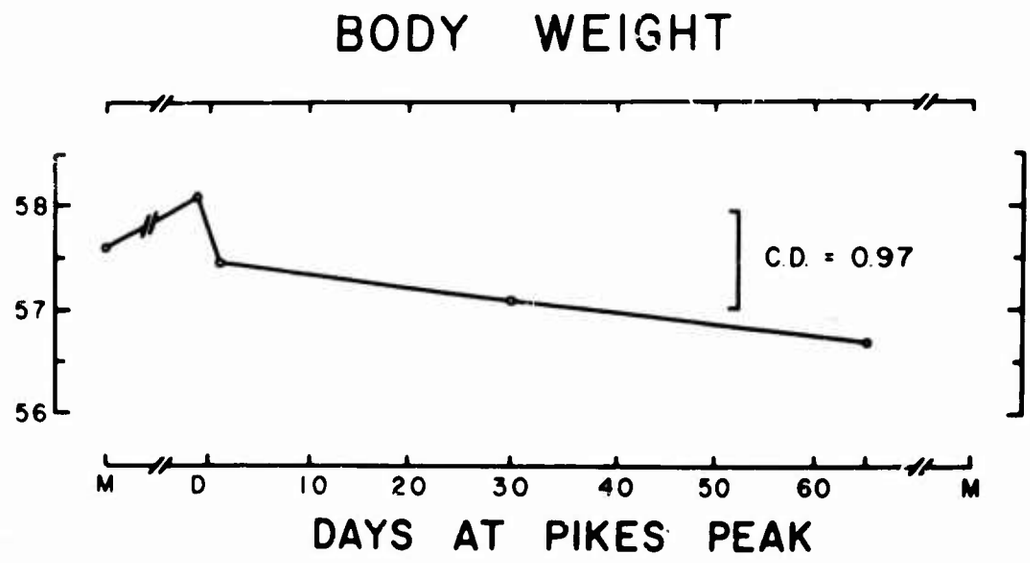


Figure 11
Alterations in the body weight of women as a function of altitude exposure. M refers to measurements made in Missouri, D to measurements made in Denver when the subjects were in transit to Pikes Peak.

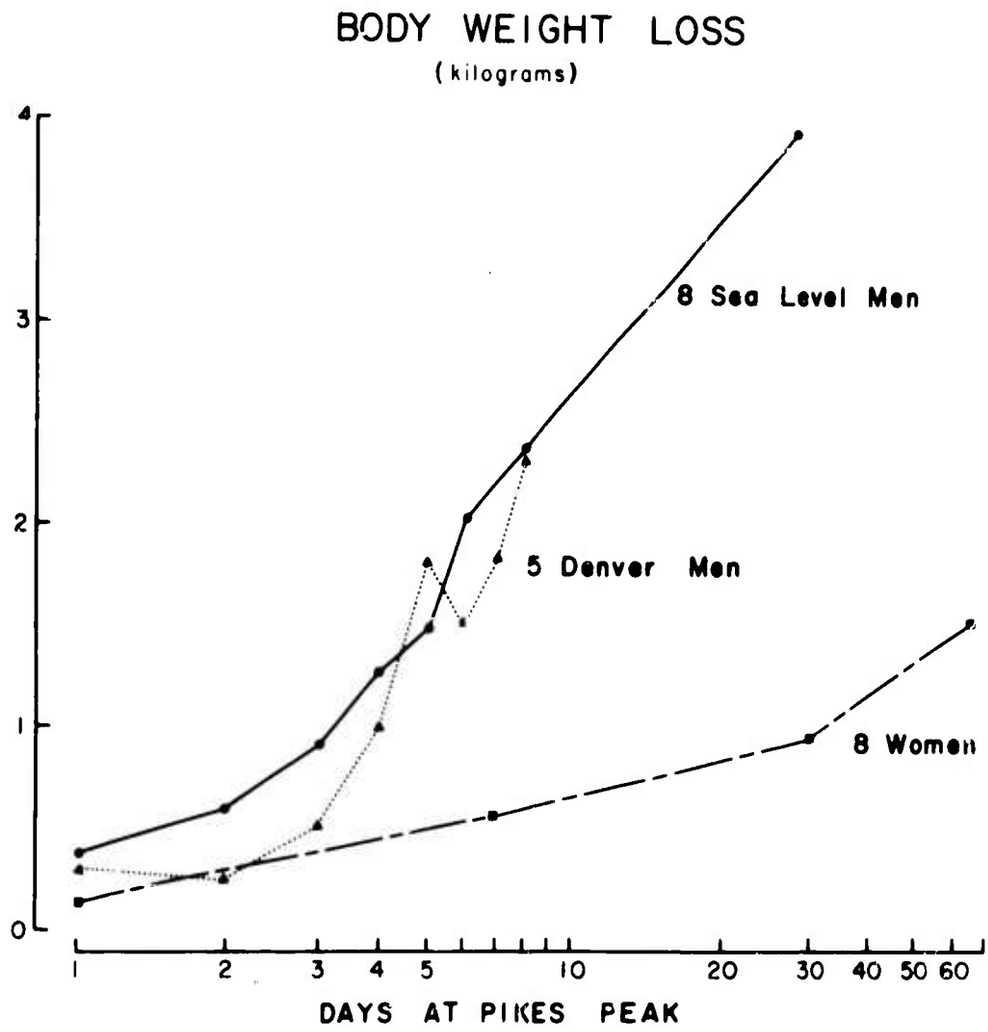


Figure 12
Comparison of the weight losses of men and women during high altitude exposure on Pikes Peak.

DR. DILL: Was this observation on a single girl?

DR. HANNON: No, this was a group of eight.

DR. DILL: How many showed a drop?

DR. HANNON: They all showed a drop.

DR. DILL: They all showed a drop?

DR. HANNON: Yes, their drops were very low, and on subsequent slides I shall show they differ markedly from men. We did make a measure here, and I think if it hadn't been for that measure we would have had real difficulty showing that they had a significant drop in body weight. They did by the time they got out here. This may be a fluid accumulation. The period between here and here is on the order of one week and they gained half a kilo which could easily have been water.

DR. CHIODI: Were they having the same physical activity at high altitude as at sea level? I mean could it be that they worked more at high altitude?

DR. HANNON: Starting two months before they went to altitude, we got them involved in intramural sports of various sorts. They participated in these every day to increase their level of physical fitness. This is dating back to the previous year, when we did see a change in our subjects' physical fitness, so we attempted to build up their level of activity to approach that which they would encounter on the mountain. Trying to do this precisely, I think, would be very difficult. It's hard to measure how much activity they had while living on Pike's Peak, but we did put them on an intramural sports program—basketball, tennis, this type of thing.

DR. DILL: Did they have any sports at Pikes' Peak?

DR. HANNON: Usually they were too tired. They did hike around outside when their day was over. They had fairly long days up there.

DR. DILL: What was the maximum drop you had in any one individual?

DR. HANNON: About, oh I think maybe a kilo and a half or two kilos, but I have some more data on this I think is even more interesting.

At first glance these data might suggest a basic difference in metabolic function, particularly as it is manifest in the body weight maintenance of men and women at high altitude. This difference, however, would seem to be more apparent than real. Thus, if we relate the loss in body weight in men and women to their estimated (on the basis of height and weight) body fat content, as shown in Figure 12, we find both men and women lose weight in proportion to their body fat content. We observe, furthermore, that the two sexes seem to fall on the same regression line. On the basis of these combined data, we can conclude that a loss of body fat may be one of the major factors responsible for the reduction in body weight at high altitude. Direct measurements of the body fat content in laboratory rats exposed to high altitude support this conclusion (43). Finally, should other measures of body fat confirm these findings, it might be practical to suggest that the Army use fat soldiers or well-endowed women for high altitude operations. We definitely favor the latter.

Further evidence favoring a contribution of body fat to the loss of weight observed at high altitude was obtained through measurements of skinfold thickness. These data, as shown in Figure 13, demonstrated a decline in thickness and presumably fat deposits in all of the areas measured except the suprailiac region where changes were minimal and not statistically significant. In all instances, the major portion of the change in skinfold thickness occurred during the first month of altitude exposure, and in two areas (umbilical and thigh) the first week of exposure produced a sharp decline.

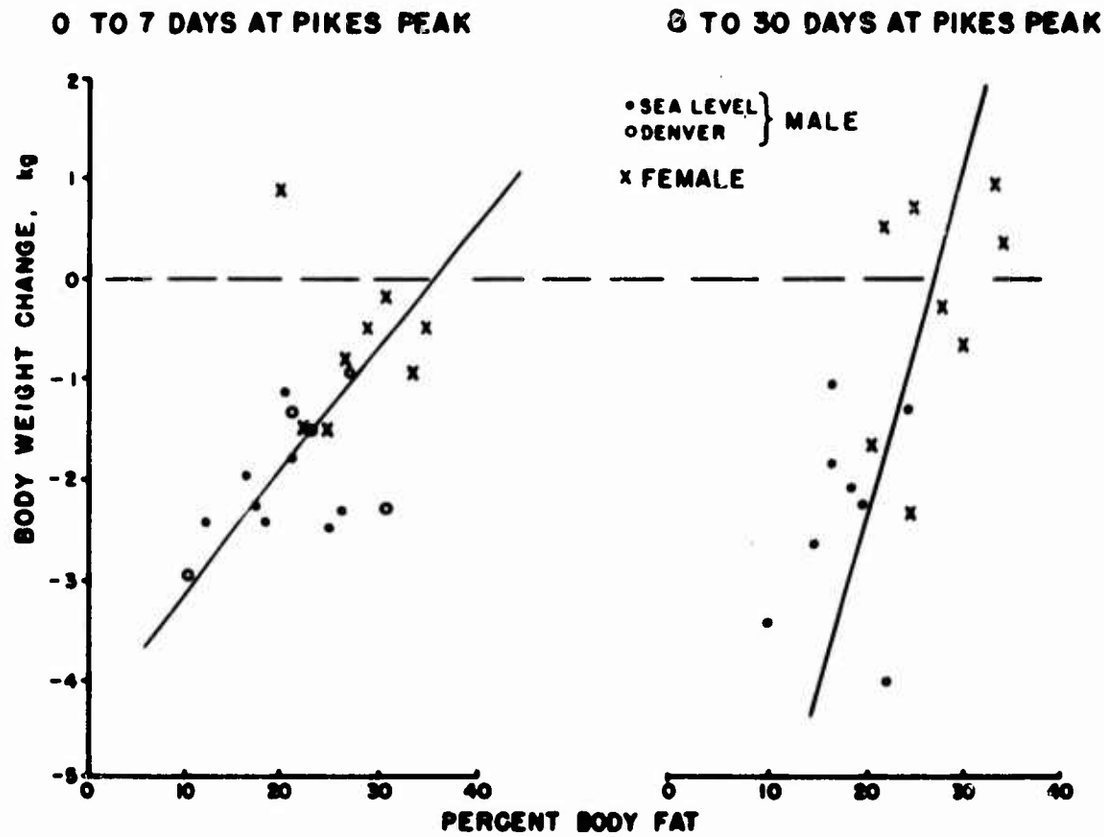


Figure 13
The effects of high altitude on the relationship of body weight loss and body fat loss, as estimated from height and weight, of men and women.

DR. BUSKIRK: This is an abrupt change. Did the same person make those?

DR. HANNON: This is an average of the eight.

DR. BUSKIRK: I mean did the same person make all the measurements?

DR. HANNON: Yes, the same person made them. The control measurements were made in Denver, so we would have them when we went to altitude, and the same technician did the measurements.

DR. DILL: What would these in themselves imply in regard to total weight loss?

DR. HANNON: To try to estimate total weight loss from the change in average skinfold thickness, you mean?

DR. DILL: Yes.

DR. HANNON: I don't know. I haven't tried this yet. You can see they are on the order of in some cases a couple of millimeters. The average I suppose is maybe a millimeter and a half to two millimeters.

DR. HORVATH: Two millimeters on the average?

DR. HANNON: Roughly, I would say.

DR. HORVATH: It would seem to me that would imply a greater weight loss than the one-half kilo that you measured.

DR. HANNON: You would think so, so this raises the question if maybe they are losing water from the skin too.

DR. BUSKIRK: That would be about a five percent reduction, so three kilos over different periods would seem like a lot.

DR. BLATTEIS: Did they eat right away or would you say they lost appetite?

DR. HANNON: They lost some appetitie, but they did eat.

DR. BLATTEIS: But the same amount?

DR. HANNON: We didn't measure this.

DR. BLATTEIS: Because if they ate less, that's part of it.

DR. HORVATH: That's at the 9th day, isn't it, that you measured that?

DR. HANNON: The first measurement is at seven days at altitude. This measurement was made one day prior to going to altitude.

In the extremities, the foregoing changes in skinfold thickness were associated with a decline in body circumference (Fig. 14). The circumference of the buttocks, however, showed no significant change with altitude exposure while the umbilical measurements, although not significantly altered overall, did show a significant decline between the first and tenth week of altitude exposure. In the thoracic region, peculiar changes in body circumference were observed (Fig. 15). At the axillary level, chest circumference at maximum inspiration was significantly increased at high altitude. This increase occurred during the first week of exposure. The axillary circumference at maximum expiration (axillary

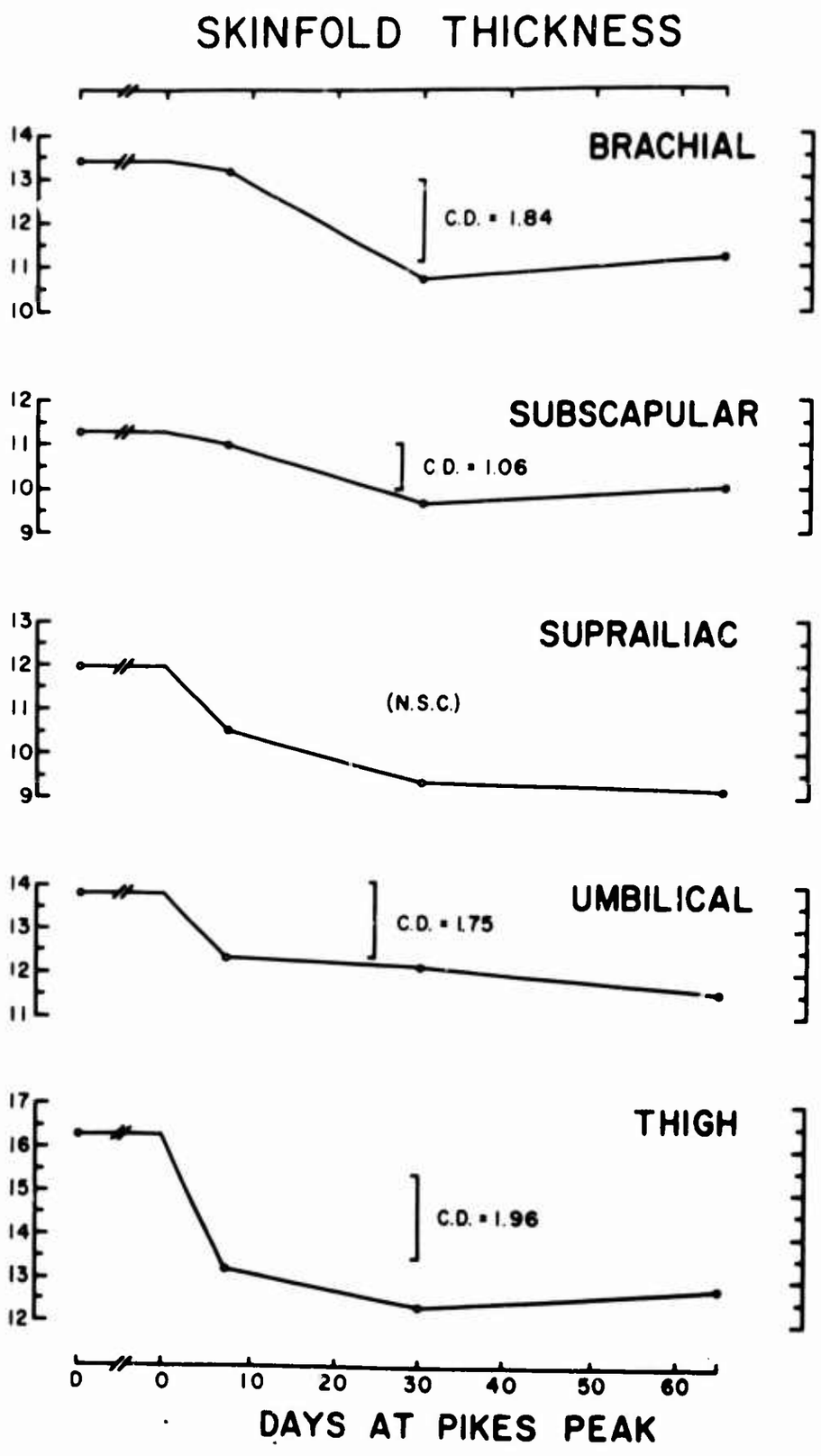


Figure 14

Effects of high altitude on the skinfold thickness of women at high altitude. D refers to the measurements made in Denver just prior to altitude exposure. C.D. refers to the Critical Difference, P _0.05, while N.S.C. refers to no significant change.

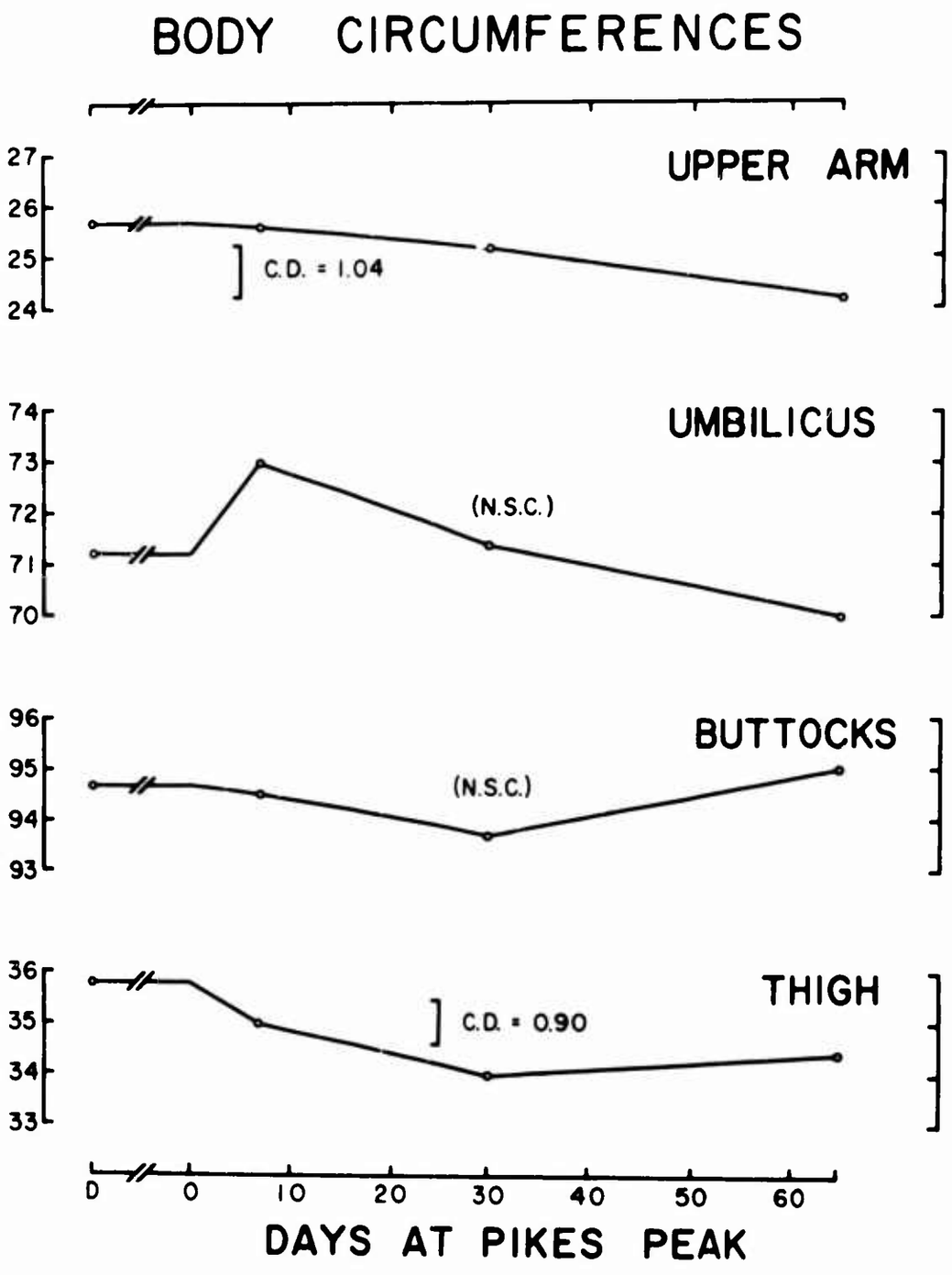


Figure 15

Effects of high altitude on the body circumferences of women.

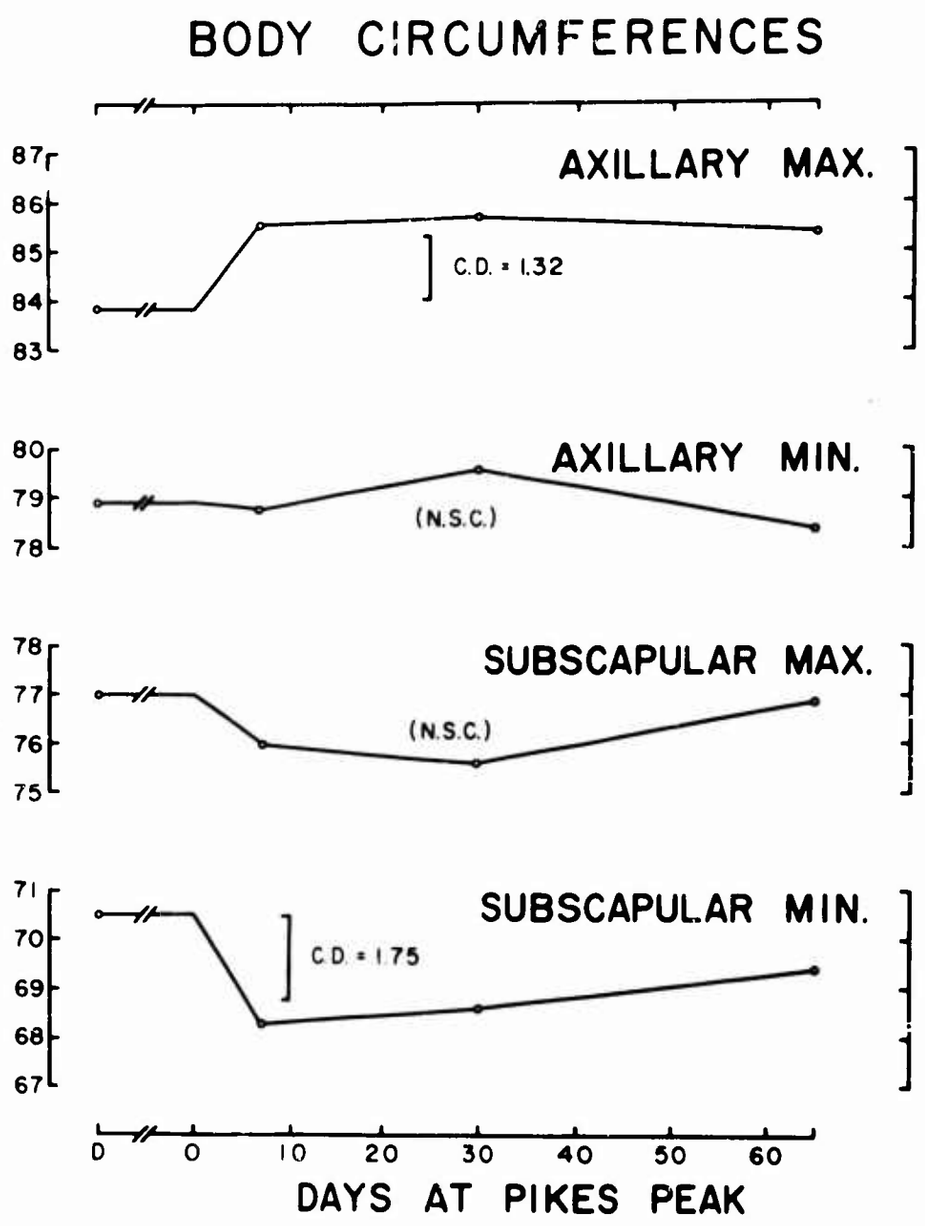


Figure 16

Effects of high altitude on the body circumferences of women.

minimum) was found to be unaffected by altitude exposure. At the subscapular level just the opposite set of changes was obtained. Namely, the circumference at maximum inspiration was unaffected by altitude exposure while the circumference at the end of forced expiration was significantly reduced. The physiological significance of these changes is difficult to fathom.

Pulmonary Function

Our studies of pulmonary function in women exposed to high altitude were limited to the various measures of ventilatory capacity and breath-holding ability (voluntary apnea). No attempt was made to investigate the alterations in pulmonary or blood gas concentrations.

It would appear that earlier information on pulmonary function at high altitude dates back to the reports of Borelli (44) and De Saussure (45). Borelli, in describing a climb of Mount Etna (10,755 feet) in 1671, stated that exercise was poorly tolerated because of the rarified air while De Saussure in describing a climb of Mount Blanc (15,781 feet) in 1796 correctly reported an increase in respiration as physiological response to the rarified air.

This increase in pulmonary ventilation, particularly during exercise, is now a well documented (46, 47, 48, 49, 50, 51) characteristic of high altitude exposure. But, as might be expected, practically all of the available information on this subject has been obtained through studies of male subjects, both human and animal. Hurtado (49), for example, estimates the ventilation of resting Morocochan residents (14,900 feet) to be 20% higher than sea level residents, and this rises to 40% if it is referred to body weight or surface area. Chiodi (46) reports resting ventilation varies with the degree of altitude acclimatization while Billings et al. (52) and Christensen (53) found ventilation during moderate work to be independent of altitude when expressed STPD. Velasquez (51) and more recently Hansen et al. (54) report an increase in ventilation expressed BTPS, both at rest and during exercise. Velasquez emphasizes the marked individual differences which may be seen, particularly with respect to the changes in ventilation as a function of time at altitude (Morococha). Thus, with increasing duration of exposure (up to 12 months) he finds some subjects show a progressive increase in ventilation at a given level of exercise while other subjects show just the opposite; namely, a progressive decline from the initially elevated values. During the first few days at altitude, Hansen et al. (54) found increased ventilation was largely achieved through an increase in respiratory rate. With more extended exposure, however, an increase in tidal volume became a major contributor. In this latter paper, ventilatory volumes (both tidal and total minute volume) were found to be lower at high altitude than at sea level when

calculated STPD. Furthermore, when calculated either BTPS or STPD ventilation increased as altitude exposure was prolonged.

A decrease in vital capacity during acute altitude exposure has been known for many years (47). It first appears at altitudes above 10,000 feet and increases with the elevation (55, 56), but its cause is uncertain. Thus, administration of pure oxygen at 18,000 feet prevents the reduction, while breathing gas mixtures which are low in oxygen does not consistently produce a lower vital capacity (55). Possibly the decrease in barometric pressure at altitude is a contributing factor. Most authors feel this decrease in vital capacity is only temporary and is replaced by an elevated vital capacity in the acclimatized individual. The evidence favoring such an increase in acclimatized individuals is very meager in the case of sea level residents who move to high altitude. High altitude natives, however, do exhibit a greater vital capacity than do sea level residents (57).

Many years ago, Mosso (58) reported a reduction in voluntary breath-holding when subjects from Turin were taken to Mount Rosa. Later, Schneider (59) found in a single subject a 50% reduction between Pikes Peak and Colorado Springs. At simulated altitudes, breath-holding has also been shown to be markedly shortened (60, 61, 62). The degree of shortening seems to be proportional to the elevation above sea level, suggesting oxygen lack as a major stimulus to the resumption of respiration. The simultaneous build-up of carbon dioxide and an increased sensitivity of the respiratory center to carbon dioxide may also contribute (63). With respect to the latter, Hurtado has reported (57) the breaking point during voluntary apnea occurs in a shorter time and with lower values of alveolar P_{CO_2} in high altitude natives than in sea level residents.

Our data on pulmonary function in women at high altitude are summarized in Figure 17. Qualitatively, most of the functional changes are similar to those observed in men. Quantitatively, they may differ greatly.

Total vital capacity (BTPS) exhibited a progressive decrease during the first week of exposure on Pikes Peak. Thereafter, it returned toward the initial low altitude value. In fact, after one month at altitude the two values were not significantly different, while at 2½ months they were essentially identical. Two weeks after the subjects returned to Missouri, they exhibited a statistically significant reduction in vital capacity, not only from their final high altitude value, but also from their initial low altitude value. The cause or functional significance of this post-altitude reduction is completely unknown.

Calculations of one-second vital capacity, expressed as percent of total vital capacity, revealed no statistically significant changes attributable to altitude exposure.

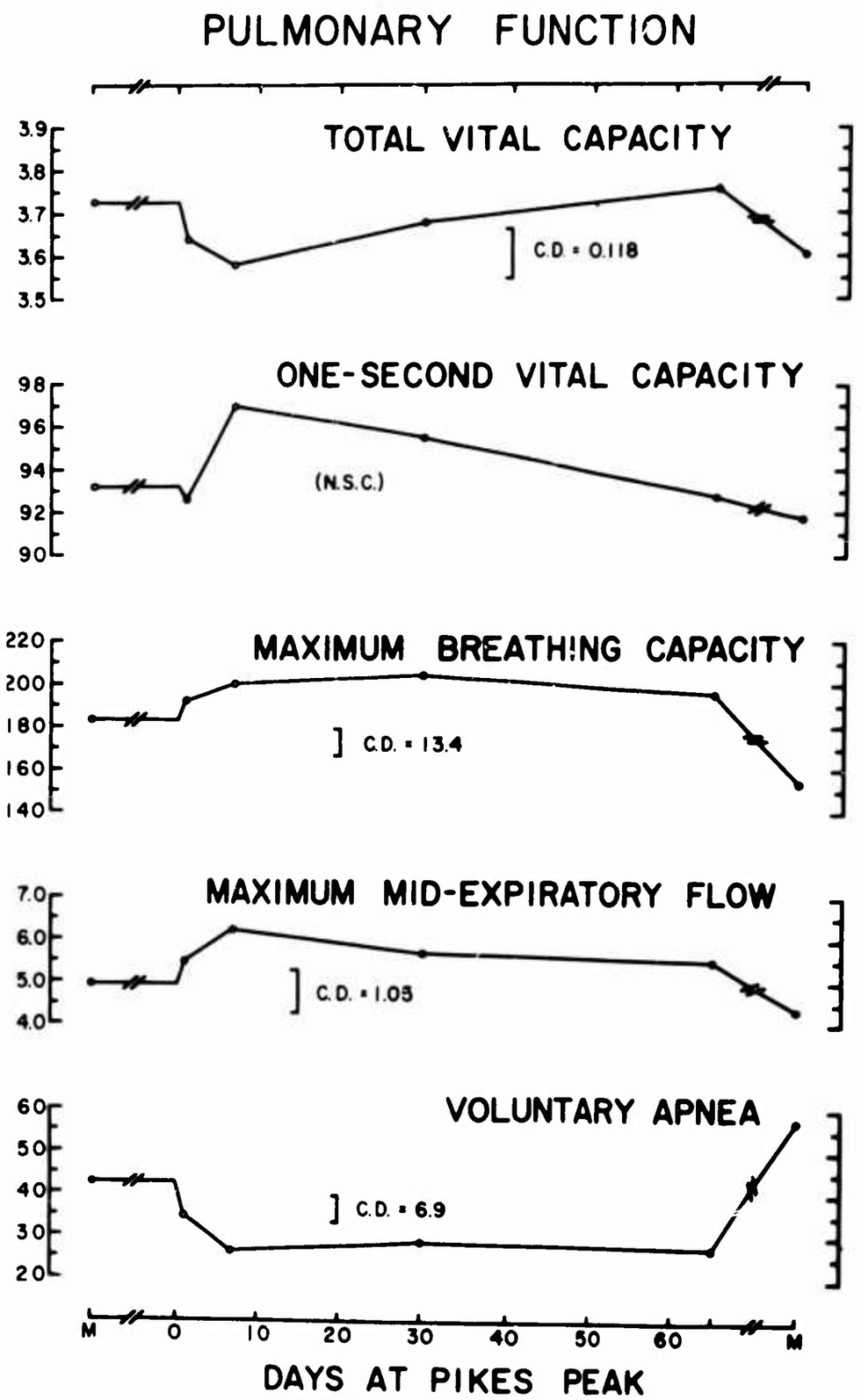


Figure 17

Changes in pulmonary function of women at high altitude. Total vital capacity is expressed in liters, BTPSD; one-second vital capacity as percent of total vital capacity; maximum breathing capacity in liters per minute, STPD; maximum mid-expiratory flow is in liters per second, BTPS; and voluntary apnea in seconds.

Maximum breathing capacity, expressed as liters per minute BTPS, increased progressively during the first week of altitude exposure, and thereafter remained constant. Upon the subjects' return to Missouri, their maximum breathing capacity declined, the mean value being significantly lower than the value obtained prior to high altitude exposure.

The altitude-induced alterations in maximum mid-expiratory flow were very similar to the alterations in maximum breathing capacity, except for the final measurements in Missouri. The mean of the latter was not significantly lower than the inital Missouri value.

Voluntary apnea measurements, i.e., breath-holding ability, were performed by each subject without significant prior warning in order to minimize, or prevent, any tendency to hyperventilate in anticipation of the test. The average of three such tests on each subject was used to compute the group mean characteristic for each period of exposure. As would be expected, exposure on Pikes Peak was associated with a marked reduction in voluntary apnea. This was statistically significant on the first day and became more pronounced by the seventh day. Thereafter, it remained constant until the subjects returned again to Missoui where, somewhat surprisingly, the average value was found to be about 50% greater than the initial Missouri value. The reason for this marked increase in breath-holding subsequent to altitude exposure is unknown. It is probably not attributable to a "training effect" since the breath-holding tests were practiced many times before the initial low altitude measurements were made. Also, it is probably not attributable to an increased resistance to hypoxia per se, since if this had occurred we might expect a gradual increase in breath-holding over the course of the summer when the oxygen carrying capacity of the blood (i.e. hemoglobin) was increasing. Perhaps the subjects acquired an increased tolerance to the accumulation of CO_2 in the blood during apnea, but no direct evidence was obtained to support this possibility.

In two instances it was possible to compare the pulmonary function measures obtained from women with similar measures obtained from men. One of these was total vital capacity (Fig. 18). In both men and women, exposure on Pikes Peak was associated with a reduction in vital capacity. The magnitude of this reduction was quite similar in both sexes during the first week or ten days of exposure, but thereafter the two groups seemed to diverge. Thus, the women tended to revert toward their initial low altitude values while the men continued to show reduced values. Interestingly, upon their return, six low altitude women exhibited an above-normal vital capacity while the men still exhibited reduced but progressively increasing values. It should be noted, however, that these

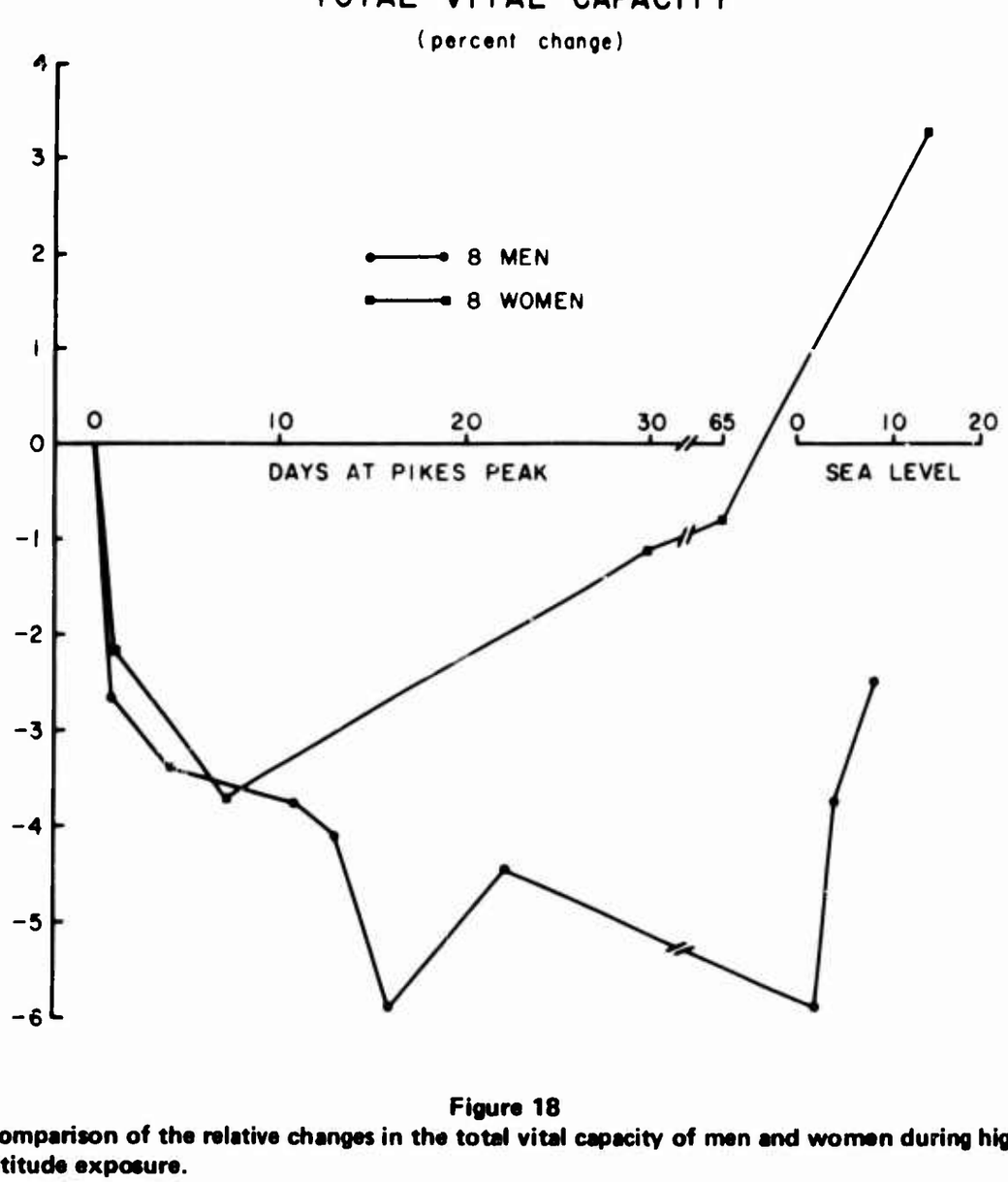
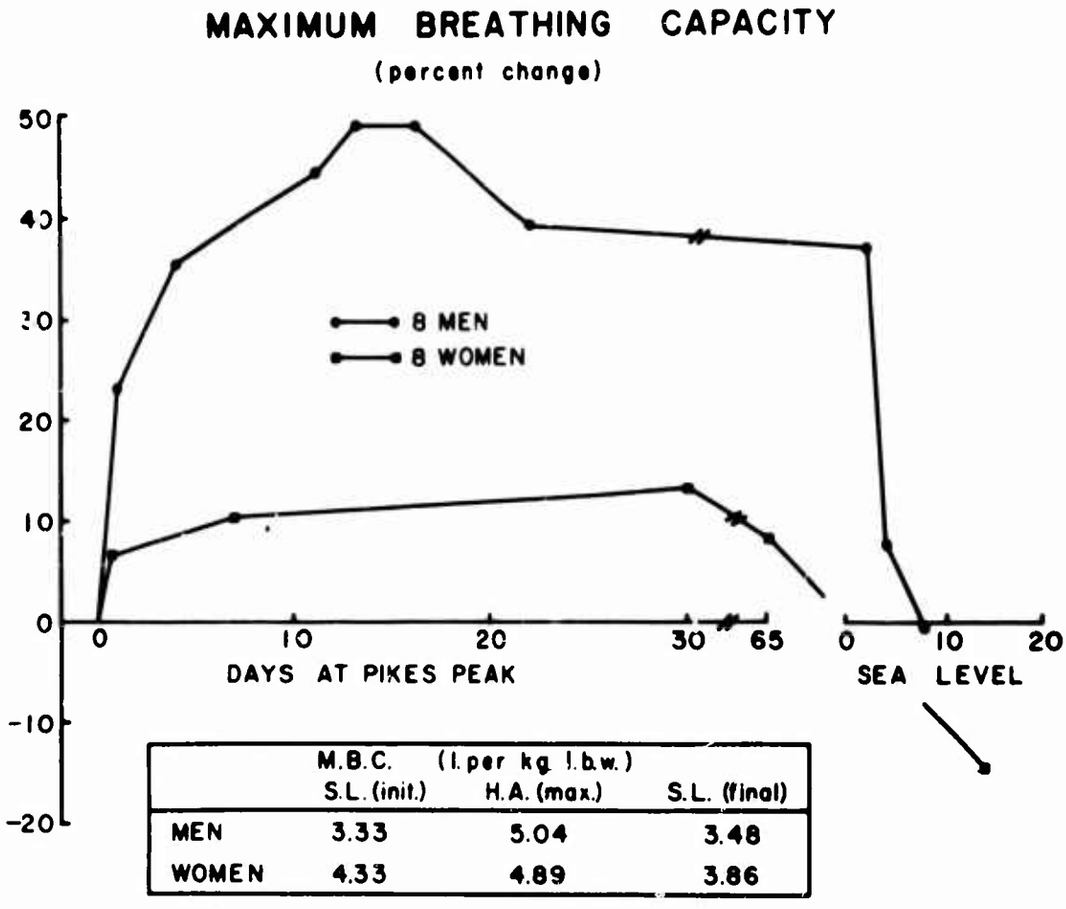


Figure 18
Comparison of the relative changes in the total vital capacity of men and women during high altitude exposure.

comparative differences are complicated by differences in the time at which the data were collected. Thus, the women were measured two weeks after their return to low altitude and the men at two, four, and nine days after their return.



	M.B.C. (l. per kg l.b.w.) S.L. (init.)	H.A. (max.)	S.L. (final)
MEN	3.33	5.04	3.48
WOMEN	4.33	4.89	3.86

Figure 19
Comparison of the relative changes in maximum breathing capacity of men and women during high altitude exposure, and a comparison of the maximum changes in both sexes as a function of estimated lean body weight.

Measurements of maximum breathing capacity were also obtained from both men and women living on Pikes Peak. As already indicated, the maximum breathing capacity of women was significantly elevated during high altitude exposure, but when compared to the same measure in men (Fig. 19) the response of women was markedly less. In fact, the increase in maximum breathing capacity was about four times greater in men than in women. This would seem to be due to the women functioning nearer their maximum achievable capacity while living at low altitude. Accordingly, the initial low altitude maximum breathing capacity of men and women was 3.33 and 4.33 liter per kg lean body mass, respectively, while the corresponding high altitude values were 5.04 and 4.89.

Electrocardiograms

Previous investigation of the electrocardiographic changes associated with high altitude exposure have been made only on male subjects. They consistently show a rightward shift of the QRS axis. At altitudes of 14,000 to 15,000 feet, for example, such an axis deviation is usually observed after exposures of one year (64) and may be seen after exposures as short as one month (65, 66).

To determine whether similar axis deviation also occurred in women, standard 12-lead electrocardiograms were taken in the supine position on all eight subjects with a Sanborn 500 Viso-Cardiette. Particular attention was given to identical placement of the individual precordial electrodes in each subject throughout the study. Tracings were taken at a sensitivity of one millivolt per 10 millimeters and all voltage (amplitude) measurements were expressed in millimeters. The R & S wave voltage in leads I, II, III, AVL, AVG as well as V_1, V_3, V_6 were expressed as the ratio R/R+S to minimize any differences in standardization between electrocardiographic tracings. Besides the direct effect of altitude on the electrocardiograms, the combined effects of altitude exposure and 30 minutes exposure to 100% oxygen (by mask), and the combined effects of altitude exposure and exercise (step test to a heart rate of about 170) were investigated. Table II summarizes all of the electrocardiographic patterns obtained from each of the leads at various times of exposure and conditions of measurement. Figure 21 graphically summarizes the major effects of altitude exposure in women, while Figure 22 depicts the comparative degrees of axis change observed in male and female subjects at different intervals of exposure on Pikes Peak.

The data obtained from the measurements made on women showed that duration of ventricular activation to be within normal limits throughout the ten-week period of high altitude exposure. After seven days on the Peak, however, the QRS axis (AQRS) exhibited a significant (P O.o5) rightward shift, and this shift increased in magnitude as the exposure was extended. Two weeks after the subject returned to Missouri, the deviation in axis had almost disappeared. Oxygen inhalation at the fourth and tenth weeks produced a leftward AQRS shift of about seven degrees, whereas strenuous exercise produced very little change in AQRS.

Only minor voltage changes were noted in the limb and precordial leads at high altitude. An altitude-induced reduction in the R/S ratio (expressed as R/R+S) was observed on the first day in lead II, after 30 days in leads AVL and V_5 and after 65 days in leads I and AVF. A small average increase in V_1 was obtained at 70 days, but this change was not statistically significant. Significant

TABLE II

ELECTROCARDIGRAPHIC CHANGES AT ALTITUDE

Elevation	QRS Axis (degrees)	Lead Voltage Changes (R/R+S)								Transition Zone	T wave V1 (8 subjects)		Heart Rate/Min.
		I	II	III	AVL	AVF	V_1	V_3	V_5		Up	Down	
Low Altitude	52.4	0.86	0.88	0.70	0.60	0.86	0.05	0.09	0.92	V_3	5	3	85
14,110 ft.													
1 Day	56.0	0.86	0.72	0.72	0.61	0.82	0.06	0.10	0.80	V_3	5	3	100
7 Days	65.4	0.81	0.74	0.74	0.46	0.82	0.08	0.08	0.89	V_{3-4}	6	2	98
30 Days	69.0	0.80	0.75	0.75	0.37	0.86	0.04	0.06	0.77	V_4	6	2	88
30 Days w/ Oxygen*	72.5	0.73	0.76	0.76	0.36	0.80	0.08	0.09	0.72	V_4	6	2	75
75 Days	72.5	0.73	0.76	0.76	0.36	0.80	0.08	0.09	0.72	V_4	6	2	76
75 Days w/ Oxygen*	63.0	0.80	0.74	0.74	0.32	0.80	0.05	0.09	0.82	V_{3-4}	6	2	63
75 Days w/ Exercise+	71.9	0.70	0.72	0.72	0.36	0.75	0.01	0.07	0.68	V_4	8	0	120
Low Altitude	57.9	0.81	0.76	0.66	0.40	0.80	0.05	0.06	0.82	V_{3-4}	6	2	68
Critical Difference (P > 0.05)	7.1	0.10	0.06	NSC**	0.22	0.05	NSC**	NSC**	0.15	–	–	–	12.6

*Tracing taken following inhalation of 100% oxygen by mask for 40 minutes

+Tracing taken following 15 minutes of strenuous total body exercise to exhaustion

**No significant change

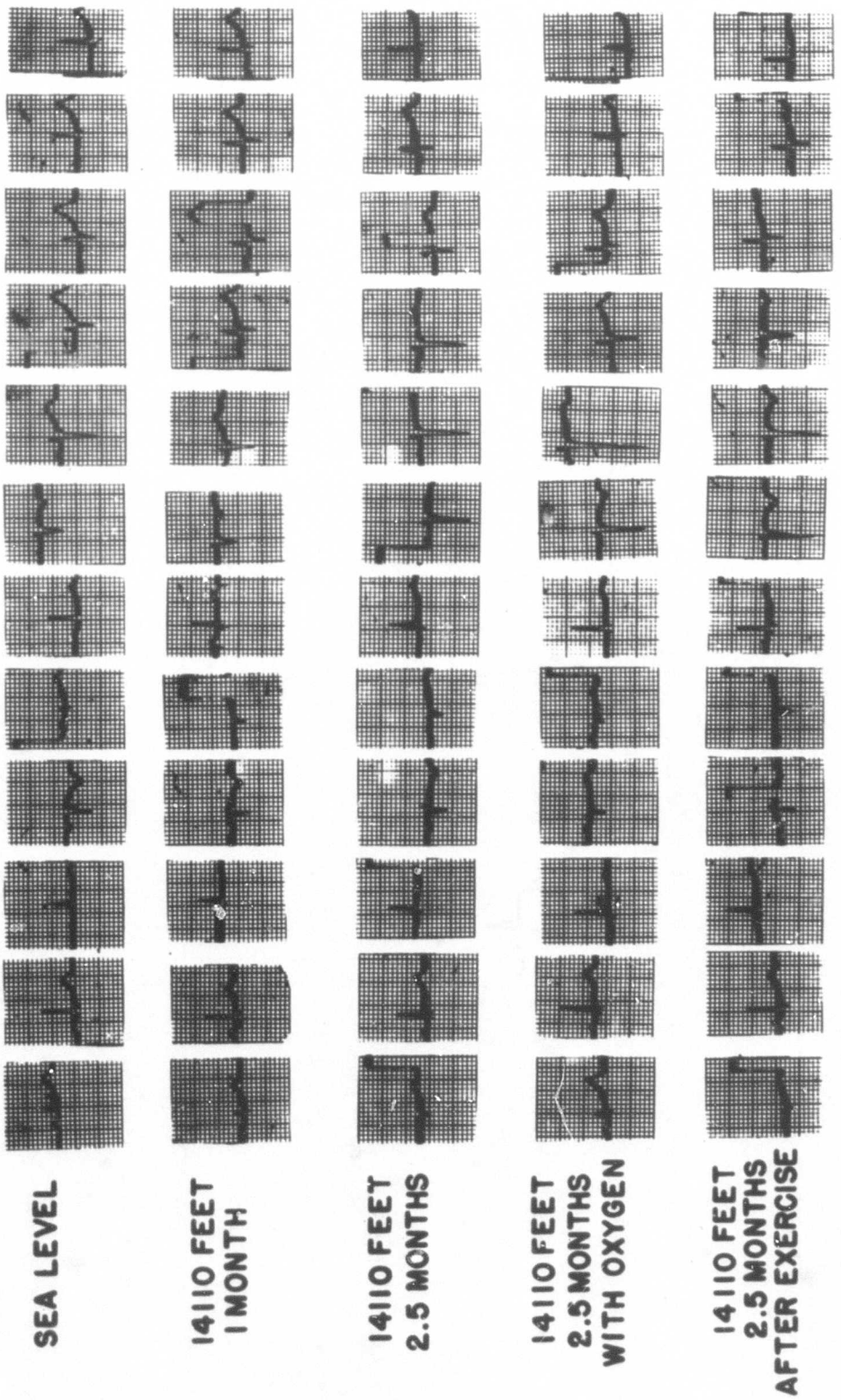


Figure 20
Electrocardiographic changes in women at high altitude.

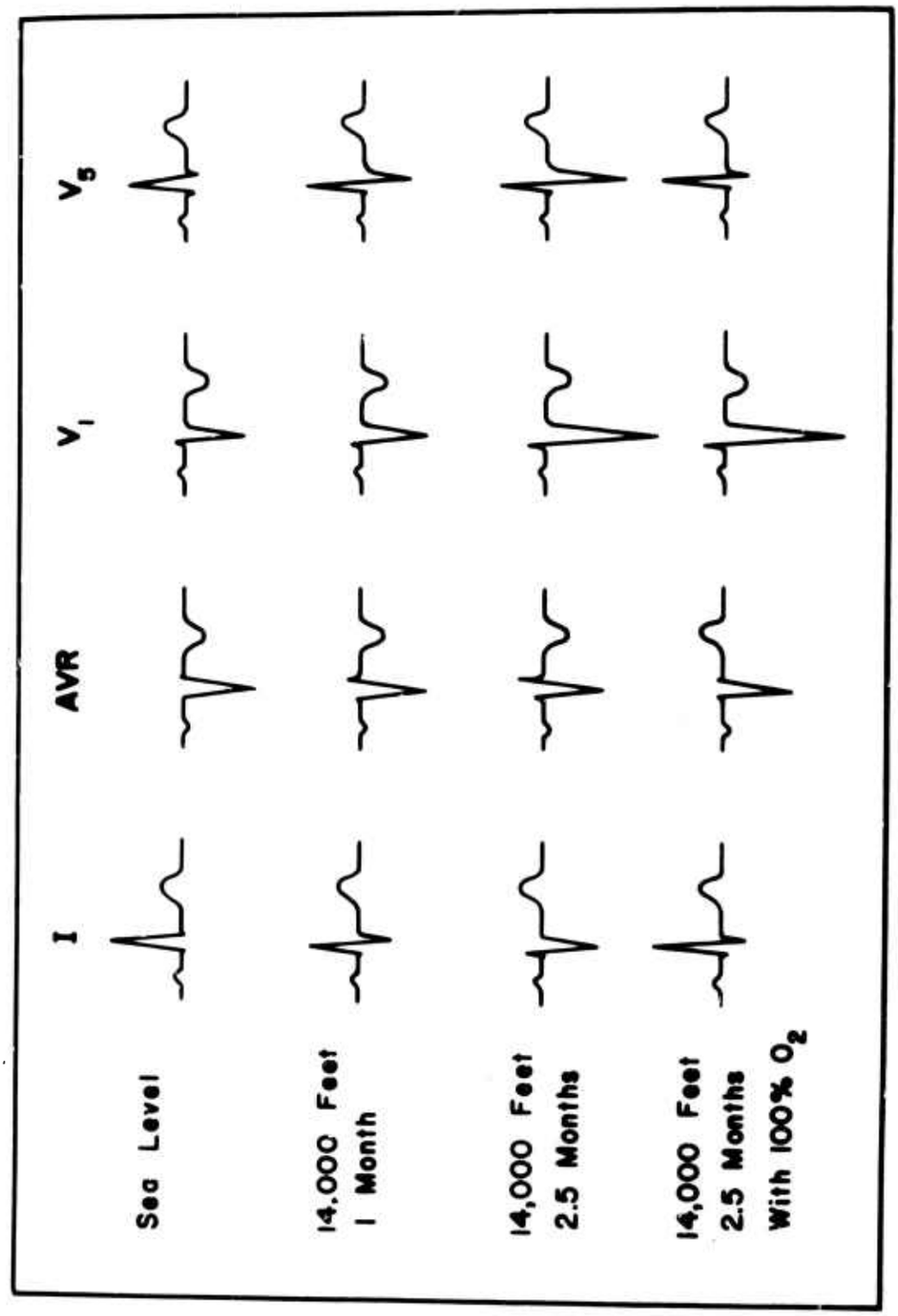


Figure 21
A summary of the major electrocardiographic changes at high altitude as reflected by various leads.

Figure 22
A comparison of the right axis deviations in men and women at high altitude.

voltage changes were not observed in leads III and AVR nor were they produced in any of the leads by oxygen inhalation or exercise.

The QRS duration in these women did not change consistently during high altitude exposure. An R_1 of 1.5 mm in leads V_3 R and V_1 was noted in one subject by the fourth week of exposure and this persisted during her entire stay. It was not present in her original Missouri tracing or two weeks after her return from Pikes Peak to Missouri.

High altitude exposure had little or no effect on atrial activation. Thus, only slight and inconsistent changes in P wave voltage and P-R interval were observed. Similarly, altitude had relatively little effect on ventricular recovery. The T wave in V_1 became upright in one subject who exhibited an inverted T wave during the initial Missouri measurements. The T wave in V_1 became upright in all subjects during exercise at altitude, but reverted to its original configuration within five minutes after the cessation of exercise.

It is of interest to compare the foregoing electrocardiographic data with data obtained from 16 men of similar ages who were measured initially at sea level and subsequently during four weeks' exposure on Pikes Peak (65). Significant ($P > 0.05$) $\bar{A}$QRS and transition zone shifts were observed in both groups by the end of the first week at altitude and became progressively greater as the exposure was extended to four weeks. The latter may be related to more leftward $\bar{A}$QRS observed in women at low altitude. Unlike women, men show marked changes in the T wave configurations in V_1 and in the limb lead voltages. Exercise in men at altitude, in contrast to women, caused a significant leftward $\bar{A}$QRS shift, even after one month exposure.

These relatively minor differences in the electrocardiographic responses of men and women to high altitude stimulate etiologic speculation, but without other associated data are probably of little clinical significance. On the other hand, the reversion of the high altitude-induced electrocardiographic changes toward low altitude characteristics during oxygen inhalation indicates that permanent anatomical changes in the myocardium were not induced, even after ten weeks of exposure. Such reversion might be expected since inhalation of oxygen rich gas mixtures has been shown (67, 68) to reduce the elevated pulmonary arterial pressure which is observed at rest and during exercise in permanent high altitude residents.

Vectorcardiography

Vectorcardiograms were taken on the eight women initially in Missouri and after ten weeks' altitude exposure utilizing an Electronics for Medicine (EFM) oscillographic recorder, and the Trask lead system with vector loop

interruption set at 400 times per second. Chest electrodes were placed at the level of the fifth intercostal space with the subjects in a supine position. The vector loops were analyzed by the method of McCall et al. (69).

Table III presents mean values and standard errors of the mean for the frontal, horizontal and right sagittal planes. Typical vectorcardiograms at high and low altitude are shown in Figure 23. The mean spatial magnitude of the Q, R and S vectors are shown in the last column. At both low and high altitude, a Q loop could be identified in the frontal plane of seven subjects while R and S loops could be identified in all eight subjects. The only significant ($P > 0.05$) frontal plane change at high altitude was an increase in R and S vector magnitude. In the horizontal plane, a Q, R and S loop was identified in all subjects at each altitude, and significant changes consisted of a decrease in the duration of the R vector and an increase in the magnitude of the S vector. A Q, R and S loop was also identified in the sagittal plane measurements of all subjects at each altitude. Here the major high altitude effect was an increase in the magnitude of the R and S vector.

The mean spatial magnitude of the S vector increased significantly at high altitude. The changes in QRS loop configuration included an increase in frontal, horizontal and sagittal loop length and in horizontal and sagittal loop width (Fig. 23). A change in the trajectory of the frontal QRS loop was noted in the two subjects and the sagittal loop in one subject at high altitude. There were no significant changes in the total duration of the QRS loop during altitude exposure.

The foregoing changes in the QRS loop at Pikes Peak, although small, demonstrated a definite accentuation in both the planar and spatial magnitude of terminal QRS force (S vector). Similar observations have been made in studies of adolescent and adult native populations living at high altitude (70). An increase in pulmonary artery pressure is present in such native populations and post-mortem examinations reveal an increased ventricular weight which tends to be concentrated in the right ventricular outflow tract (71). This anatomical modification probably accounts for the vectorcardiographic deviations seen in such people. An increase in resting pulmonary artery pressure was also observed (64) in young adult subjects during the course of 12 months' exposure to 14,900 feet. It would seem reasonable, therefore, to suggest that the development of increased QRS magnitude at high altitude, as seen in the present study of women, represents a response of the right ventricle to an increased workload, imposed by an elevated pulmonary artery resistance. It should be emphasized, however, that the time required to develop the right myocardial hypertrophy seen in native populations is at present unknown. It evidently takes longer than

TABLE III

VECTORCARDIOGRAPHIC CHANGES AT ALTITUDE

	Frontal Plane (mean ± S.E.)		Horizontal Plane (mean ± S.E.)		Rt. Sagittal Plane (mean ± S.E.)		Spatial Magnitude of Vectors (mean ± S.E.)	
	Low Altitude	14,100' for 75 days	Low Altitude	14,110' for 75 days	Low Altitude	14,100 for 75 days	Low Altitude	14,100' for 75 days
Q Angle (degrees)	195.9±28.7	197.1±29.5	120.9±28.3	322.8±28.6	324.6±20.9			
Q Magnitude (mv.)	0.12±0.02	0.16±0.03	0.24±0.06	0.28±0.05	0.18±0.06	0.15±0.12	0.25±0.14	0.33±0.13
Q Time (msec.)	11±2	12±1	12±3	10±1	15±3	12.5±7		
R Angle (deg)	42.8±3.2	48.1±5.1	330.4±22.2	358.7±8.6	107.2±11.6	97.8±8.4		
R Magnitude (mv.)	1.06±0.14	1.14±0.14*	0.90±0.13	0.90±0.10	0.79±0.06	0.92±0.09*	1.40±0.32	1.49±0.38
R Time (msec.)	42±7.3	36±3	49±6	37±2*	46±7	36±2		
S Angle (deg.)	203.9±31.7	239.6±36.5	233.6±24.5	260.2±6.0*	188.2±13.3	192.8±14.7		
S Magnitude (mv.)	0.18±0.04	0.27±0.06*	0.31±0.05	0.52±0.07*	0.33±0.09	0.56±0.06*	0.41±0.17	0.75±0.26*
S Time (msec.)	64±10	52±2	67±8	50±2*	66±6	53±3		
Length (cm.)	1.21±0.16	1.38±0.12*	1.01±0.15	1.03±0.11	0.90±0.12	1.10±0.12		
Width (cm.)	0.35±0.05	0.38±0.03	0.60±0.07	0.71±0.07*	0.60±0.09	0.75±0.08*		
Length/Width (cm.)	3.7±0.6	3.8±0.4	1.9±0.3	1.6±0.3*	1.7±0.2	1.5±0.2		
QRS Duration (msec.)	80±3	65±2	86±11	66±1	84±11	69±2		
QRS Loop Trajectory (8 subjects)								
Clockwise	2	1	0	0	6	7		
C. Clockwise	3	5	8	8	0	0		
Fig. of Eight	3	2	0	0	2	1		

*Represents a significant change (P>0.05) from sea level value.

the 10-week exposure used in these studies of women, since the altitude-induced changes in AQRS observed during the ECG measurements disappeared during oxygen inhalation.

Figure 23
Typical vectorcardiographic traces in women acclimatized to low and high altitudes.

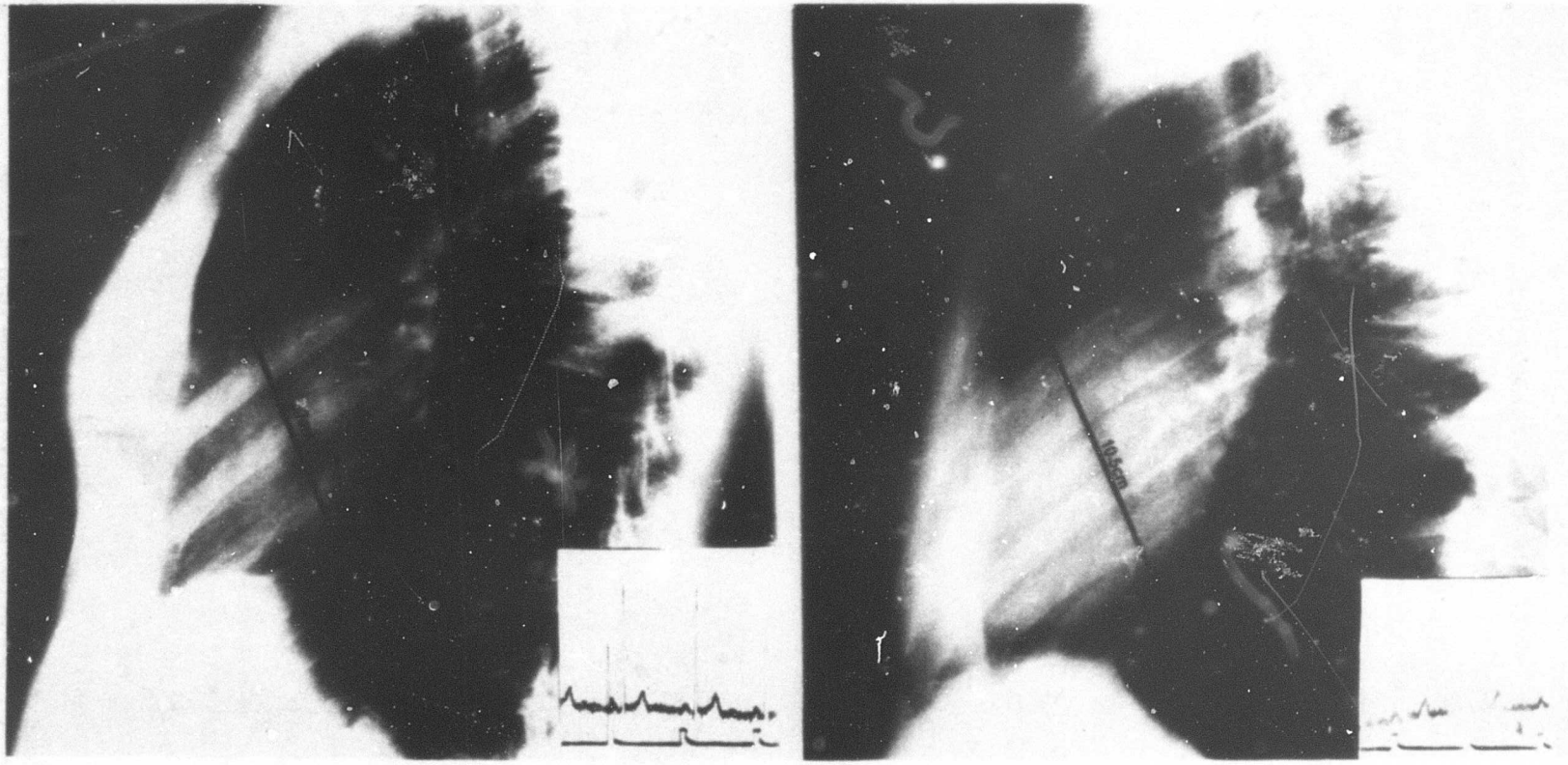


Figure 25
Lateral dimensions of the heart at low (left) and high (right) altitudes as determined from x-rays electronically triggered (see insert) to coincide with diastole.

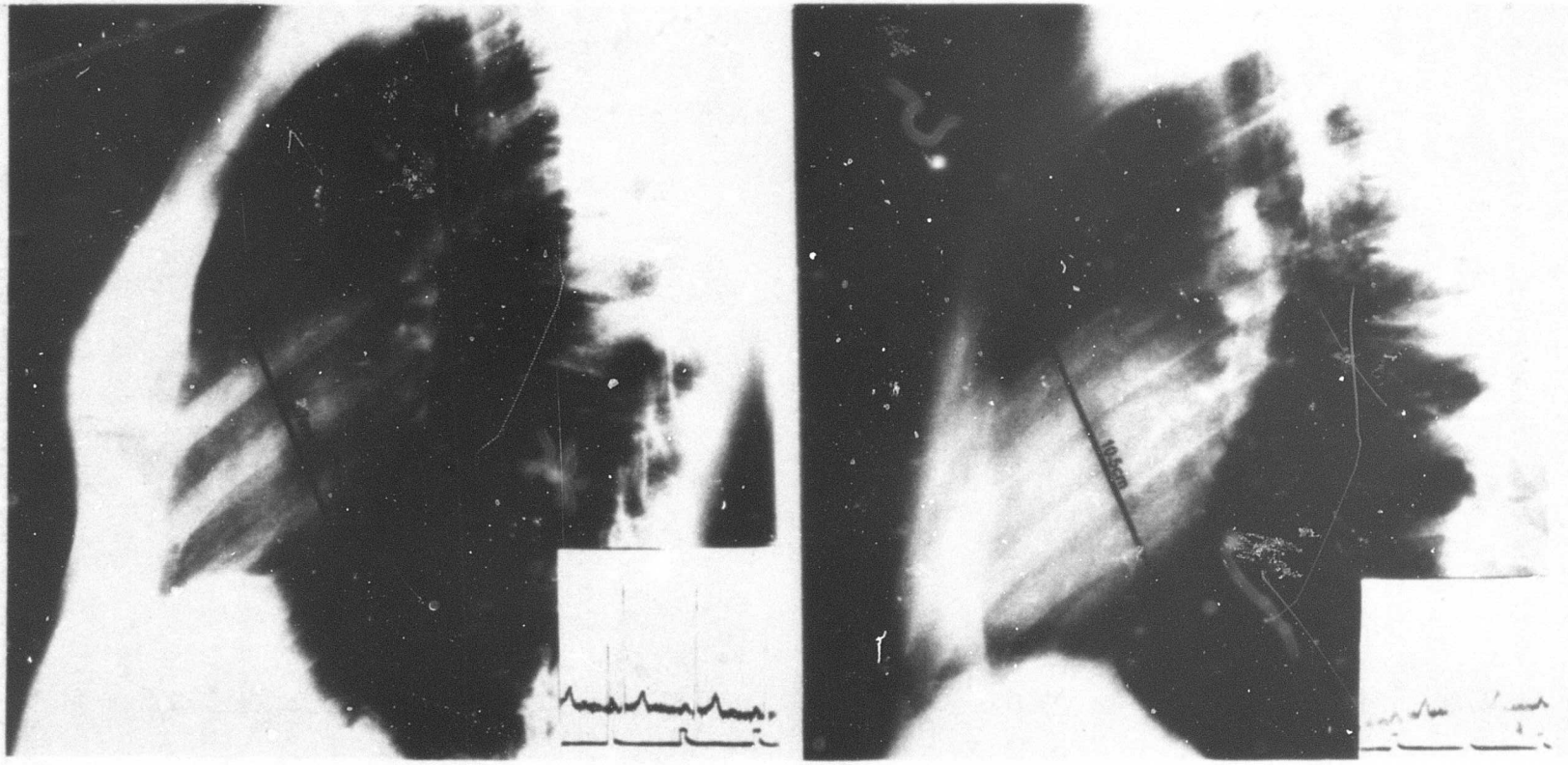


Figure 25
Lateral dimensions of the heart at low (left) and high (right) altitudes as determined from x-rays electronically triggered (see insert) to coincide with diastole.

TABLE IV

RADIOGRAPHIC CHANGES IN HEART SIZE

(PA and Lateral Views)

Measurement* (cm.)	Low Altitude (mean ± S.E.)	14,110 ft. (75 Days) (mean ± S.E.)	Significance (Paired t - test)
Long Diameter (L)	14.3 ± 0.39	13.4 ± 0.39	P<0.05
Transverse Diameter ($T_1 + T_2$)	11.9 ± 0.38	11.1 ± 0.39	NSC+
Broad Diameter (B)	11.0 ± 0.37	10.9 ± 0.21	NSC+
Lateral Diameter (LD)	9.0 ± 0.37	9.6 ± 0.20	P<0.05
Pulmonary Artery Diameter (PA)	1.2 ± 0.09	1.5 ± 0.08	P<0.05
Heart Volume (cc)	754 ± 48.0	750.7 ± 40	NSC+
Heart Area (sq. cm.)	133.0 ± 5.1	124 ± 4.7	P<0.05
Diaphragm Level (cm.) (from rt. 10th rib)	1.9	2.1	NSC+

*See Figures 24 and 25
+No significant change

These data reveal a significant decrease in the long diameter of the heart, but no significant change in transverse or broad diameters. Calculated frontal area decreased at high altitude, which would signify a slight reduction in overall heart size. An altitude-induced increase in anterior-posterior diameter was observed in the lateral view and in the measurements of proximal pulmonary artery diameter. Heart volume and the inspiratory diaphragmatic level, as measured from the tenth rib, were not altered by high altitude exposure.

Comparing these measurements with similar measurements reported in the literature reveals many conflicts in data and interpretation. Loewy and Mayer (74) and Whitney (75), for example, state that the heart may dilate during hypoxic exposure. LeWalt and Turrell (76) and Graybiel et al. (77) feel that it may increase or decrease in size, while Keys et al. (78) and Harris and Hansen (79) state that there is no change during high altitude exposure. The best evidence to date supports the view that a small but gradual reduction in heart size occurs during the first month of high altitude exposure. This change might result from a reduction in cardiac filling as manifested by the observed reduction in stroke volume during the first several weeks at altitude (80). An increase in radiographic heart size, however, has been found in subjects exposed to high

altitude for one year (64) and is frequently present in long-term residents (81, 82). Recent improvements in the technical design and functioning of radiographic equipment justify some legitimate criticism now of previous x-ray evaluations of heart size change at altitude. Thus, early studies utilized prolonged exposure time (0.5 seconds or longer), incorporated only one view of the heart for measurements and had poor control over the period of the cardiac cycle during which the exposures were made In spite of these factors, the consistency with which heart size changes have been noted in altitude-exposed subjects warrants the above conclusion (77).

In our studies of women, the calculated mean frontal area was significantly reduced at altitude in spite of only minimal changes in mean transverse diameter. The finding of an increase in mean lateral anterior-posterior heart diameter at altitude suggests that the reduction in heart size as judged from the frontal view is not a uniform reduction, and in fact may be an erroneous interpretation. This opinion is supported by the lack of a significant change in heart volume, a calculation which incorporates measurements taken in both frontal and lateral views. The change in heart size of women cannot be accounted for by gross differences in ventilatory volume at the different altitudes, as the mean diaphragmatic level during full inspiration was found to be essentially the same at each elevation. Our findings of a reduced heart size at two and one-half months' exposure, as judged from the posterior-anterior view, is in agreement with the findings of Graybiel et al. (77) in subjects exposed to very high altitudes for one month; however, the overall heart size in the present study was probably not changed to any appreciable degree (See Figure 26).

The prominence of the larger pulmonary artery branches seen in women has also been observed in men residing at high altitude for one month (79) and for one year (64). This change most likely represents dilatation which is secondary to an increase in pulmonary arteriolar resistance, and possibly to an increase in the percentage of total blood volume present in the lesser circulation at altitude.

RADIOGRAPHIC HEART CHANGES

PA & LATERAL VIEWS

(LOW ALTITUDE vs 14,100 FT. FOR 10 WEEKS)

	SIGNIFICANT CHANGES PAIRED t TEST
TRANSVERSE DIAMETER	DECREASED IN 6 SUBJECTS NO STATISTICAL CHANGE (11.9 → 11.1 cm)
LATERAL DIAMETER	INCREASED (9 → 9.6 cm)
FRONTAL HEART AREA	DECREASED (133 → 124 sq cm)
HEART VOLUME	UNCHANGED
PULMONARY ARTERY DIAMETER	INCREASED (1.2 → 1.5 cm)
DIAPHRAGMATIC LEVEL	UNCHANGED

Figure 26

Statistical evaluation of the major changes in heart dimensions during high altitude exposure.

RESPONSES OF MEN AND WOMEN

Heart Rate

An increase in heart rate is perhaps the earliest, most readily recognized circulatory response to high altitude exposure (29). Tachycardia usually appears in resting sea level residents when the oxygen partial pressure of the inspired air approaches 110 mm Hg, which is equivalent to an elevation of about 10,000 feet (29, 83). Thereafter, the rate increases progressively as inspired oxygen partial pressure decreases to about 85 mm Hg, but more rapidly as the partial pressure is reduced to 50 or 60 mm Hg. A doubling of the heart rate accompanies breathing low oxygen gas mixtures at these latter partial pressures (84, 85). Such high rates, however, cannot be maintained (86). In fact, it was demonstrated many years ago that continuous breathing of very low oxygen mixtures eventually leads to a slowing of the heart (87, 88).

The magnitude of the tachycardia observed during actual altitude exposure depends upon a number of factors, including the elevation, the duration of exposure, and the conditions under which the measurements were made. Furthermore, there is usually considerable inter-subject (89) but not intrasubject (90) variation. Except during maximum exercise at moderately high altitude, i.e., 12,000 to 14,000 feet, the heart rate is greater at all levels of activity (90). Kellogg (50), for example, in exercise studies conducted at White Mountain (12,470 feet) found maximum heart rates at high altitude to be similar to those observed at low altitudes, at least in most of his subjects. Christensen and Forbes (91) observed a marked deterioration (up to 40-50 beats/minute) of the maximum heart rate during their Chilean expedition, and Schilling et al. (92) reported two of his subjects at Morococha (14,900 feet) could not exceed a pulse rate of 156 while a third reached a rate of 170. At 14,000 feet Astrand (93) could not raise his heart rate above 140 beats per minute, but Balke et al. (94) and more recently Vogel et al. (80) reported decreases in maximum rates ranging from five to fifteen percent. Interestingly, Vogel et al. (80) found no improvement in the maximum rate of young subjects on Pikes Peak even after three weeks' exposure. This was true for both trained and untrained individuals. Peruvian natives living at Morococha, on the other hand, are reported to have maximum heart rates comparable to those of subjects at sea level (95). At elevations above 14,000 feet, such as those encountered in Himalayan expeditions, a marked reduction in the maximum heart rate is always observed (41, 96).

Very meager data are available on the cardiovascular responses of women to high altitude. The one subject in Grollman's study (1) exhibited an increase in resting rate of about 30 beats/minute (58-88) on the second or third day of exposure; this was reduced to about 15 beats/minute on the tenth day, where it

remained relatively constant to the twentieth day at which time the experiment terminated. Her resting cardiac output, on the other hand, was not increased on the first and second day of exposure but increased thereafter. The lack of change during the first two days on Pikes Peak was attributed to altitude sickness – this lasting for a period of 36 hours. A maximum increase in resting cardiact output of almost 100% occurred on the fifth day of exposure, after which a decline was observed. Even after 20 days, however, the output was still some 30 to 40 percent over the low altitude value. This is in contrast to recent information (80) on men which shows the cardiac output to approach sea level values after about three weeks exposure at the same site. In fact, in measurements on himself, Grollman exhibited near normal outputs after ten days' exposure.

In our studies of college women, the measurements of heart rate were taken from electrocardiographic records which were made after 15 minutes of supine rest. The data show (Fig. 27) a marked increase on the first day of exposure and a progressive decline thereafter. Low altitude values were reached by the tenth week of exposure, and, interestingly, significantly ($P<0.05$) depressed values were observed two weeks after the subjects returned to Missouri.

When these data are compared to data obtained from soldiers under similar exposure conditions, the women appeared (Fig. 28) to exhibit a relatively greater tachycardia. This apparent sex difference should be accepted with caution, however, since one is never really sure in such studies that the experimental conditions are exactly alike. In the case of Grollman and his wife, similar degrees of tachycardia were observed.

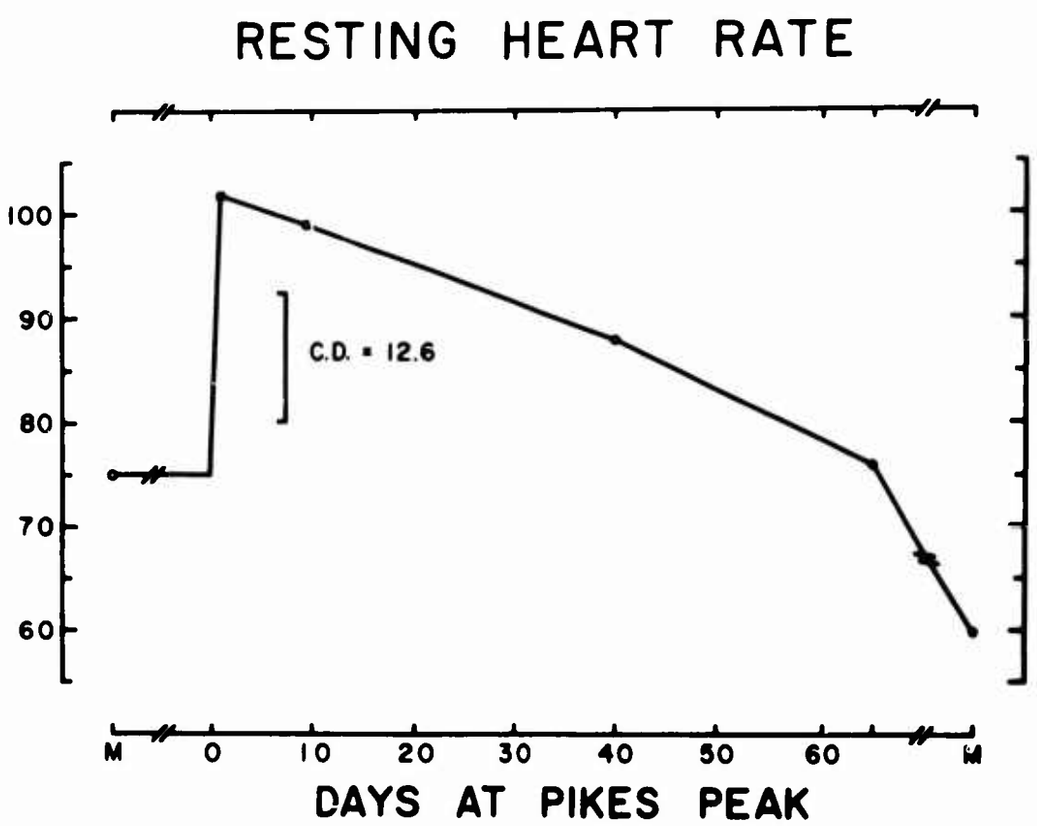


Figure 27

Effects of high altitude acclimatization on the heart rate of women.

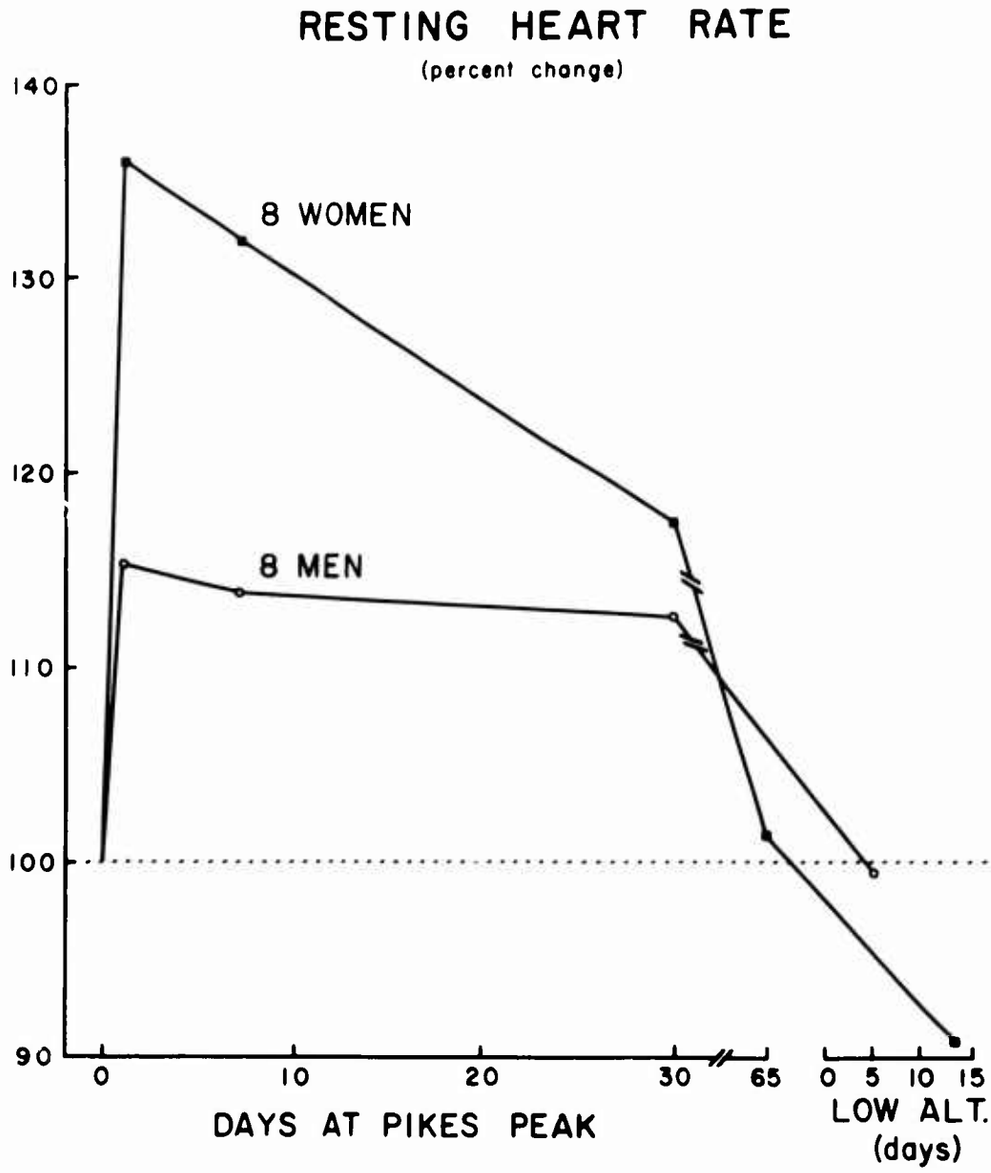


Figure 28

Comparison of the relative changes in heart rate of men and women at high altitude.

Leucocytes

Available information concerning the effects of high altitude on the levels of white blood ceels is quite conflicting. In animals a temporary leucocytosis has been reported during the early stages of hypoxic exposure (97, 98). In humans Hurtado (99.100) and Chiodi (101) observed relatively normal total leucocyte counts in Peruvian natives, but an increase in lymphocyte percentage. Cullumbine and Kottegoda (102) reported an increase in neutrophil and lymphocyte concentrations after exposure to 6,000 feet for about a week. Much earlier, Webb (see Douglas et al. [8]) in observations made on residents of Colorado Springs (6,000 feet) found the total leucocyte count to be about normal, but differential counts revealed an elevated lymphocyte level and a decreased polymorphonuclear cell level. When Webb extended these observations to members of the Douglas expedition he found exposure on Pikes Peak to be associated with a marked increase in lymphocyte percentage. Reynafarje (103) also observed relatively normal total leucocyte levels in high altitude (14,900 feet) Peruvian natives but elevated levels in newcomers. In contrast to these reports Lawrence et al. (104) in studies of Morocochan Indians and students transported to high altitude found no significant changes in either the total white cell counts or the differential counts, although there was a suggestion of a slight increase in the percentage eosinophils of natives when they were moved from Morococha. In one of the few studies of high altitude pulmonary edema Menon (105) reported on white cell counts made on 95 patients. The total count was raised in 75 of these, in one instance to 33,000. The leucocytosis was neutrophilic in all cases, the proportion of neutrophils being 72 to 87 percent. He observed no reduction in eosinophil count, and in 19 cases the marked leucocytosis was observed in the absence of a high body temperature (74 patients exhibited a low-grade fever upon admission).

Our differential white cell measurements in women do little to clarify inconclusiveness indicated in the above reports. They show (Fig. 29) only three statistically significant effects; namely, an increase in the lymphocyte percentage and a decrease in the monocyte percentage when the subjects went from Missouri to Pikes Peak, and a significant decrease in the eosinophil percentage when the subjects returned from Pikes Peak to Missouri. In the case of eosinophils and monocytes the overall picture of these alterations would not be inconsistent with a gradual seasonal, rather than altitude, effect. The lymphocytes, however, exhibited a marked increase (about 40%) between the first day and the first week of exposure, with the latter level being maintained throughout the course of the study. In this respect, at least, the altitude response of women is similar to that reported by Hurtado (99, 100), Chiodi (101), and

Webb (see ref. 8) for men living at a similar elevation. The physiological significance of this response is unknown.

Hematocrit and Hemoglobin

Observations of an increased hemopoietic activity during high altitude exposure date back to the time of Paul Bert (106) and Viault (107). Bert, who was no doubt influenced by the fact that western man rarely resided at high altitude, felt the elevated red cell levels were only achieved after residence at high altitude for several generations. Viault, however, showed the change in red cell number could occur quite rapidly. Thus, in a three-week trek through the Andes, he observed an increase from about five million to about eight million per cubic millimeter.

Since these early investigations, the relationship of high altitude exposure to hemopoietic activity has been extensively studied. These studies show the hematocrit, or hemoglobin level, of various native populations to be closely correlated with the elevation at which they reside (106). In some cases this maybe lead to exceptionally high hemoglobin values. For instance, Merino (108), Hurtado et al. (109), and more recently Reynafarje (103), observed hemoglobin levels in Morocochan Indians as high as 20.8 g per 100 ml. of blood. In the older studies of Dill, Talbot and Consolazio (110, 111) values as high as 22.9 g per 100 ml were observed in Andean miners residing at 17,500 feet. In non-residents, the hemoglobin level at high altitude, even after extended exposure, is not usually as high as that observed in the local native population. In this respect, Reynafarje observed (112) hemoglobin levels of 19.5 g per 100 ml in sea level subjects residing in Morococha for six months, while Pugh reported (13) an average hemoglobin level of 20.5 g per 100 ml in Mount Everest climbers who stayed for extended periods of time at 19,000 feet. Perhaps Paul Bert's feeling that generations of high altitude exposure are required to induce a hemopoietic response may be partially true in terms of maximum red cell levels which can be achieved. In fact, significant changes may be observed after only a few days, but as we shall see later, such early changes do not necessarily indicate a true increase in total red cells.

Increases in hematocrit and hemoglobin are usually observed shortly after the onset of altitude exposure. In fact, Gregg et al. (113) found an increase in hemoglobin and erythrocyte concentration within 30 to 60 minutes after the onset of exposure to a simulated altitude of 15,000 feet. Very probably, responses occurring this quickly are attributable to either hemoconcentration or to red cell mobilization from reservoirs such as the spleen. Such an effect was

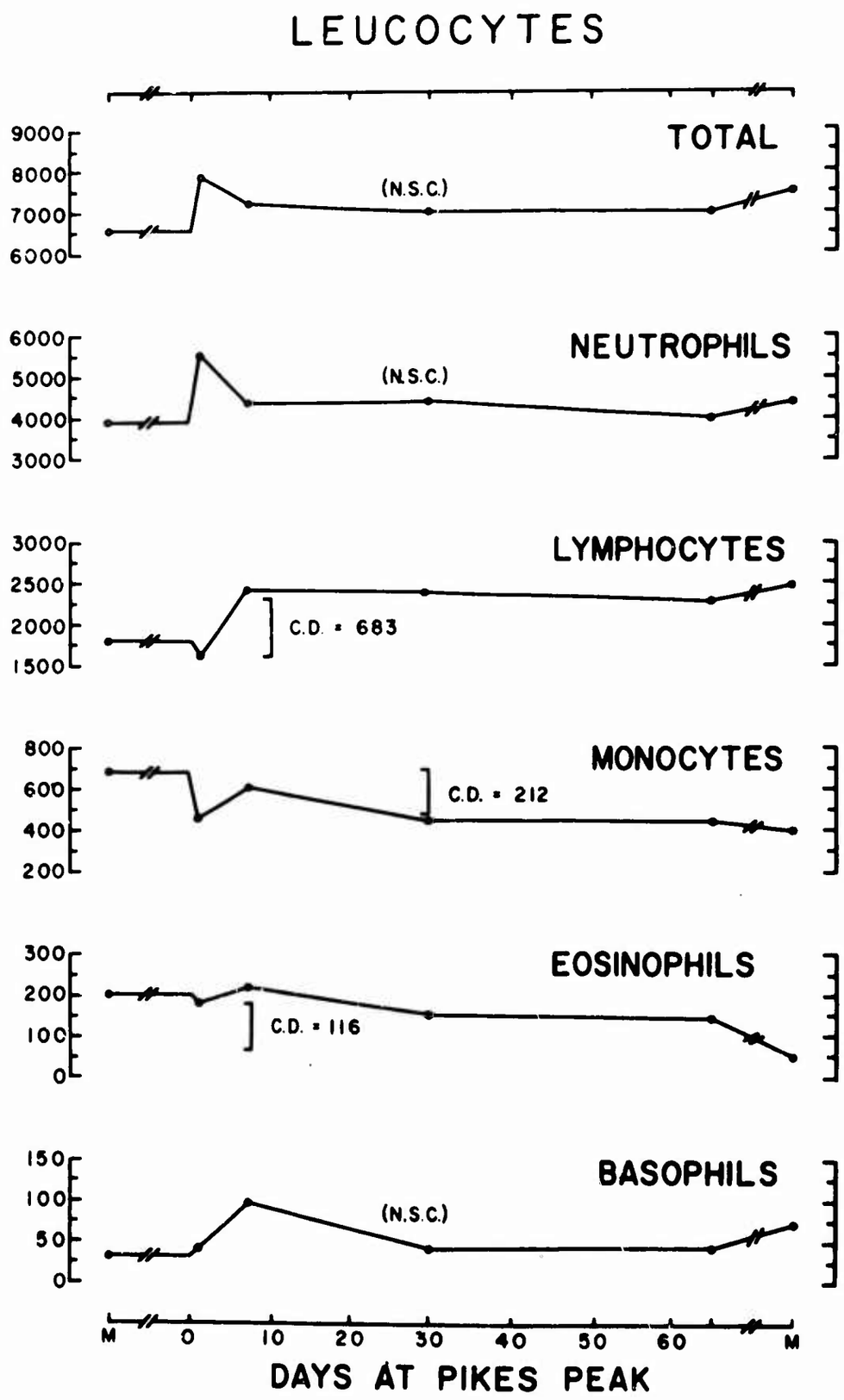


Figure 29

Alterations in the blood leucocyte count of women during high altitude exposure.

also postulated by Schneider and Havens in 1915 (114) to explain the increase in hemoglobin and red cell number which they observed during the first two or three days of exposure on Pikes Peak. Recent studies, however, have shown true changes in erythropoietic activity may occur very shortly after the onset of high altitude exposure. Thus, Reynafarje showed (103) the average red cell iron turnover rate of eight subjects increased from 0.37 to 0.54 mg/day/kg body weight within two hours after their arrival at Morococha. The highest turnover rate (0.91 mg/day/kg body weight) was observed after seven to fourteen days' exposure but eythropoietic balance was not achieved even after eight months' exposure. This increase in red cell iron turnover is associated with an increased rate of intestinal iron absorption (115, 116, 117) and requires an adequate level of iron in the diet (118).

Only limited and widely scattered data are available on the hemoglobin and hematocrit levels of women at high altitude. For the most part, such data were obtained from local residents of high altitude areas, but occasionally actual studies of the changes in females have been made. All of the available information, insofar as we can determine, are summarized in Table V.

TABLE V

Hemoglobin and Hematocrit Values of Women Residing at Various Elevations

Location	Elevation	No. Subj.	Hemoglobin	Hematocrit	Ref.
Sea Level	0	100	13.7	41.2	248
Columbia, Mo.	700 ft.	8	13.4	40.3	*
Columbia, Mo.	700 ft.	8	14.3	43.0	**
Asheville, N.C.	2,210 ft.	5	13.5	40.5	121[Δ]
Waynesville, N.C.	2,645 ft	2	13.4	40.2	121[Δ]
Highlands Camp, N.C.	3,850 ft.	7	12.7	38.1	121[Δ]
Denver, Colo.	5,280 ft.	40	14.5	43.2	249
Colorado Springs, Colo.	6,000 ft.	2	14.3	42.9	120[Δ]
Mexico City, Mexico	7,000 ft.	100	15.2	45.5	250
Ouray, Colo.	7.780 ft.	6	16.3	48.9	120[Δ]
Long Lake, Calif.	11,000 ft.	2	16.2	44.4	119
Camp Bird Mine, Colo.	11,380 ft.	2	15.6	46.8	120[Δ]
Tom Boy Mine, Colo.	11,500 ft.	3	15.6	49.8	120[Δ]
Pikes Peak, Colo.	14,110 ft.	6	14.9	44.6	*
Pikes Peak, Colo.	14,110 ft.	8	16.6	49.6	**

*Present study – no dietary iron supplementation (see text).

**Present study – dietary iron supplementation (see text).

[Δ] These hemoglobin measurements were made with a Gowers-Haldane hemoglobinometer. The original values, which are expressed as percent of the male value of 100 at sea level, were multiplied by 13.8 to obtain grams per 100 ml. Hematocrits were obtained by multiplying the hemoglobin values by 3.0.

To the values contained in this table we might add the measurements Grollman made on his wife during their stay at Pikes Peak (1). At the end of twenty days' exposure she had a hemoglobin of 136 percent, but unfortunately the author gives no sea level values nor does he indicate the actual grams of hemoglobin represented by these percentage values. It is noteworthy, however, that she acheived her maximum values between the 11th and 15th day of exposure. The data of Smith et al. (119) which is included in the above table was made after 30 days of exposure, and in one of these individuals, too, higher values were obtained during the middle portion of the sojourn than at the end. In this latter report, the hematocrit to hemoglobin ratio was rather low, i.e., 2.74, which would suggest an error in one of the measurements–probably hemoglobin. FitzGerald (120) also made some measurements on herself shortly after arrival at Pikes Peak and reported a hemoglobin value of 120 percent (about 16.5 g/100 ml). Since her value at Colorado Springs prior to departure was 105.5% (about 14.5 g/100 ml) this altitude change probably reflects hemoconcentration (see discussion below).

In our initial pilot study of six women which was conducted in the summer of 1964, we found only a small increase in hematocrit, even after 2½ months' exposure on Pikes Peak. This surprised us somewhat, particularly since all of the subjects seemed to adapt quite well to life at high altitude. In fact, one of our best adapted subjects in terms of work performance on a bicycle ergometer had an initial low altitude hematocrit of 30.5 which only increased to 36.5 over the course of the summer. The meagerness of their response suggested, however, that the level of dietary iron intake might be playing an important role in determining the magnitude of high altitude polycythemia. Consequently, in designing our subsequent study of Missouri subjects, an iron supplementation program was instituted. This consisted of one 5-grain tablet of $FeSO_4$ taken by each subject daily, commencing three months prior to high altitude exposure and continuing through their entire period of residence on Pikes Peak. Even in Missouri, this supplementation had an effect. Thus, between March and June their average hematocrit rose from 40.3 to 43.0–which would indicate they were initially in a relative iron deficiency state. Presumably, the deficiency did not exist when they were brought to Colorado. Upon exposure to Pikes Peak, they exhibited a rapid increase in hematocrit and hemoglobin which was qualitatively similar to that seen previously in male subjects (Fig. 30). Quantitatively, of course, their hematocrit response curve was lower than that seen in males since they started from a lower point. Most important, however, their erythropoietic response to high altitude was both qualitatively and quantitatively different from that seen during the preceding year with girls

receiving no iron supplementation (Fig. 31). For instance, after two and one-half months' exposure, the subjects receiving iron had a hematocrit of 49.6 while those not receiving iron had a nematocrit of 44.6. Similar suggestions of iron deficiency anemia are seen in the data (Table V) collected by FitzGerald (121) in the mountains of North Carolina. And it is of interest that Hurtado (99) found a considerable portion of Morocochan natives (14,900 feet) had normal red cell counts. He states, "A normal sea level count is not incompatible with health at high altitudes," which is similar to the conclusion we reached with respect to the anemic girl in our initial study.

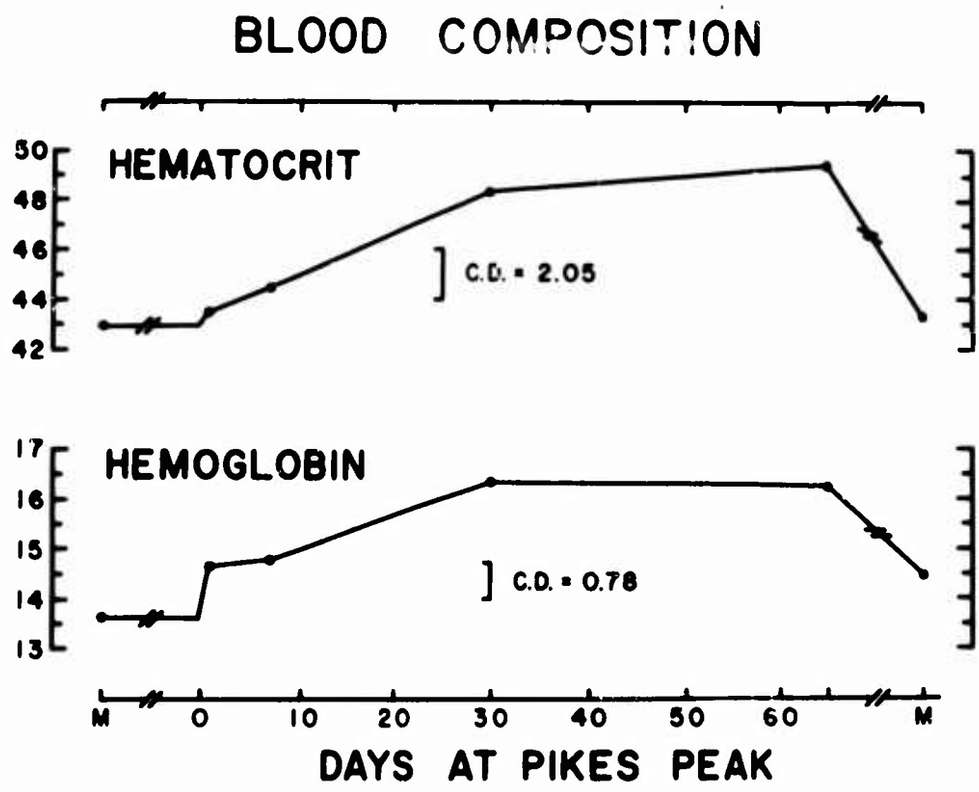


Figure 30
Hematocrit and hemoglobin (G./100 ml) changes in women as a function of high altitude exposure.

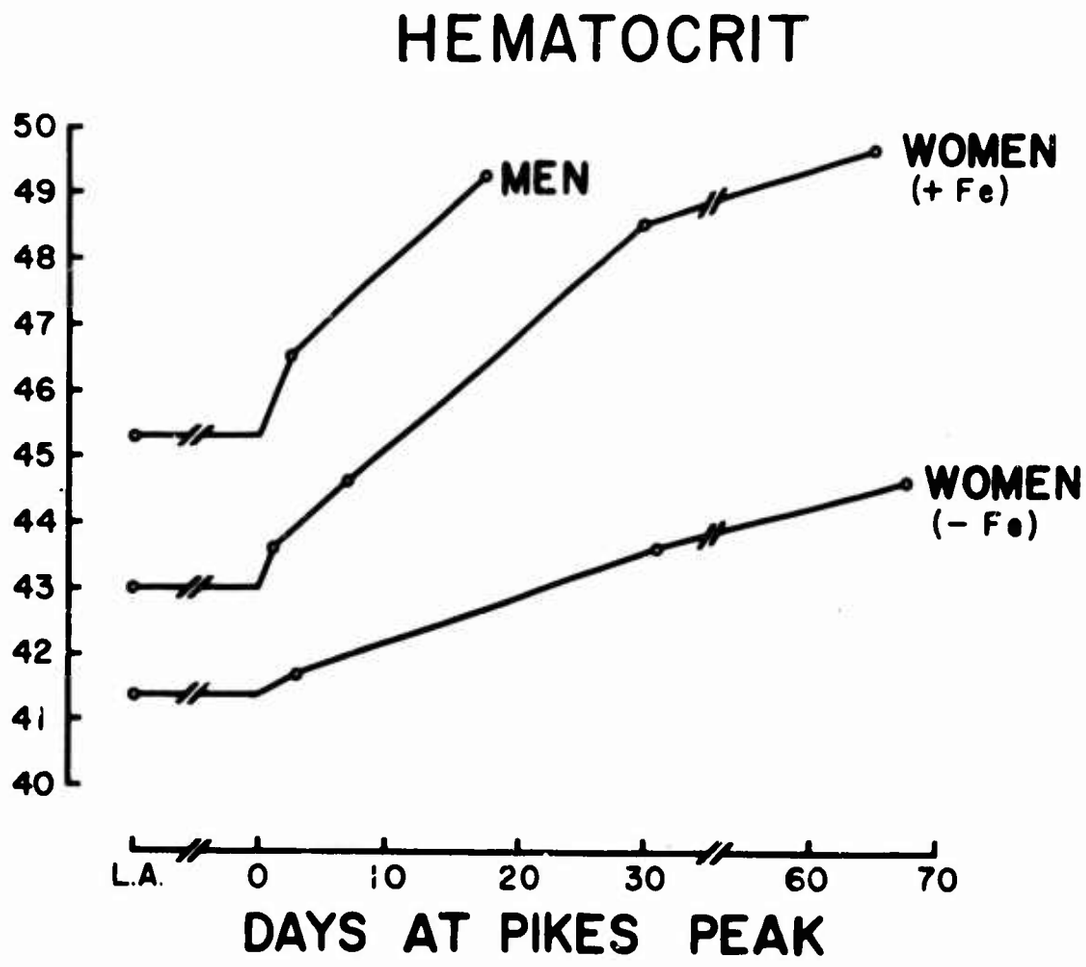


Figure 31
Comparison of the altitude-induced changes in hemoglobin of men and women at altitude. The curves in women depict the effect of dietary iron supplementation.

DR. BRAUER: Were the men on an iron supplement?

DR. HANNON: No, the men were not.

DR. BRAUER: Do you have blood volume data to go with this?

DR. HANNON: Yes, shortly.

DR. DILL: What do studies of hemoglobin in women show? Isn't that 41.3 merely the generally accepted standard?

DR. HANNON: I think so, yes. I think you're right, but this again is based on women subjects. Women in the population are not getting supplementary iron; apparently they're partially anemic all the time.

DR. DILL: How do you know the men wouldn't have gone 45 or 47?

DR. HANNON: They may have. As I say, this is put together from two different studies and we weren't even thinking about iron at the time we were doing the study of men. I think it should be done to see if it will make any difference.

DR. BUSKIRK: It has been done. I've seen at least two reports in the literature, I think, and as I recall the differences aren't very large at all.

DR. HANNON: On men subjects?

DR. BUSKIRK: Yes.

DR. DILL: Now on these women that you show here on supplementary iron, what was your initial value before they got on iron?

DR. HANNON: That was the first slide, it was 40 as an average.

DR. DILL: This group of women that you show on supplementary iron had a value of 40?

DR. HANNON: Yes.

DR. DILL: Before you gave them iron?

DR. HANNON: They were on iron, 600 milligrams per day for three months, then they went from 40 or a little over 40 to up here.

DR. DILL: Did they have any untoward effects from that amount of iron?

DR. HANNON: Apparently not. At least they didn't complain of any to us, but it has been said that young women are deficient in iron. I don't know any detailed studies of this, perhaps some of the clinical people here have more information on that than I do.

DR. DILL: What do we know about the iron content of the ordinary average mixed diet, what is the total amount of iron ordinarily—anyone know? It depends on the diet, of course. Is there any expert here who wants to venture an estimate? Is 600 milligrams likely to be two or three times as much as in the ordinary diet?

DR. HANNON: I would think so.

DR. HORVATH: What's the hemoglobin?

DR. HANNON: It follows this pattern very similarly.

DR. BUSKIRK: Seltzer at Harvard did a series of lean and obese women, and had about this same difference. It's fairly regular.

DR. HORVATH: Iron in obese women—you mean it's related to the excess fat?

DR. BUSKIRK: No, I think it's a little lower in the obese women as I recall.

DR. GROVER: We studied 200 adolescent women, and of that group only two were greatly iron deficient.

DR. DILL: Are they any better at tolerating altitude? Is there any reason for thinking that they really need that iron and that extra hemoglobin?

DR. HANNON: No, there isn't. This is the interesting thing about this, in fact in this lower group here there is one girl who came up to Pikes Peak with a hemoglobin of 9 grams percent when she got there. Her hematocrit was around 31. She tolerated altitude beautifully, didn't have any trouble at all. We did give her some iron and she made it up to a hemoglobin of 11, but she had no trouble at all tolerating the altitude. She happened to be a girl from Colorado, and the subjects from Colorado generally have very few symptoms of mountain sickness at Pikes Peak. She didn't even seem to be particularly fatigued.

DR. EVONUK: Dr. Hannon, wouldn't a more meaningful answer be given by a determination of the iron — —

DR. HANNON: Yes, it possibly would. As I say, I think we're going to have to go back and look at it again. There is certainly a difference whether we give them iron or not. We could hardly believe this data when we collected it—that we would get so poor a response, particularly after over two months at altitude, that we would have such a low increase in hematocrit.

DR. EVONUK: Your cousin, Dr. Reynafarje, worked on this on some males in Peru. Do you recall his findings with iron supplementation?

DR. REYNAFARJE: I don't know.

DR. BRAUER: as this rabbits?

DR. REYNAFARJE: No, it was on humans.

DR. HANNON: Well, this sort of thing has been seen in animals at least down in your laboratory in South America, and I think the conclusion there was that it didn't seem to improve their tolerance to altitude, particularly whether they had more iron or not, isn't that correct?

DR. BRAUER: I think that was related only as a function of the forthcoming hematopoesis, that there was an increased absorption of iron initially. Is there a sex difference in the oxygen association curve, Dr. Dill?

DR. DILL: I can't answer that. Not that I know of.

DR. CHIODI: I did some of that and I don't think there was much difference.

DR. HANNON: It's this sort of thing, I think, that stimulates interest in future problems at altitude with women.

DR. DILL: It certainly does stimulate a lot of interest in Geritol.

Blood Volume

As already indicated, high altitude exposure increases hemopoietic activity. This response, in turn, will eventually lead to an increased volume of circulating red cells and, if the plasma volume does not change, an elevated blood volume. The latter has been repeatedly observed in the natives of Morococha, Peru (14,900 feet) by Hurtado and his coworkers (49, 100) as well as others (103, 104, 108, 112, 122). Hurtado et al. (49) compared these natives to Lima residents and found total blood volumes to be 120.8 and 86.5 ml per kg, respectively. Red cell volumes were 74.1 and 38.8 ml per kg while plasma volumes were 46.1 and 47.1 ml per kg. Somewhat lower total blood volume (100 ml per kg), red cell volume (67.2 ml/kg) and plasma volumes (32.9 ml/kg) were reported for another group of Morocochan Indians by Merino (122). Elevated blood volumes have also been observed in other native populations, some of these living at considerably lower altitudes than Morococha. Proceeding to such lower altitudes, Hurtado (49) found the residents of Oroya, Peru (12,240 feet) to have an average total blood volume of 108.7 ml per kg. Lozoya Solis reported (123) an average total blood volume of 92.4 ml per kg for residents of Mexico City (7,140 feet) and Lippman (124) obtained an average value of 87.3 ml per kg for four men living in Davos at an elevation of 5,000 feet. This last value is somewhat higher than the average blood volume reported by Metz et al. (125) and Ellis (126) for natives of Johannesburg (5,740 feet) and by Huey and Holmes (127) in residents of Denver (5,280 feet). In fact, these investigators all obtained total blood volumes which were similar to those commonly seen (126) in sea level residents, i.e., 75 to 80 ml per kg. On the basis of available data, therefore, it would appear that elevated blood volumes are usually encountered in native populations when they reside above 5,000 feet.

Prolonged high altitude exposure, both actual and simulated, has been shown to cause an increase in the blood volume of some animal species. Rotta (128), for example, found alterations in dogs native to Morococha which were very similar to those observed in the native human population. Thus, in a group of nine animals, he reports a 44.5% greater packed cell volume but the same plasma volume as dogs living in Lima. A similar increase in the blood volume of

dogs was reported by Reissmann (129) who exposed his animals to a simulated altitude of 20,000 feet for a period of 10 to 12 weeks. In this instance, it was shown that the blood volume remained constant during the first two weeks of exposure, increased about 25% during the next three weeks, and remained relatively constant thereafter. As will be seen later, this pattern of change during acclimatization to altitude differs in many respects from the patterns reported for humans.

Laboratory rats have been extensively used to investigate the altitude-induced increase in hemopoietic activity and ultimate increase in blood volumes. Johnson and Feigen (130) exposed Long Evans and Slonaker Wistar rats of both sexes to an elevation of 12,470 feet for varying periods up to 260 days. They found an increase in the total blood volume of both strains, with the Slonaker Wistar female showing the greatest response. Fryers (131) measured the blood volume of rats exposed to a simulated altitude of 15,000 feet for ten days and found an increase in the total blood volume from a sea level value of 49.7 to 59.6 ml/kg. After 35 days at this elevation, followed by 13 days at 20,000 feet, a volume of 74.4 ml/kg was obtained. These values seem somewhat lower than those usually observed in rats (130). Pawel et al. (132) reported a 31% increase (estimated on the basis of hematocrit change) in the blood volume of rats exposed to 18,000 feet for one to three months. In these animals brain blood volume, estimated by measurements of capillary size and number, increased about 11.7%. The number, length and diameter of the brain capillaries were markedly increased. In fact, these authors estimated the capacity of this capillary bed was tripled. Also, Anthony and Kreider (133) exposed rats and mice to a simulated altitude of 20,000 to 22,000 feet. In the rats, using Evans Blue, they found a 40% increase in total blood volume after 50 days. Measurements of noncapillary blood volume with vinyl casts showed a 62% increase in rats after three or four weeks' exposure, while mice showed a 112% increase. In the case of rats, subtraction of the noncapillary (vinyl) volumes from the total blood volume (Evans Blue) showed that high altitude exposure caused a greater increase (about 60%) in the volume of the larger vessels (arteries, arterioles, venules and veins) than in the capillaries (about 25%). The latter, it should be noted, is not nearly as great as the above-indicated increase in brain capillary volume reported by Pawel et al. (132). Histological evidence of an increase in the number and diameter of capillaries in the brain of acclimatized rats has been presented by Mercker and Schneider (134), in the kidney by Kindred (135) and Altland and Highman (136), and in the skeletal muscles of guinea pigs by Valdivia (137). It is of interest that the pulmonary vascular bed has been implicated by Monge et al. (122) as a major depository for the added

blood volume found in Morocochan Indians. In these high altitude natives, the pulmonary circulation contained 19.4% of the total blood volume as compared to 15.2% found in residents of Lima. Even during acute hypoxia there are reports of an increase in pulmonary blood volume (138, 139, 140). However, in all of these investigations, the accuracy of the data is subject to serious question because of technical limitations in the procedures which were employed (83).

Measurements of blood volume changes during acute exposure to hypoxia or high altitude has produced many conflicting reports, particularly in humans. In our own measurements on women, utilizing the Evans Blue technique, we found (Fig. 32) the total blood volume to be reduced on the first day of exposure, decreased even further after one month and only showing a slight tendency for recovery after 2½ months on the Peak. This decrease could be attributed almost entirely to a reduction in plasma volume which became progressively more intense during the first month of exposure. The plasma volume reduction, furthermore, would appear to account for a large fraction of the increases in hematocrit and hemoglobin noted earlier (Fig. 30). In fact, when the volume of circulating red cells was calculated from the venous hematocrit and plasma volume, a slight but significant ($P \leq 0.05$) reduction was observed on the first day of exposure. Thereafter, the average values for the eight girls remained low, but not significantly so, until the last altitude measurement, whereupon normal values were again obtained. A similar reduction not only in red cell volume (Fig. 33) but also in plasma volume (Fig. 34) was observed in an earlier study of men conducted at Climax, Colorado (141).

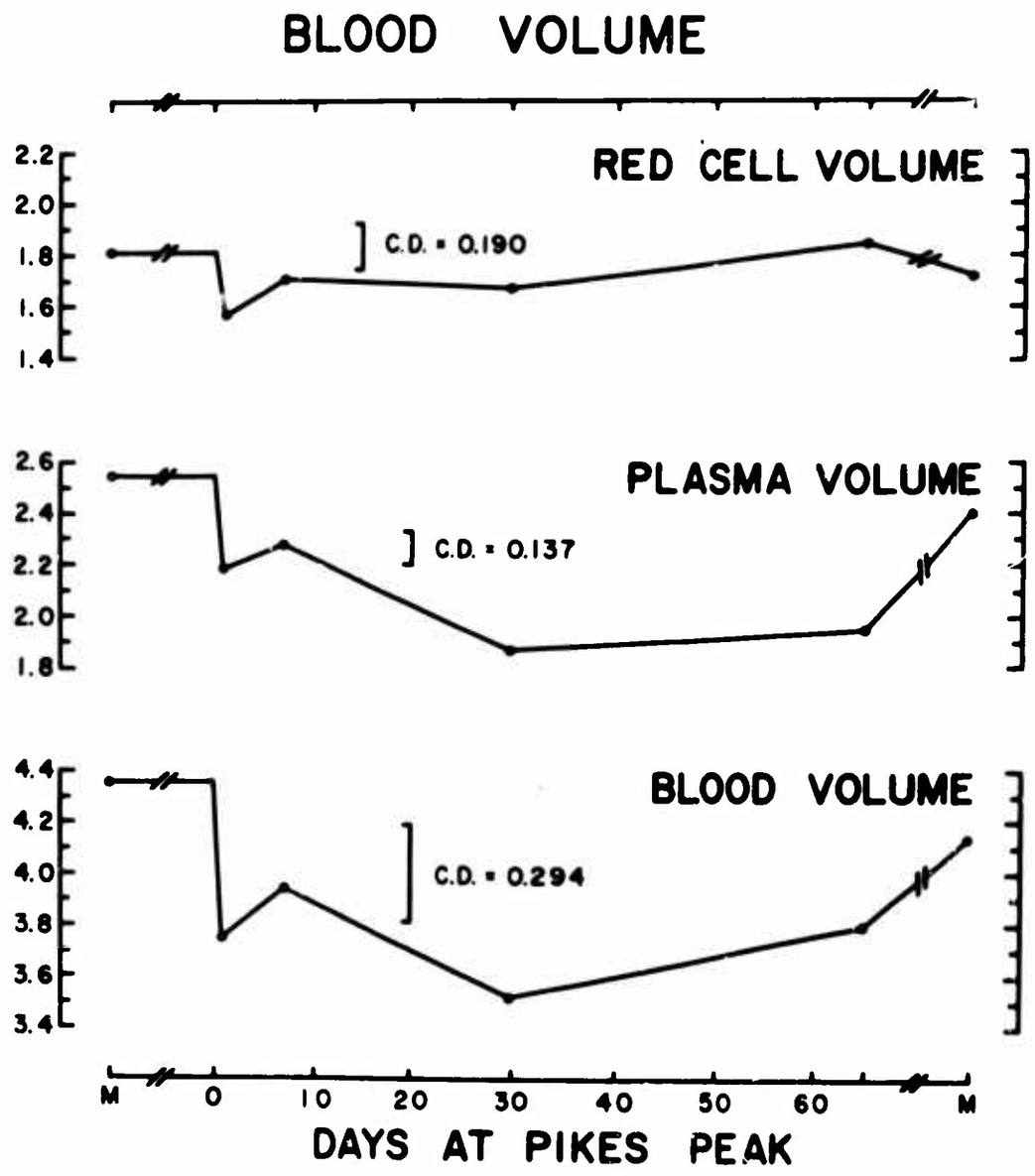


Figure 32
The effects of high altitude exposure on plasma, red cell and total blood volume of women as determined with the Evans Blue procedure.

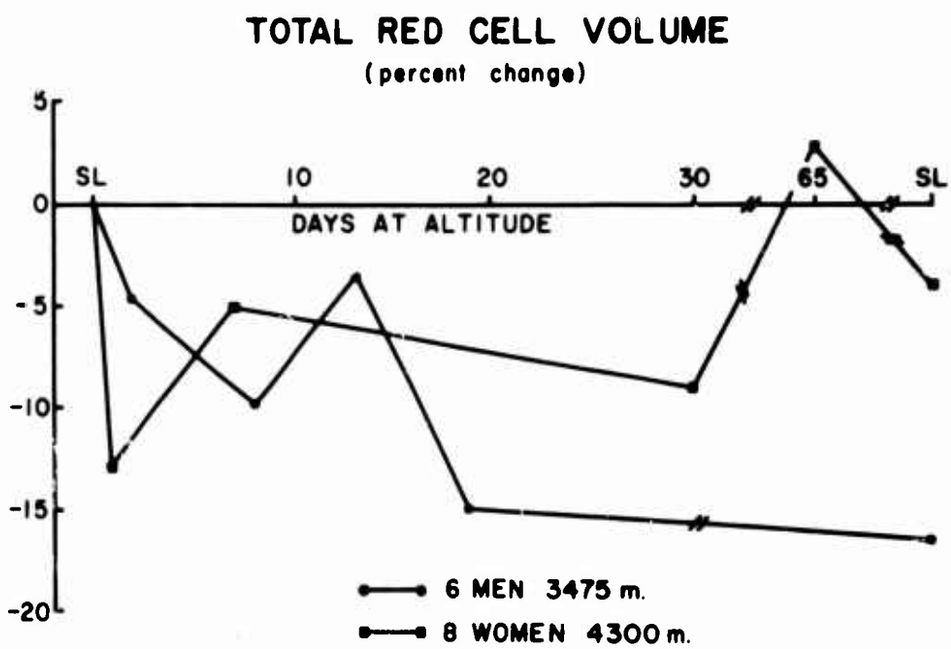


Figure 33
Comparative alterations in the total red cell volume of men and women during high altitude exposure. The individual values represent the mean percentage change from the initial low altitude value, sea level in men and Columbia, Missouri (700 ft.) in women.

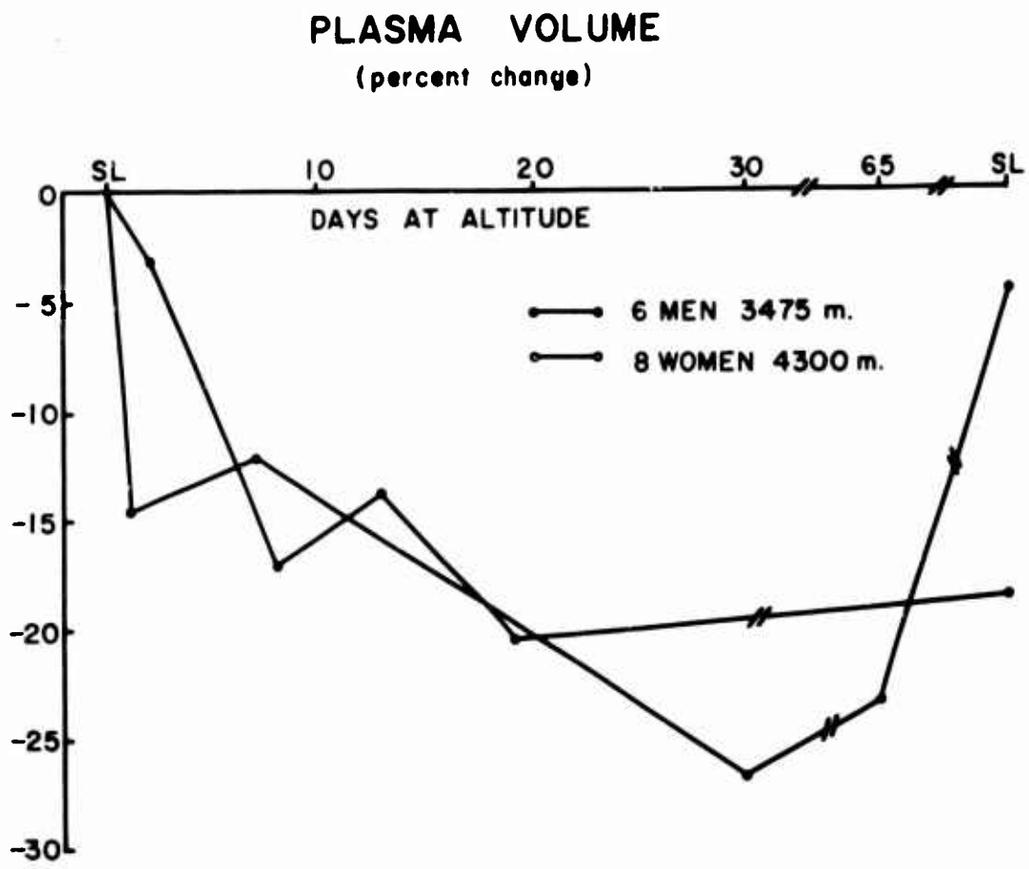


Figure 34

Comparative alterations in the total plasma volume of men and women during high altitude exposure. The individual values represent the mean percentage change from the initial low altitude value.

DR. HORVATH: Are these ten minute samples or are these – –

DR. HANNON: No, these are ten minute samples, but we did run extended samples on ourselves at the time we were doing this, because we started worrying about the method and the distribution at altitude or the dilution at altitude. We could see no particular difference in this, but again this is on men and not on women that we were doing this.

DR. DILL: Again that isn't a very big change. Did you assume that the body hematocrit is 91% of the peripheral hematocrit?

DR. HANNON: No, in this case we didn't.

DR. DILL: Well, this I think is a generally accepted figure. I think Gibson's original figure was 91% and there is a consensus that this value ranges from about 89 to 94, which could well vary from person to person, and maybe this – –

DR. HANNON: I think this could well be true. It would be much better I think to have drawn our samples from the arterial blood rather than from the venous blood.

DR. DILL: No, that doesn't make any difference, it's not that. I wouldn't be in the least disturbed by that change there.

DR. HANNON: The average reduction was on the order of 20%. I think Dr. Buskirk has similar data on men, don't you, on plasma volume?

DR. BUSKIRK: Yes, and I will present some information on Thursday. This is pretty consistent, when you look very carefully through the literature.

DR. BRAUER: What about circulating hemoglobin?

DR. HANNON: If you calculate circulating hemoglobin it tends to go down.

DR. REYNAFARJE: Blood volume shows a tendency to increase at sixty days.

DR. HANNON: It is not significant between here and here, this is the sixty days.

DR. REYNAFARJE: I mean blood volume.

DR. HANNON: Blood volume, yes, it is not significant either.

DR. REYNAFARJE: Yes, but after say three months or more we go over the basal level, because in natives the blood volume is increased but mainly the red cell volume is highly increased. Do you think that this will be – –

DR. HANNON: Yes, presumably if we stayed long enough we would see this, but apparently two and a half months was not long enough.

DR. DILL: I am surprised that your red cell volume doesn't increase more than that, because your direct result here in plasma volume shows a slight upward trend from 30 days to 60 plus days and your hematocrit increased from 43 to 49.

DR. HANNON: Right.

DR. DILL: So why doesn't your red cell volume increase more than that curve indicates? You remember your hematocrit in these women increased from 43 to 49.

DR. HORVATH: And about a 13% increase in hematocrit.

DR. DILL: And you have a slight increase in plasma volume and a rather moderate increase of 10%.

DR. HANNON: I think percentagewise – –

DR. DILL: It is not more than a 10% increase in red cell volume.

DR. HANNON: Well, these calculations are based on hematocrit.

DR. DILL: Yes, I know they are, but that is really the thing that puzzles me. Here's something else: Is your blood volume increased during that latter period?

DR. HANNON: Yes, it tends to increase.

DR. DILL: Both because of increase in red cell volume and plasma volume?

DR. HANNON: There are some changes in the blood water content.

DR. DILL: Yes, this will show.

DR. HANNON: That we will see in a little bit. The scale changes between here and here, I will go back and check that. I think it's all right, but it does look different there.

It is our feeling that such reductions in red cell volume are probably attributable to a measurement artifact. In calculating total red cell volume by the conventional Evans Blue procedure, venous hematocrit is assumed to represent total body hematocrit. That this is not a valid assumption is established by blood volume measurements where plasma and red cell volumes are independently measured. If, for example, total red cell volume is determined by the dilution of Cr^{51} labeled red cells and total plasma volume is determined by the dilution of I^{131} -labeled serum albumin then total body hematocrit would equal the sum of these volumes divided into the red cell volume times 100. This hematocrit is smaller than the usual venous hematocrit; hence, the ratio of body hematocrit to venous hematocrit at sea level has been shown to be about 0.91 (142). In some instances, investigators have calculated their high altitude red cell volumes utilizing this, or a similar, correction factor. But such corrections do not necessarily resolve the measurement error, since they are based upon the assumption that the ratio of body to venous hematocrit is unaffected by high altitude exposure. In one instance, at least, this assumption has been shown to be invalid. Metz, Levin and Hart (125) thus found that residents of Johannesburg (5,740 feet) had a higher ratio (0.962) than nearby sea level residents (0.902). This potential source of error would also apply to most other high altitude blood volume measurements where plasma volume indicators and venous hematocrits used to compute red cell and total blood volume would lead to an underestimation of the red cell volume. It is of interest that a five to ten percent increase in this ratio would account for most of the early reduction in red cell mass observed in women (Fig. 33).

Insofar as we can determine, double indicators were employed in only one other study of blood volume at high altitude. This was conducted by Lawrence and his coworkers (104) in Lima and Morococha, Peru, where P^{32}-tagged red cells were used to estimate red cell volume and Fe^{59} was used to estimate plasma volume. These investigators reported a decrease in plasma volume and blood volume in a group of 14 students who were taken to altitude for periods ranging from 12 hours to 10 days. By the P^{32} technique, blood volume decreased from 4.2 to 3.7 liters and by the Fe^{59} technique from 4.2 to 3.8 liters. An average, but not statistically significant, reduction in red cell volume (i.e., 1.9 to 1.8 liters with P^{32} and 2.1 to 1.9 liters with Fe^{59}) was also reported. These investigators did not calculate the body to venous hematocrit ratio in their subjects, but when this is done, we find an increase from 1.055 to 1.070

between Lima and Morococha. Since the Lima value, 1.055, is considerably above the usual value for sea level residents, 0.90 – 0.91, it would appear that their measurements of either red cell volume or plasma volume were in error. Of the two, the estimation of plasma volume with Fe^{59} appears to give low values. When expressed on a body weight basis, these investigators obtained a plasma volume of 35.3 ml per kg for Lima residents. In contrast, Metz et al. (125) report a plasma volume of 43.96 ml per kg in their sea level residents, which is typical of the values found by other workers. Both groups, one using Cr^{51} and the other P^{32}, reported similar red cell volumes, i.e., 30.53 and 31.95 respectively.

There appears to be only one other instance where blood volume responses to high altitude were investigated in women. This is contained in the report of Smith et al. (119) describing the hematological changes they observed in a group of four men and two women during a sojourn at Long Lake (11,000 feet) in the Sierra Nevada mountains of California. Utilizing carbon monoxide, Brilliant Vital Red and hematocrits to estimate the various volume components, they reported no change in either plasma or red cell volume during the first few days of exposure in the group as a whole. Thereafter, the hematocrit, hemoglobin, red cell volume and blood volume all showed a progressive increase with maximum levels being reached after three weeks of exposure. For a number of reasons, the data contained in this report are difficult to interpret, especially those concerned with the responses of women. Thus, there were only two women and both were sick, not with mountain sickness but with apparent respiratory infections, during much of the sojourn. In one, no high altitude measurements were made with the dye procedure and in this instance red cell volume, plasma volume and total blood volume all increased when estimated on the basis of CO dilution and hematocrit. In the other woman, the CO procedure usually gave similar high altitude increases while the dye procedure gave slight decreases in all the volume components. That plasma indicators and venous hematocrits can produce erroneous values at high altitude has already been mentioned. Brilliant Vital Red dye, in addition, would seem to produce plasma volume values which are far greater than those observed with Evans Blue or I^{131}-tagged serum albumin. Hurtado et al. (100), for example, found no change in high altitude plasma volume when the measurements were made with Brilliant Vital Red but a 23.1% decrease when the measurements were made with Evans Blue. A more serious measurement error occurs when the carbon monoxide procedure is used to assess red cell and total blood volume since this gas reacts with both hemoglobin and myoglobin. The inherent overestimation of red cell volume by this procedure, even at sea level, is compounded at high altitude by an increase in body

myoglobin content (25, 118, 143-8).

Many of the early workers employed carbon monoxide to investigate the changes in blood volume at high altitude. Very probably this procedure more than any other factor is responsible for the apparent conflicts we see when the data obtained in these older studies are compared with those obtained more recently. In the older literature we find general agreement among investigators that increases in red cell and sometimes blood volume are observed shortly after arrival at high altitude. Douglas, Haldane, Henderson, and Schneider (8), for example, found a large increase in total red cell volume after the first few days at Pikes Peak, but interestingly, three of their four subjects exhibited slightly reduced plasma volumes during the early stages of high altitude exposure. Similar data have been reported by Smith et al. (119), Asmussen and Consolazio (149), Laquer (150), Burker et al. (151) and more recently by Lahiri (152) and Pugh (42). It should be noted, however, that Douglas et al. (8) and Burker et al. (151) were concerned about the techniques of measurement, especially the carbon monoxide procedure. Douglas et al. state: "Because we have not taken into account in this connection a possible increase in the amount of hemoglobin in the muscles; if there had been such an increase, the real volume of blood would have been less than the apparent, and might, in fact, had the increase in muscle hemoglobin been very great, have been the same as under normal circumstances at sea level."

In the more recent literature, where superior techniques were used, we find that the increase in red cell volume in humans takes longer to become apparent than was previously supposed. As already indicated, Lawrence et al. (104) reported no change or perhaps a slight decrease in exposures lasting up to ten days. Merino (108) reported a definite increase (7% to 49%) in six sea level subjects after 18 to 21 days' exposure at Morococha; however, he may have overestimated red cell volume because of the aforementioned difficulties with the Brilliant Vital Red procedure. Perhaps the best data on the relationships between blood volume and duration of exposure has been provided by Reynafarje (103, 112) who studied ten sea level subjects taken from Lima to Morococha for a period of one year. He found an increase in total red cell mass after the first month of exposure; this increase progressed until the eighth month of exposure, after which it remained relatively constant. Initially, he found a decrease in plasma volume, but by the end of the second month at altitude this decrease was offset by the increase in red cell mass such that normal total blood volumes were again achieved. Thereafter, blood volume increased progressively until the end of the study. During latter stages of the investigation (i.e., between 8 and 12 months) increases in plasma blood volume increased. One of

Reynafarje's most important observations was that red cell volume, plasma volume and total blood volume do not achieve the levels seen in Morocochan Indians, even after exposure for one year.

When his data are compared to those presented here for women, we find a distinct difference between men and women in this area. Thus, although both sexes exhibit an initial decrease in plasma volume, men seem to recover from this more rapidly than women. The increase in red cell mass progresses more rapidly in men than in women. Our data on red cell volume indicated only a tendency for an increase after two and one-half months' exposure, whereas Reynafarje's subjects exhibited a very pronounced increase at this period of exposure.

Women appear to revert to normal hemoglobin and hematocrit levels much more rapidly following altitude exposure than men. In this experiment presented here, normal values were achieved within two weeks after the girls returned to Missouri (Fig. 30). Merino (108) studied a group of four male subjects who had been acclimatized to Morococha for 18 to 21 days and then returned to Lima and found four or five weeks were required to achieve sea level values again. Even longer periods are required when Morocochan natives are brought to sea level (103, 108). Finally, we found reduced total blood volumes even at the end of our study, whereas male subjects exhibited normal or elevated blood volumes at a comparable time. It is not felt that the altitude difference in the two studies (14,100 feet versus 14,900 feet) would exert a major influence on these sex differences.

DR. CHIODI: In that case, the difference in altitude I think is too much to compare because I found out that 4,000 meters would be the critical point where they would start to show greater increase, the man at 3,400 instead of the women at 4,300.

DR. HANNON: This is the only data we had to do this calculation.

DR. CHIODI: That is just my objection to comparing that, because it is just in the critical point where the changes could be so different in one and the other due only to the difference in altitude.

DR. DILL: Pugh has values on red cell volumes at altitude.

DR. HANNON: Yes.

DR. DILL: High altitudes, but several altitudes.

DR. HANNON: Well, I think Dr. Buskirk has data that is very comparable to the other data and is at 13-what, Bus?

DR. BUSKIRK: 13.1

DR. DILL: There are two sets of pertinent data from Peru, one was Reynafarje's, if I am not mistaken; he measured the red cell volume again directly with the dye method on plasma in five medical students who went from Lima to Morococha and one or another of them was examined during the first ten days. He found increases in red cell volume in every man, and the range I think was 14 to 22 percent. On the other hand Evans was down a few years later, and Balthazar can correct me on this. His subjects were all examined once during the first ten days. He didn't publish individual values but he stated on the average that there was no change in red cell volume during the first ten days. Are you familiar with this?

DR. REYNAFARJE: Are you talking about the work of my cousin?

DR. DILL: Yes.

DR. REYNAFARJE: He used radioactive ion absorption, and he found it to be very early, at two days, 48 hours, highly increased iron and at eight days it was higher, above the normal.

DR. HANNON: I might point out that this data here on women is not statistically significant, it's not significantly different from what it was at sea level. The only point was this first day here. The rest of it was within the normal range of statistical data.

DR. HORVATH: You must have tremendous variation in the samples – –

DR. HANNON: There is a variation.

DR. HORVATH: – – to get ten percent, doesn't it . . . have you analyzed this on the basis of individuals? Have you compared data?

DR. HANNON: The only place it was significant in the women was at this point right here. The rest of it was not.

DR. DILL: Well, let me ask you if those changes in hematocrit – that smooth curve that went from 43 to 49 – were those significant differences?

DR. HANNON: Oh, yes.

DR. DILL: Well, then how can you help have significant difference in hemoglobin, total hemoglobin?

DR. HANNON: Well, because of the variations in the blood volume.

DR. DILL: In blood volume?

DR. HANNON: Yes, there tends to be much more variance in blood volume than in hematocrit measurements.

The reduction in plasma volume during acute exposure to simulated or actual high altitude was perhaps first recognized in 1895 by Grawitz (153, 154) who observed a hemoconcentration at high altitude and attributed this to dehydration. It was not until the report of Dreyer and Walker in 1920 (155), however, that this effect of hypoxia became generally accepted. Interestingly,

these latter authors presented no data of their own; in fact, they conducted no experiments at all. Rather, they recalculated Abderhalden's data (156, 157) on rats and rabbits exposed to high altitude at St. Moritz (6,000 feet). Abderhalden, who also studied the altitude responses of swine and oxen, showed the total amount of hemoglobin per animal was not appreciably altered at high altitude, although the amount of hemoglobin per kg body weight, as well as the percentage value of hemoglobin and red cells, increased (158). Since his altitude animals weighed less he concluded the blood was concentrated but red cell production was not increased. Dreyer and Walker showed these changes observed by Abderhalden were probably attributable to a reduced plasma and blood volume, particularly during the early stages of exposure. During longer exposure they showed that about half the increase in hemoglobin percentage could be attributed to hemoconcentration and the other half to new red cell formation.

Besides Abderhalden, a number of other early investigators obtained evidence of a reduced plasma volume at high altitude although usually they did not recognize it as such. Weiss (159), for example, was unable to detect any alteration in the amount of hemoglobin per kg in animals exposed to 4,000 feet even though the number of erythrocytes per ml of blood was increased. Somewhat similarly, Jaquet (160) found no change in the blood volume of animals kept at 5,000 feet even though the hemoglobin percentage and total body hemoglobin content was elevated. Other data showing hemoconcentration and a probable reduction in plasma volume are found in the reports of Douglas et al. (8), Schneider and Havens (114), Gregg et al. (113), Sundstroem and Michaels (161), Verzar (140), Dallwig et al. (162), Bunge (163), Ehrlich and Lazarus (164), Margaria and Sepegno et al. (165), Corbett and Bazett (166), Campbell and Hoagland (167), Gaule (168), Gemelli (169), Culpepper (170), Bürker (151), Richards (171), Houston and Riley (48), Hurtado (99) and Birley (172).

With the advent of procedures to measure plasma volume directly, or indirectly, loss of plasma from the circulation during acute hypoxia and high altitude exposure has been observed repeatedly. In humans, such losses have been reported by Pugh (13, 42), Lahiri (152), Lawrence et al. (104), Asmussen and Consolazio (149), Merino (108), Reynafarje (103, 112), Asmussen and Nielsen (173), and Consolazio et al. (141). It is this plasma volume reduction which accounts for most, if not all, of the hemoconcentration and blood volume reduction observed during acute altitude exposure.

Abderhalden (174) was perhaps the first investigator to interpret this hemoconcentration as a compensatory response for increasing the oxygen carrying capacity of the blood. Similar interpretations are found in the reports

of Douglas et al. (8), Gregg et al. (175), Schneider (89) and Asmussen and Consolazio (149), and Houston and Riley (48). Such a compensatory mechanism, coupled with an elevated cardiac output (80) would assure adequate tissue oxygenation during the early stages of exposure. Eventually, however, both of these early responses disappear to be replaced by an increase in total red cell volume, in men and most animals at least, and an improved capacity of the tissues to extract oxygen from the blood. In women, the duration of hemoconcentration appears to be much longer than in men.

At one time several investigators, including Schneider and Havens (114), thought that the hemoconcentration was attributable to red cell mobilization from body stores. Scott (176) and Lamson (177), however, could find no stores of sufficient magnitude to account for the observed changes in hematocrit.

The mechanisms responsible for the reduction in plasma volume are far from clear. That it is not due to a simple dehydration of the blood is shown in Figure 34 where maximum whole blood water loss is observed to be less than three percent. Or, if we consider an increase in total plasma protein concentration as indicative of dehydration, we see a rise from 7.3 to 8.0 grams per 100 ml, or about 10%. By contrast, a 20% reduction in blood volume was observed (Fig. 32), which was seven or eight times greater than the measured water loss. Similar comparison will account for less than half of the observed decrease in plasma volume. Interestingly, the increase in plasma protein concentration seems to be about equally distributed among the various serum protein components (Figs. 35 & 36).

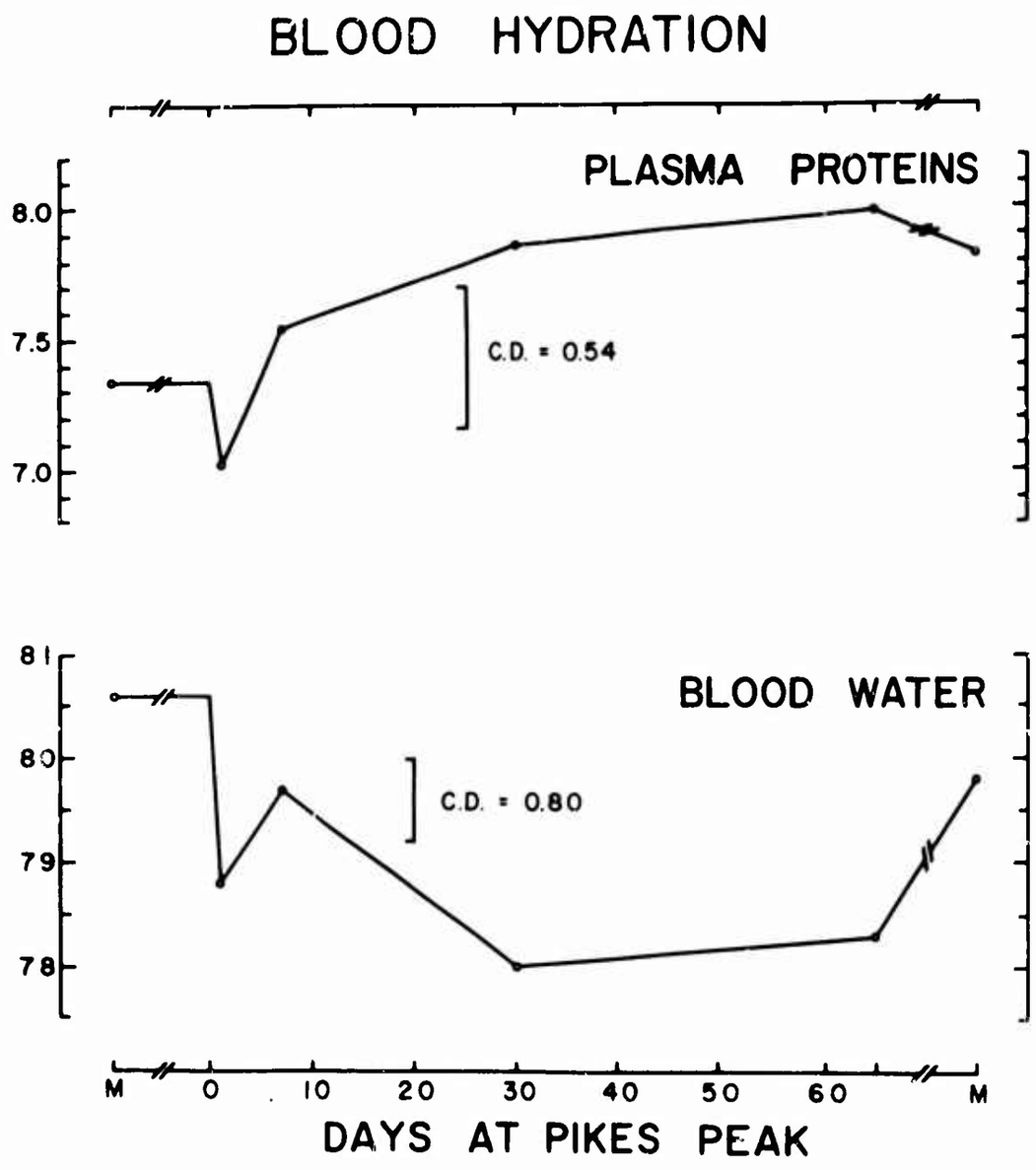


Figure 35
Effects of high altitudes on the plasma protein concentration (G./100 ml) and blood water content (ml/100) of women.

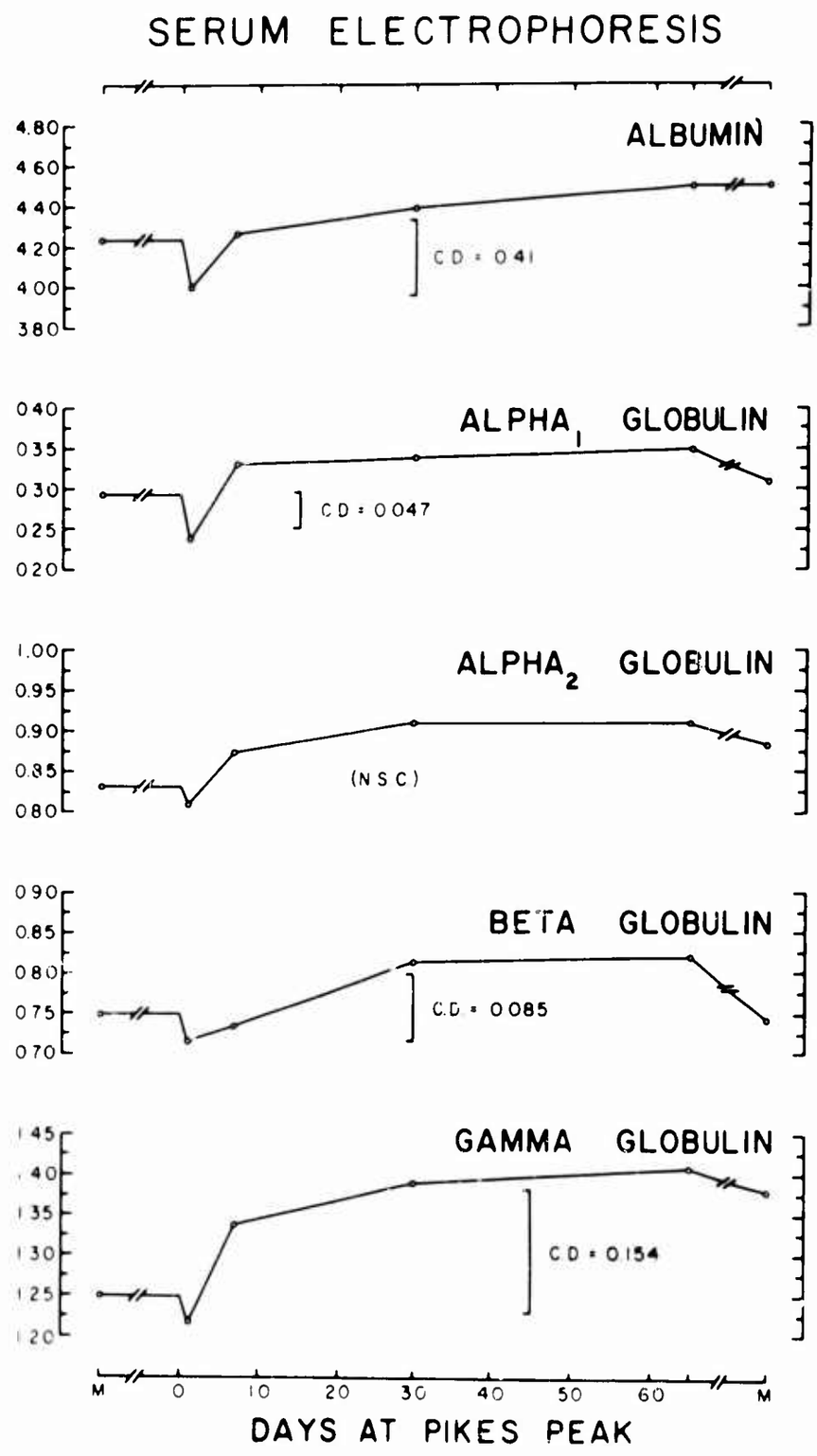


Figure 36

Alterations in the individual serum proteins of women during high altitude acclimatization. The values obtained, through integration of the areas under electrophoretic-densitometer curves, are expressed in G/100 ml of serum.

DR. DILL: I might remark here, again making the same statement that I made this morning, that this is what we found roughly in young men, but in myself – instead of coming down like that I went up about 15% at the end of seven days in plasma volume. My curve went right up roughly in the opposite direction.

DR. HANNON: After seven days?

DR. DILL: Seven days. The only single determination of seven days I was up was about half a liter, which would be about 15% I believe.

DR. HANNON: We figured we would be back to control levels at about two and a half months, but they weren't; as I say we didn't expect this either.

DR. CHIODI: They also measured plasma proteins in those students Dr. Reynafarje took up, and I think there was some increase in the natives and long-time residents. He found, and I also found, the same – that there is not much increase in protein, the protein would be around 7.2, 7.3, and I never saw a figure so high.

DR. HANNON: Yes, in our studies of men, we have done I think three or four studies where plasma proteins have been measured and they always go up in men in every study we had, and as I say, these are separate studies.

DR. DILL: What about the total amount of plasma protein? If you multiply that 8 percent by your decreased plasma volume you might even have less total plasma protein.

DR. HANNON: That is correct, it does go down and this makes you wonder where it went. In our laboratory we have done some work in relation to thyroid function at altitude, but part of the study was concerned with plasma protein synthesis and degradation. An increased rate of plasma protein

degradation was found, and there was indirect evidence of a reduced synthesis of plasma protein. Now this gets a little bit into the realm of nutrition. Dr. George Kline, who used to be here, has done some studies of rats where he has measured the incorporation of labeled amino acids into tissue proteins in the rat. He didn't look at blood in this particular case, but he did look at a number of different organs and he found that in the liver at least, and one other organ, I believe it was the spleen, the conversion or incorporation of labeled amino acids in the proteins is markedly reduced during the early stages of altitude exposure, one or two days. Other tissues such as the muscle were not particularly affected. The labeled amino acid that is not incorporated is oxidized so it turns up as CO_2 in these animal studies. There are suggestions then that there are marked effects of altitude on protein metabolism, particularly at one or two days of exposure.

DR. HORVATH: Your critical difference – would suggest that you had absolutely no change in plasma proteins from the very first day.

DR. HANNON: Yes, just from this point there were none, true.

Other evidence which would rule out major blood dehydration during altitude exposure is found in Figure 37, where changes in serum and urine osmolarity are summarized. Instead of an increase as would be expected if the serum were dehydrated, we found a significant decrease during the early stages of altitude exposure. The cause of this decrease will become apparent later when the effects of altitude on serum electrolytes are considered. Finally, there is considerable evidence in the literature showing dehydration to be of minor importance, at least insofar as the early stages of hemoconcentration in humans are concerned. Grawitz (153, 154) suggested the elevated ventilation associated with hypoxia may lead to excessive water loss and this, in turn, causes hemoconcentration. An increased rate of water loss from the skin was reported by Galectti and Signorelli (178). Yet, Gregg et al. (175) and Dallwig et al. (179) observed hemoconcentration in humans and animals subjected to experimental conditions where perspiration and evaporation were normal or subnormal. Furthermore, Gregg et al. (175) obtained hemoconcentration within 15 to 20 minutes without any noticeable increase in sweat gland activity. Against the theory that it is due to an increased activity of the kidneys as originally suggested by Birley (172) from his observations on aviators, Gregg et al. (175)

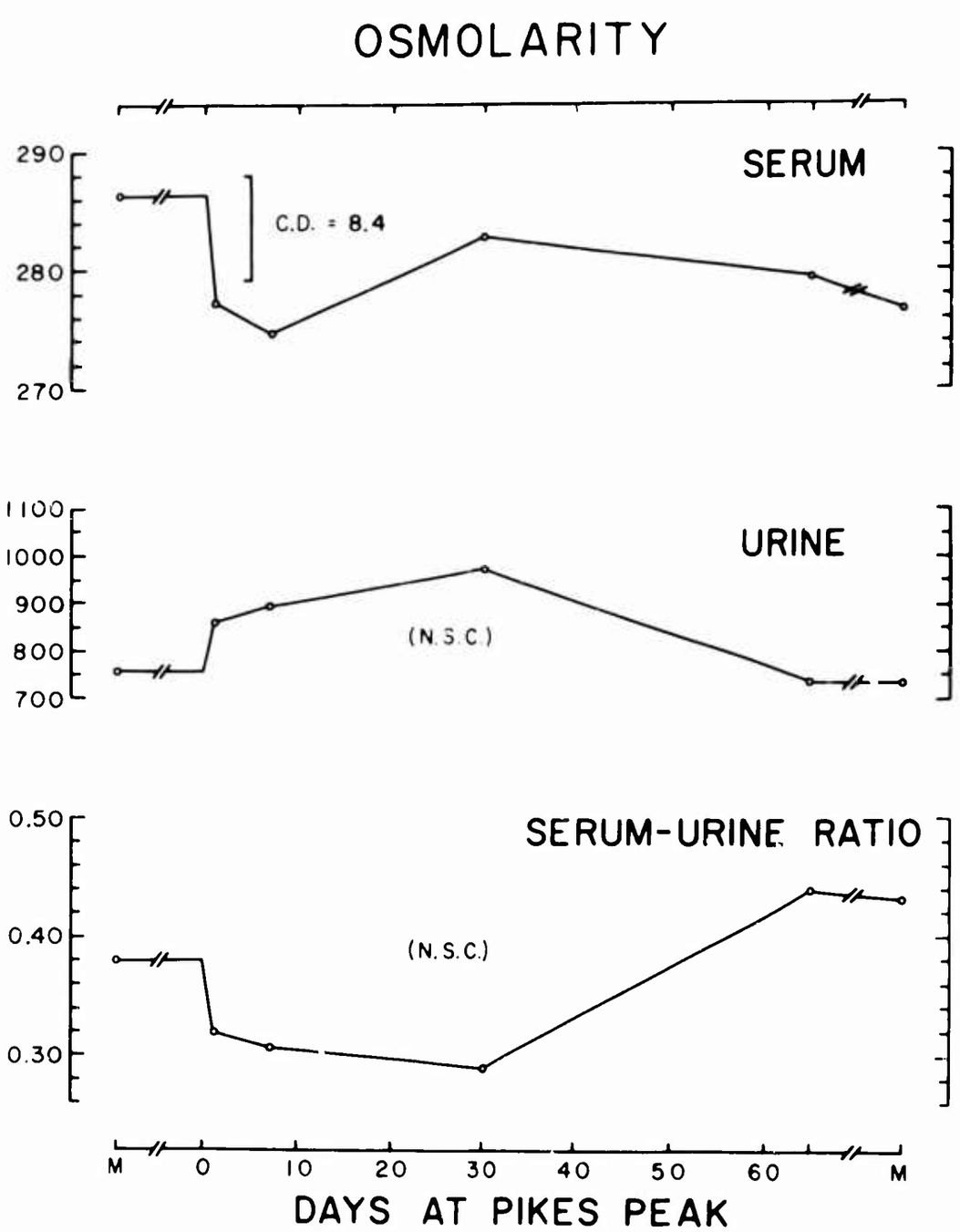


Figure 37
Effects of high altitude on the osmolarity of serum and overnight urine of women. Values are expressed as m osm/l.

showed that the time in which concentration occurs (within 15 minutes in some aviators) is too short and the volume of urine eliminated is too small. Also, in their measurements of body weight before and after hypoxia exposure, these latter investigators could find no evidence whatsoever of an elevated water loss. Many workers, nevertheless, feel water loss may contribute to the plasma volume reduction observed in longer exposures in male subjects or in laboratory animals. This was the conclusion of Asmussen and Nielson (173) who calculated on the basis of indirect measurements that about one-half of the plasma volume reduction in men can be attributed to extracellular water loss. In two of three fasting subjects, they found a greater 24-hour weight loss and urine formation at an ambient pressure of 450 mm Hg than at 760 mm Hg. Pugh (13) also attributed much of the plasma volume reduction observed during the recent Mount Everest expeditions to hyperventilation and a concomitant excessive evaporation. In laboratory rats, Johnson and Feigen (130) observed an increased concentration of plasma protein and electrolytes during acute exposure and attributed these changes to dehydration of undetermined cause. It is also noteworthy that many investigators have reported an increase in the urine flow of unanesthetized mammals and humans (35, 36, 180-186). Unfortunately, there is a paucity of direct information on water balance or body water content during acute or chronic high altitude exposure.

The foregoing leads us to the rather obvious conclusion that plasma solids including protein are lost from the circulation during acute altitude exposure. The cause of this loss has been a subject of considerable speculation, but little definite data. Bunge (163), for example, thought it was due to vasoconstriction and a consequent increase in plasma leakage into the tissues since he observed hemoconcentration without an increase in plasma solids. There is general agreement, however, that arterial pressure remains at or near sea level values during high altitude exposure (83, 89). Oliver reported (187), without substantiating data, an increase in the venous pressure of two subjects exposed to 5,800 feet on Arosa. A similar, unsubstantiated report was made by Sewall (188) for newly-arrived Denver residents. Such an increase in venous pressure could lead to an augmented rate of plasma loss, but, unfortunately, there is very little supporting evidence. In fact, Schneider and Sisco (189) found a long-term resident of Pikes Peak to have a lower, rather than higher, venous pressure at high altitude. In addition, they found a fall in venous pressure in four out of five of their own party sojourning on Pikes Peak for five or six days. Antecubital venous pressures measured during acute hypoxia induced by the rebreathing procedure seem to vary according to the degree of hypoxia; the pressure falls slightly with a moderate reduction in oxygen partial pressure and rises when

severe hypoxia is imposed (90). Nahas et al. (190), in extensive studies on dogs, found no change in the pressure of the superior and inferior vena cava or in the atrium when the animals breathed 8% oxygen mixtures. These last investigators did, however, observe a small (2 to 3 mm) increase in the small veins of the forepaw during hypoxia. Such a venous pressure increase, by influencing capillary pressure, could cause a movement of fluid from the vascular to the extravascular space. Insofar as we can determine, only Schneider and Sisco (189) attempted measurements of capillary pressure at high altitude. Aside from the obvious technical limitations of the procedure used (191), their results were of uncertain value since the high altitude measurements were made at a lower environmental temperature than the low altitude measurements. These authors believed, nevertheless, that the true capillary pressure, in contract to the elevated pressure they actually measured, was reduced by high altitude exposure.

Ellis believes (126) the decrease in plasma volume at high altitude is attributable to the lower barometric pressure. That is, low barometric pressure could cause a lowering of tissue distensibility (mechanical pressure required to distend tissues) and thereby facilitate an increased transudation of fluid from capillaries to interstitial spaces. He cites the occurrence of edema of the skin and lungs on rising to high altitude as evidence supporting this theory. Gray et al. (192) found such skin edema, while Fulton (193) and Armstrong (180) found lung edema in subjects exposed to simulated altitudes of about 30,000 feet. The latter two investigations reported tenseness, itching and pain, with urticaria, hyperemia and ecchymosis of the skin during decompression sickness. Such symptoms would suggest an increased flow of blood and lymph into the skin and subcutaneous tissues. In women, at least, this theory of plasma volume loss seems highly unlikely. Thus, we observed none of the foregoing symptoms and found no evidence of pulmonary edema. Furthermore, actual measurements show (Fig. 14) a high altitude decrease rather than an increase of skin thickness. Perhaps the most convincing argument against this theory is found in the work of Gregg, Lutz and Schneider (194) who observed similar degrees of hemoconcentration, presumably due to plasma loss, when subjects were exposed to an ambient pressure of 380 mm Hg or to a gas mixture containing 10% oxygen at sea level pressure.

A more likely hypothesis is that hypoxia causes a transfer of fluid, i.e., lymph flow and volume could readily lead to the changes in plasma volume observed at high altitude. Thus, Crandall et al. (195) and Landis and Pappenheimer (196) have estimated the daily lymph flow in the normal individual to be two to four liters. This is equal to, or greater than, the plasma volume. Furthermore, on the basis of intravenously injected albumin and

globulin, Wasserman and Mayerson (197, 198, 199) have estimated the total 24-hour flow of protein through the capillary walls approximates that contained in the plasma.

To the best of our knowledge, no direct measurement of extra-vascular space has been made at high altitude. A considerable body of indirect evidence, however, would support the foregoing hypothesis. Asmussen and Nielsen (173), for example, estimated on the basis of plasma volume, sodium, potassium and serum protein measurements, that one-half of the plasma volume reduction they observed in two hypoxic subjects could be attributed to fluid leakage from the capillaries to the extravascular space. In a third subject, the entire plasma volume reduction could be ascribed to such a transfer. Measurements of lymph flow during hypoxia give further support to this hypothesis. Maurer (200, 201), Warren and Drinker (202), and Warren, Peterson and Drinker (203) accordingly observed increases in flow from the neck, heart and left thoracic duct during moderate and severe anoxia. Gesell also reported (204) an increase in thoracic duct flow during anoxia and showed further that flow diminished during recovery from the anoxic episode. In a more systematic study, Beznak and Liljestrand (205) demonstrated an inverse relationship between respired oxygen tension and lymph flow from the right and left thoracic ducts of cats and dogs. Thus, in the right thoracic duct, a flow reduction of about 30% was observed in breathing oxygen while flow increases ranging from 11 to 95% were observed when the animals breathed 10% O_2 in N_2. Measurements in the left thoracic duct, which mainly drains the abdominal viscera and has a much greater flow rate than the right duct, yielded similar results during oxygen breathing, i.e., a reduction in flow. Unfortunately, Beznak and Liljestrand did not investigate the effects of hypoxia on left duct flow. Many years ago, Lamson (177) reported that lymph formation in the viscera, particularly in the liver, may play an important role in regulating plasma volume. And more recently, a major portion of thoracic duct flow has been shown to originate in the liver (206), probably because of the large capillary pores found in this organ (207). Interestingly, lymph flow from the limbs is much more resistant to hypoxic change than flow via the thoracic duct (208-212). McMichael and Morris (211), for example, found no change in lymph formation in the arm when subjects were breathing 9.5% oxygen, while Warren, Peterson and Drinker (203) observed a doubling of lymph flow from the right thoracic duct in dogs respiring 10% oxygen. Hendly and Schiller (209), furthermore, showed that edema of the hind legs of rats did not occur until the blood oxygen content was less than 5%.

Quite recently, Evans et al. (213) studied thoracic duct lymph flow in guinea pigs exposed to a simulated altitude of 14,000 feet and found a

progressive increase from control level of 0.86 ml per hour to 1.23 ml per hour after five days' exposure. Interestingly, these increased flows in the altitude animals were obtained while the animals were outside the chamber at sea level pressure. The latter would obviously suggest that the factors or mechanisms responsible for increased lymph flow during hypoxia remain operative even when the animals are brought to normal pressure. In fact, these investigators found even greater flows (1.89 ml per hour) three days after altitude exposure was terminated.

It seems unlikely that changes in capillary permeability are responsible for the increases in lymph flow observed under conditions of mild or moderate hypoxia. In fact, total oxygen lack for varying periods, depending upon the tissue, is usually a necessary prerequisite for changes in capillary permeability (214). Although increases in capillary permeability during hypoxia have been postulated by Maurer (200) and Warren and Drinker (202), these investigators observed decreases rather than increases in lymph protein content during the periods of augmented flow. Stead and Warren (212) furthermore found no significant increases in the protein content of edematous fluid collected from the extremities of patients with severe generalized hypoxemia. A more likely explanation for the elevated lymph flow is a hypoxia-induced increase in capillary surface area. Increases in the number and diameter of capillaries in various tissues, as indicated earlier, have been observed during high altitude acclimatization (134, 137). But even during the early stages of exposure, decreases in peripheral resistance (80) are probably caused by an increase in the number of functional capillaries, and hence overall capillary surface area.

Electrolyte Metabolism

In view of the well-know effects of hypoxia on acid-base balance of the arterial blood, compensatory changes in mineral metabolism have long been suspected as a major contributing factor to high altitude acclimatization. Thus, as early as 1919, Haldane et al. (87) showed that the hyperventilation and elevated rate of carbon dioxide loss during hypoxia were accompanied by reduced ammonia formation and excretion in the urine. Haldane et al. (87) reported, furthermore, that the excretion of acid during moderate hypoxia was reduced from one-half to one-third of normal values. Sundstroem (214), in studies on himself on high plateaus in the southwestern United States, also observed a decrease in NH_3 excretion but immediately thereafter, when he journeyed to Pikes Peak, he observed a large temporary increase. The latter he attributed to "the failure of the kidneys to excrete the fixed alkalies to a sufficient extent." A similar increase in NH_3 excretion was reported by Boutwell

et al. (215) during a series of brief exposures to simulated altitudes of 18,000 to 35,000 feet. These latter investigators, like many others previously, observed marked increases in fixed base excretion. Haggard and Henderson (216) emphasized the fact that after exposure to hypoxia and the development of hypocapnia and alkalosis, the kidneys restore the H_2CO_3; $NaHCO_3$ ratio of blood by excretion of $NaHCO_3$, or other Na salts.

Aside from these direct effects of hypoxia on the renal control of blood acid-base balance, alterations in blood electrolyte levels may also result indirectly through changes in salt and water intake or loss in the urine. In humans, Armstrong (180) observed marked increases in urine flow during brief exposures to a simulated altitude of 12,000 feet in a hypobaric chamber. This was also observed by Berger et al. (181), Pincus and Hoagland (217) and Burrill et al. (218) in subjects breathing hypoxic gas mixtures for brief periods of time. In contrast, Alving et al. (219) reported no change in the urine volume of five subjects exposed to simulated altitudes of 18,000 feet for four to six hours. In rats, Silvette (184, 185, 220) and Swann et al. (35, 31) observed polyurea during hypoxic exposure which could be abolished by posterior pituitary extract, dehydration and barbiturates; Swann observed negative water balances during hypoxia which were attributable in large part to increased evaporative water loss. Mefferd and Hale, in extensive studies (221-226) of excretion patterns of rats exposed to various adverse environments, reported normal water consumption in altitude acclimatized rats, but after fasting for 24 hours these rats showed a markedly greater reduction in water intake and urine formation than that observed in control animals. In dogs, conflicting data on renal function have been reported. Anesthetized animals were reported by Malmejac (227) and Van Liere and coworkers (24) to respond to hypoxia with oliguria. This was also observed by Toth (228, 229) in the majority of his anesthetized animals, but in unanesthetized animals he found just the opposite; namely, hypoxia usually produced polyurea. Stickney et al. (186), in an extensive study of urine formation under various anesthetic and hypoxic conditions, concluded "that generally mild anoxia produces a polyurea and severe anoxia, an oliguria, but the incidence of either is affected by the type of anesthetic used." Significantly, these investigators never found oliguria in the unanesthetized animal. More recently, Alexander (230) reported an increase in urine flow in unanesthetized dogs during brief exposure to 8% oxygen.

As already indicated, hypoxic exposure is associated with an increased excretion of fixed bases and a decreased excretion of acid. More specifically, many investigators have reported an elevated rate of Na, K and Cl loss during hypoxia (182, 218, 219, 228-232). Usually, the increase in Na and K exceeds the

increase in Cl. The adrenal cortex seems to play a critical role in this response since Lewis et al. (232) showed adrenalectomized dogs on maintenance doses of DOCA exhibited similar increases in K excretion during hypoxia, but no increase in Na or Cl excretion. Similar observations were reported by Langley and Clarke (182). Other observations on Na, K and Cl excretion are included in the report of Asmussen and Nielson (173) who obtained conflicting results in two subjects exposed to 450 mm Hg for several days and the work of Mefferd and Hale (226) on rats where reductions in Na and K excretion were observed in fasting, altitude-acclimatized rats. This latter response is probably attributable to a differential effect of fasting in reducing the urine volume in the hypoxic animals. In another report, these investigators observed relatively normal rates of Na and K excretion in fasted, acutely-exposed animals (222). With respect to the mechanisms underlying these elevated rates of electrolyte loss, McCance and Widdowson (223) reported hyperventilation per se could lead to an increased Na, K, Cl and H_2O excretion and a reduced urea excretion in humans. Singer (234) in reporting similar results, concluded hyperventilation caused an increased $KHCO_3$ excretion as a result of renal tubular exchange of K for H ions. Further data supporting such exchange mechanisms are found in Alexander's studies of dogs (230).

Data on the excretion of other electrolytes are relatively scarce. Mefferd and Hale observed a decreased P and unchanged or lowered Ca and Mg excretion in altitude acclimatized rats (222, 225, 226). In acutely exposed animals they found lowered Ca and P levels and elevated Mg levels (222). Interpretation of their data is difficult, however, due to a differentially reduced urine formation in fasted high altitude animals compared to fasted control animals.

Aside from the urine excretion of electrolytes, and perhaps more pertinent to the present study of women, Williams (235) measured the salivary Na and K concentration of three men and one woman during a protracted and unbroken sojourn above 15,000 feet in the Himalayas. When compared to their own values obtained at lower elevations (below 10,000 feet) exposure to the higher elevations was associated with elevated rates of Na excretion and reduced rates of K excretion. Both responses to high altitude were somewhat more pronounced in the woman than in the men. Williams attributed these changes to an altitude-induced inhibition of aldosterone secretion. This conclusion is compatible with the results published twenty years earlier by Lewis et al. (232) and Langely and Clark (182). Quite recently, Williams (236) confirmed his own prediction in studies of hypoxic rats.

In other tissues, Harris, Mefferd and Restivo (237) observed a decreased concentration of Ca, P, and Mg in the incisors of altitude-exposed rats. Reeves

(238) observed similar changes in the bones of rats.

In a comparison of the altitude responses of Long-Evans and Slonaker-Wistar rats of both sexes at White Mountain (12,400 feet), Johnson and Feigen (130) found all groups except the Long-Evans males exhibited an increase in myocardial sodium after 260 days' exposure. The increase appeared to be gradual since only the Long-Evans females exhibited an increase with moderate exposures (i.e., 30-60 days). Interestingly, acute exposure (4-10 days) was associated in males of both strains with a reduction in myocardial Na, but with an increase in females of both strains. This apparent sex difference had a tendency to persist through moderate exposure. The K concentration in chronically exposed animals declined in both sexes of the Long-Evans strain, while in the Slonaker-Wistar strain the males exhibited an increase and the females no change. There were no general trends in K concentration with shorter exposures. In both strains, acute exposure was associated with a reduction in myocardial Cl in males, but with an increase in females. This sex difference persisted through moderate exposure in the Long-Evans rats. With prolonged exposure all groups exhibited an increase in myocardial Cl concentration.

Biddulph et al. (239) investigated the electrolyte concentrations in heart, liver, and muscle tissue of anesthetized dogs breathing 8% O_2 for one hour but failed to find any significant changes in Na, K or Cl.

Considerable data have been accumulated on the serum electrolyte changes associated with hypoxic exposure. The physiological significance of these data in many instances, however, is difficult to interpret because of the peculiar experimental conditions employed by the investigators. In fact, detailed and systematic investigations of the serum electrolyte changes associated with high altitude acclimatization are rare indeed. As an example of a report which is difficult to interpret, Thorn et al. (240) exposed rabbits to a simulated altitude of 25,000 feet for four hours daily over a period of 21 days. The animals which survived (about 30%) exhibited a 6 meq/l reduction in serum Na and 4 meq/l reduction in Cl subsequent to an overnight fast at normal barometric pressure. In a similar study at 18,000 feet in which all of the animals survived, a 5 meq/l loss of Na but no change in Cl was observed.

The serum Na level in dogs is unaffected by acute hypoxic exposure. This lack of change has been reported by Biddulph et al. (239) in anesthetized animals breathing 8% O_2 for one hour. It has also been observed in unanesthetized dogs by Alexander (230) after 45 minutes of exposure to 8% O_2, by Lewis et al. (232) after 24 hours' exposure to 10.5% O_2, by Ziegler (241) after 150 minutes' exposure to 5% O_2 and by Thorn et al. (240) after daily

four-hour exposures to 25,000 feet for 55 days. In their studies of rats, Johnson and Feigen (130) found an increase in Na during acute (4-10 days) exposure, which they attributed to dehydration associated with translocation from low to high altitude. With longer exposures, serum sodium tended to revert to normal or in some groups to subnormal values. In studies conducted at simulated altitude, Sundstroem and Michaels (242) also observed an initial increase followed by a subsequent decline, which reached subnormal values in the acclimatized animals. Five-hour exposure of humans to a pO of 98 mm Hg was shown by Lewis et al. (232) to be without effect on serum Na levels. However, with longer exposures a slight decrease has been observed. This reduction was reported by Dill et al. (110) to range from 1.6 to 3.5 meq/1. in the ten male members of a high altitude expedition to Chile in 1935. In our own measurements of women, the reduction in serum Na (Fig. 37) was much more marked, decreasing from 148 to 140 after the first day of exposure and to 136.5 at the end of the study. It should be noted that this change may be magnified by the rather high values obtained in the initial low altitude measurements. The latter suggested some initial dehydration was present, but if the terminal altitude values are compared with those obtained two weeks after their return to Missouri an altitude reduction of about 5 meq/1. is still observed. This is more than twice the reduction observed by Dill et al. (110) in male subjects and implies a sex difference in electrolyte response to altitude. In high altitude residents Hack et al. (243) found the serum Na level of Johannesburg (5,770 feet) males averaged 2 meq/1. lower than serum Na level of Capetown males. Hurtado et al. (244), however, found no difference in a comparison of men from Lima and Morococha. Miners living in Quilcha, Peru (5,340 m), however, were shown by Dill et al. (110) to have an average serum Na concentration of 134.3 meq/1., which is even lower than the values we obtained in women.

Breathing an atmosphere of 8% O_2 for periods of 45 minutes to one hour has been shown by Biddulph et al. (239) and Alexander (230) to cause a slight but significant lowering of serum K levels. A more marked lowering has been observed by McQuarrie et al. (245) and Ziegler (241) in dogs breathing 5 to 9% O_2 for periods ranging up to 24 hours. In the case of Ziegler's experiments, serum K levels were reduced to about one-half the normal value. In cats, Kline (246) found an 18% decline after exposure to a simulated altitude of 28,000 feet for 90 minutes while exposure to 40,000 feet caused a 58% increase. Interestingly, Kline found a 19% decrease in nephrectomized animals exposed to 28,000 feet which indicates a shift of K from the intra- to the extra-vascular space. Whether it was deposited in the intracellular space as might be anticipated is not known. In their studies of intermittent exposure, Thorn et al. (240) found

no alterations in dogs and a slight (0.7 meq/1.) increase in rabbits. Male rats were shown by Sundstroem and Michaels to exhibit a marked increase in serum K levels during three weeks' exposure to an air pressure of 300 mm Hg. Similar results were later obtained by Mefferd and Hale (225) in male rats exposed for six months to 380 mm Hg and by Johnson and Feigen (130) in male rats acclimatized to 12,400 feet for a period of 260 days. In this last report, however, acute exposure of female rats produced an elevation of serum K similar to that seen in males, whereas chronic exposure produced normal or reduced K levels. Brief five-hour exposure of humans to 10.5% O_2 was shown by Lewis et al. (232) to be without effect on serum K levels. A similar lack of change was reported by Dill et al. (110) for mountain sojourners, and by Hack et al. (243) for residents of Morococha. Resident miners in Quilcha, Peru, however, were shown by Dill et al. (110) to have exceptionally high (7.6 meq/1.) serum K levels. In our own studies of women (Fig. 38) a slight initial reduction was observed. Although their levels remained low duirng the remainder of their exposure to altitude, the differences between low and high altitude means were not statistically significant after the first month.

In view of the well-known reduction in blood bicarbonate levels at high altitude, a compensatory increase in serum Cl level might be expected to maintain the total negative ions at or near their normal level. Such a compensation has not been consistently observed. Accordingly, Biddulph et al. (239) found no alteration in serum Cl in anesthetized dogs breathing 8% O_2 for 45 minutes while Alexander (230) observed only a slight increase in unanesthetized dogs breathing 8% O_2 for one hour. Ziegler (241), likewise, found no alterations in the Cl level of dogs breathing 5 to 9% O_2 for 150 minutes as did Thorn et al. (240) in their discontinuous exposure experiments.

In this last report, a slight decrease in serum Cl was observed after repeated discontinuous exposures of rabbits to 25,000 feet but no change after exposures to 18,000 feet. In rats, Sundstroem and Michaels (242) found a transient increase in Cl level during exposure to 300 mm Hg but no change during exposure to 360 mm Hg. Johnson and Feigen (130) observed significant serum Cl increases in the males and females of both strains of rats during the entire period of high altitude exposure, i.e., from 4 to 260 days. In man, Lewis et al. (232) found a slight (2 meq/l) increase after five hours' exposure to 98 mm Hg air pressure. Houston and Riley (48), on the other hand, reported a significant increase in only one of four subjects exposed for one month to simulated altitudes ranging up to 22,000 feet. In their comparison of male students from Johannesburg and Capetown, Hack et al. (243) observed a 2 meq/l greater Cl concentration in the high altitude group. A somewhat greater (104.6 to 109.0

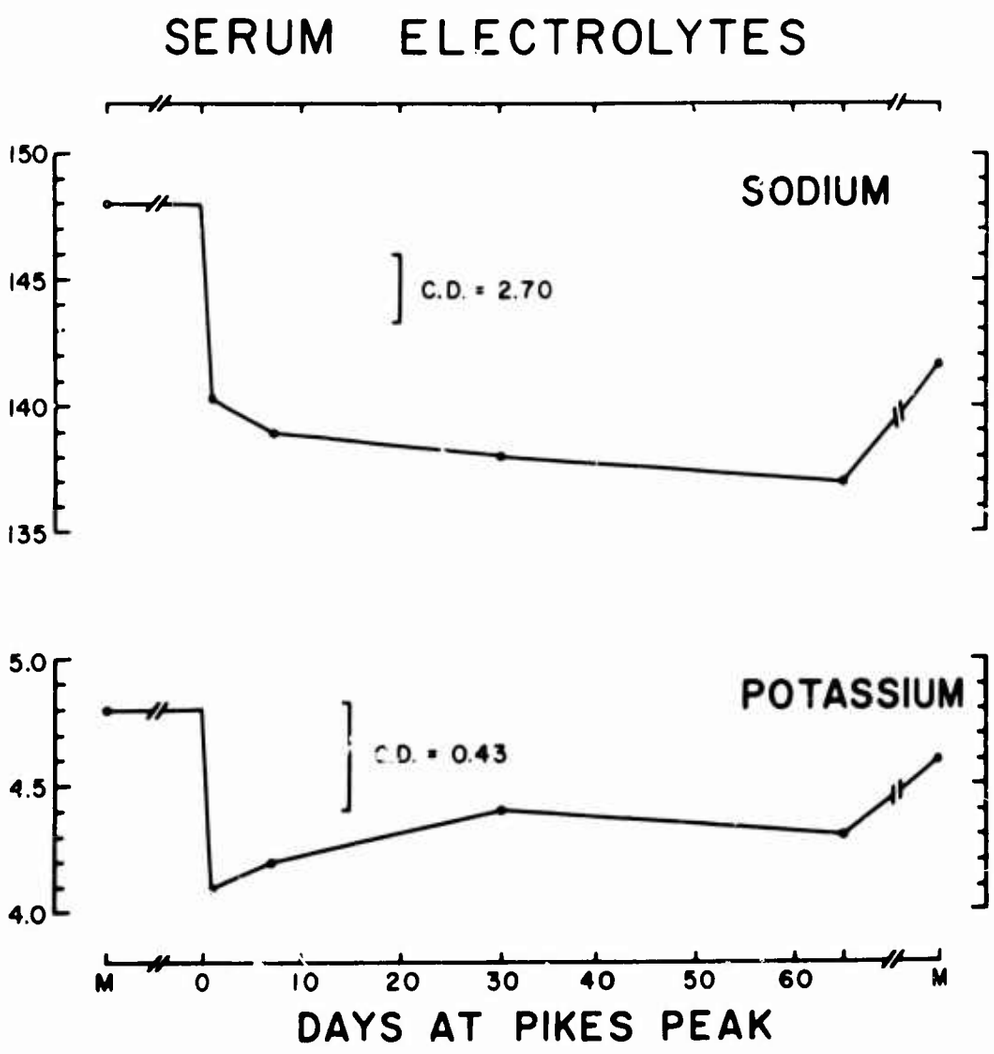


Figure 38
Serum sodium and potassium values, determined by flame photometry, of women during high altitude acclimatization. The values are expressed in meq./l.

meq/l) elevation of serum Cl level was observed by Dill et al. during their sojourn in the Andes. Residents of Morococha as shown by Hurtado et al. (244) also exhibit a higher (106.2 meq/l) Cl level than Lima residents (99.5 meq/l) while the Quilcha miners exhibited even higher levels (108.7 meq/l) than the Morocochans (110). The girls in our study on Pikes Peak exhibited an increase in serum Cl which reached a maximum value (110 meq/l) after exposure for one week (Fig. 39). Thereafter, it tended to decline somewhat but remained significantly elevated even after two and one-half months' exposure.

Serum phosphorus levels undergo a marked decrease during brief exposure to very low O_2 tensions. This has been observed by Ziegler (241) and McQuarrie et al. (245) in dogs and in humans by Lewis et al. (232). In rats, Sundstroem and Michaels (242) reported longer exposures led to elevated serum P levels, while the degree of this elevation was inversely correlated with the atmospheric pressure to which the animals were exposed.

Abderhalden (247), in studies of dogs, obtained a few very variable data which suggested an increase in serum phosphate content during prolonged exposure to high altitude. The altitude at which he worked was quite low, however. Mefferd and Hale (225) confirmed the elevation of serum P levels in acclimatized rats, control animals having a concentration of 4.1 meq/l as compared to 7.2 meq/l in the acclimatized animals. In contrast to these rather large changes in acclimatized rates, male residents of Johnannesburg (243) and Morococha (244) have essentially the same serum P levels as sea level residents. Such normal values in high altitude residents are not too surprising in view of the changes we observed in women at high altitude (Fig. 38). Thus, a rather large and transient increase was observed during the first month of exposure, but normal values were observed thereafter.

Data on serum Ca and Mg concentrations during hypoxia or high altitude exposure are rather scarce. Abderhalden et al. (247) reported a slight increase in the serum Ca levels in dogs subjected to mild but prolonged altitude exposure. Sundstroem and Michaels (242) and later Meffered and Hale (225) found no alterations in either component during acclimatization of rats to reduced pressures, nor did Ziegler (241) during brief exposure of dogs to low O_2 tensions. Sundstroem and Michaels (242) observed much greater increases in the magnesium content of red corpulscles than in the serum of altitude-exposed rats. They attributed this to an elevated reticulocyte content of the red corpuscular mass. Finally, Dill et al. (110) found normal serum Ca levels in their Andean sojourners and Quilcha miners as did Hurtado et al. (244) in Morocochan Indians. In our studies of college women, we found a slight increase in Ca which barely reached statistical significance by the end of the summer. This increase

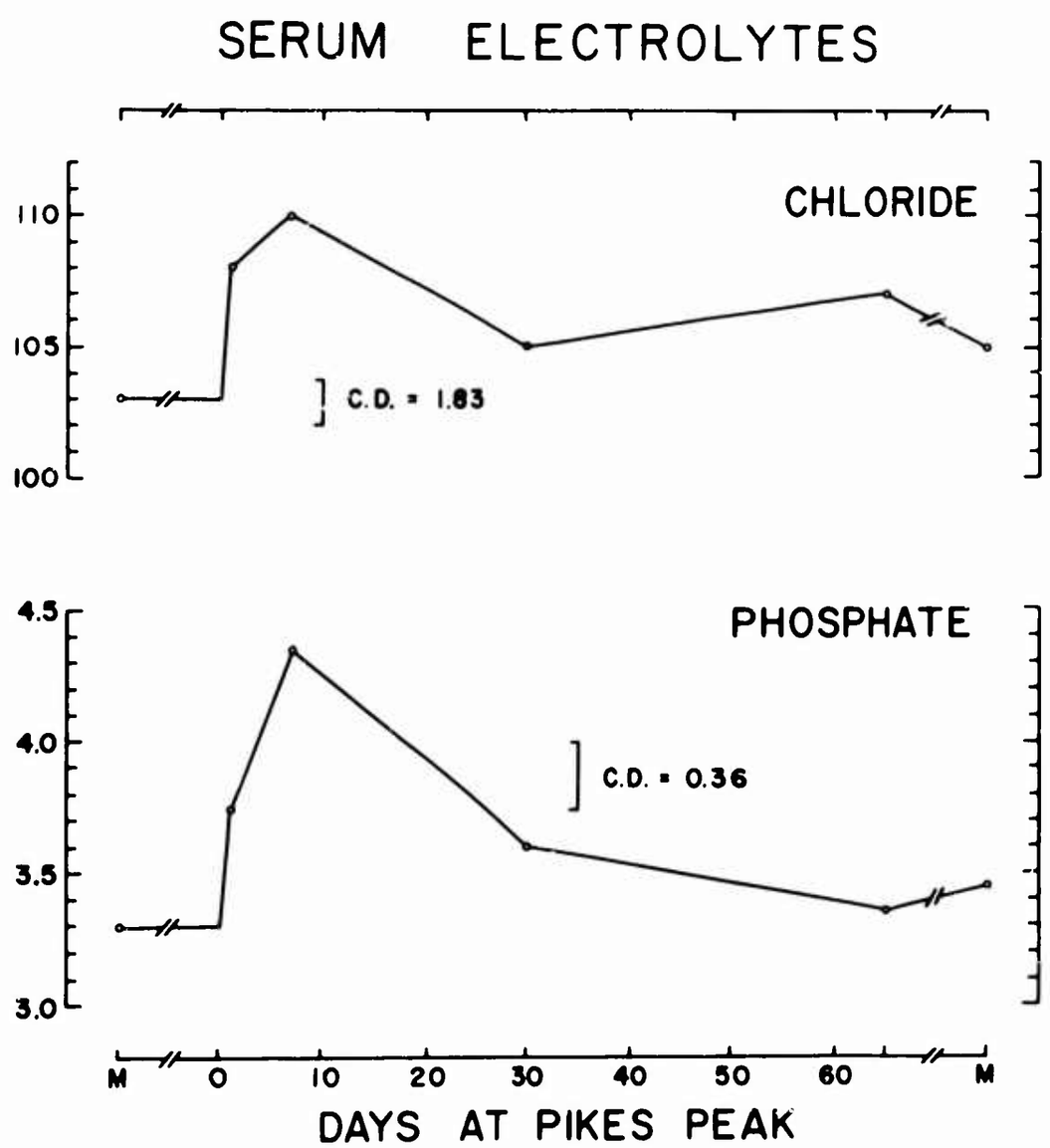


Figure 39
Serum chloride and phosphate values, determined chemically, of women during high altitude acclimatization. The values are expressed in meq./l., an average valence of 1.5 being assumed for phosphate.

could be attributed to the slight blood dehydration which was also observed (Fig. 34). Serum Mg levels exhibited a relatively large decline (1.9 to 1.5 meq/l) on the first day of exposure and, following a partial recovery, remained significantly reduced throughout the course of altitude exposure and for two weeks after the return to Missouri (Fig. 40).

The net effects of the foregoing alterations in serum electrolytes of women at high altitude are shown in Figure 41. Total cations (Na, K, Ca, Mg) were abruptly reduced upon exposure to altitude and decreased even further as the subjects became acclimatized. The sum of the anions which were measured (Cl and PO_4), on the other hand, exhibited a transient increase during the early stages of exposure, but returned to near normal levels after one month on the Peak. The difference between measured cations and anions was markedly reduced with the onset of altitude exposure and remained low throughout the study. This latter change probably reflects the loss of serum bicarbonate at altitude, since during this same period of time the levels of blood hemoglobin and serum protein, which also contribute to the anion content of the blood, were increasing. During the first week or so of exposure, the loss of total cations, about 8.5 meq/l, was almost exactly compensated by the increase in Cl and PO_2, about 8 meq/l. Thereafter, however, such compensation was not present and other anions, probably hemoglobin and protein, were increasing their contribution to the negative ion content of the blood. It seems probable that the contribution of bicarbonate to the negative ion content of the blood is not improved with high altitude acclimatization. Thus, low HCO_3-levels were observed in Morocochan Indians by Hurtado et al. (244).

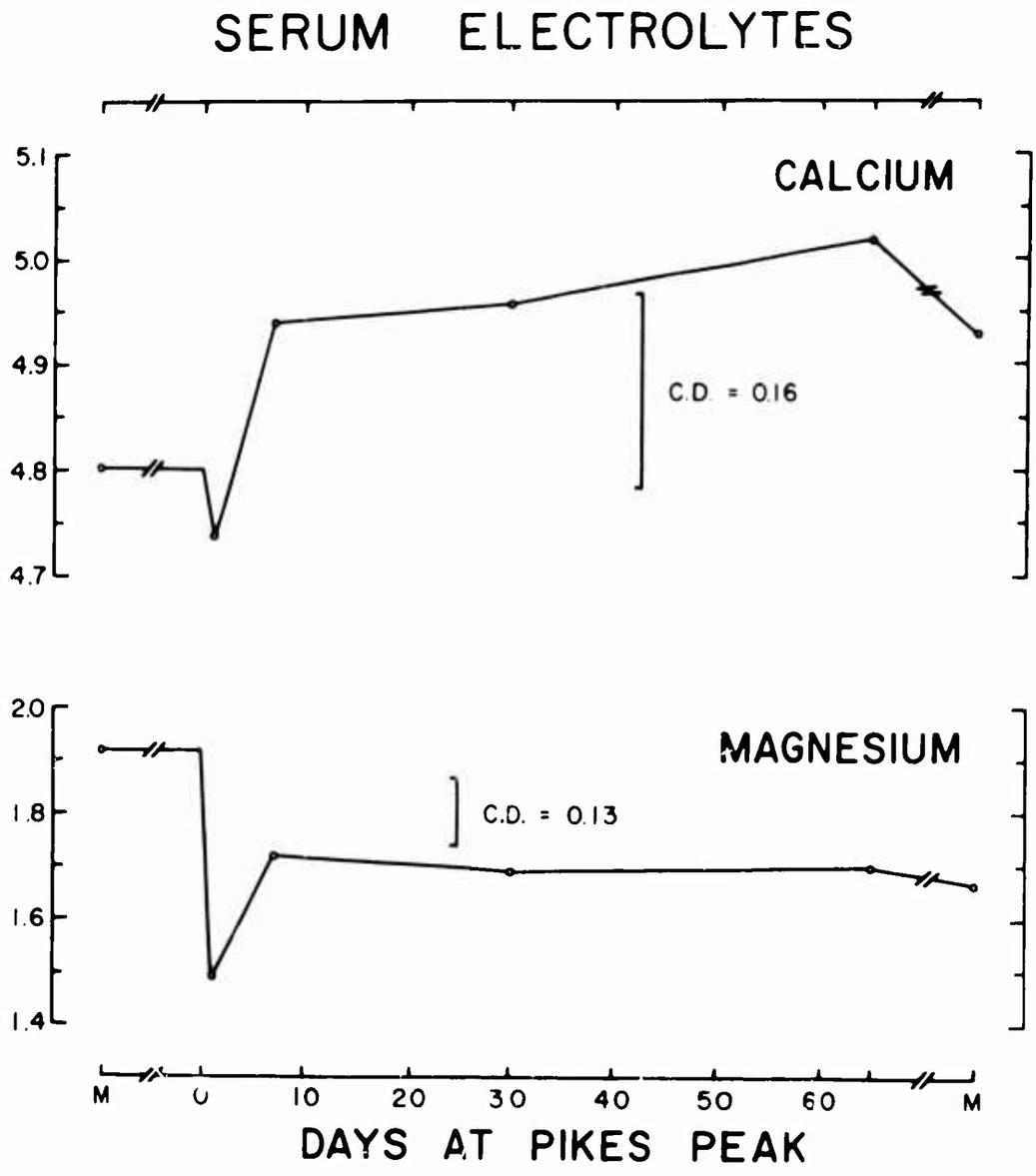


Figure 40
Serum calcium and magnesium values, determined by atomic adsorption spectrophotometry, of women during high altitude acclimatization. The values are expressed in meq./l.

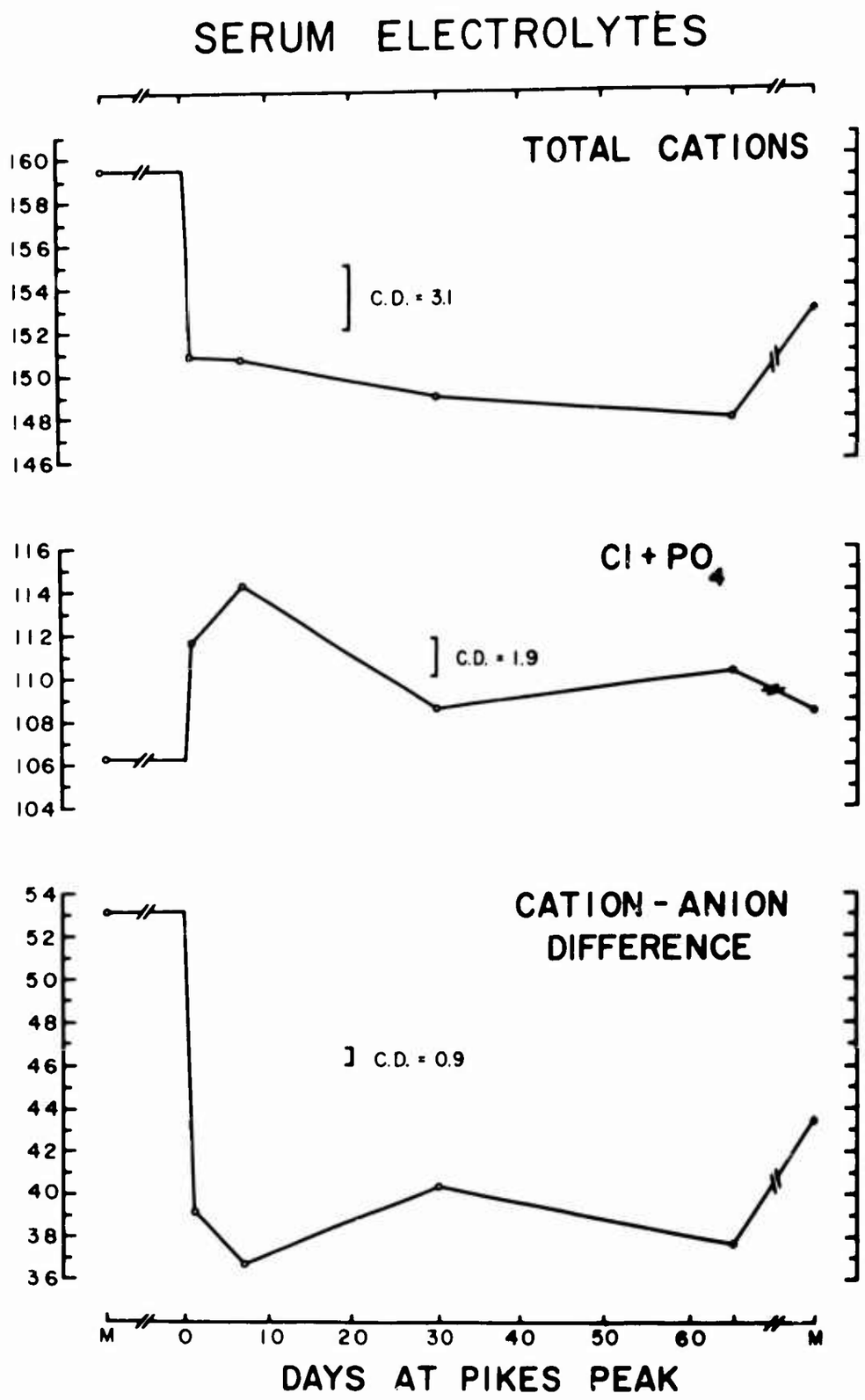


Figure 41
Summary of the net electrolyte changes in women during high altitude acclimatization. The values are expressed in meq./l.

DISCUSSION

DR. CHIODI: I want to ask a question about the x-ray picture of the heart. If I would follow my experience and what I know from the Peruvians, I would say it was just the reverse. From an anatomical point of view it has been shown by the Peruvians that there is a dilation and a hypertrophy of the heart.

DR. HANNON: Yes, in the native people.

DR. CHIODI: Yes, in native people, but when you spend 60 days there, two months, it was going down. How do you explain that?

DR. HANNON: Well, I think the interesting thing here is the electrocardiogram measurements, the changes you see in this right axis deviation. If you put the subject on oxygen for 30 minutes, in this case pure oxygen, it went right back to what it was at sea level. So that the indications of an anatomical change are practically nil in these subjects.

DR. CHIODI: Yes, but it has been shown there are changes in the electrocardiogram at high altitude.

DR. GROVER: I don't know of any study that defines how rapidly you get an anatomical change in the amount of right heart muscle or the rise in PA pressure. Our own recent studies indicate no change in the first ten days. What you may get in two months I don't really know, but I suspect that the time is not long enough to get the changes you see in the long term resident.

DR. HANNON: Well, the evidence seems to suggest it. I don't know whether I mentioned it, but the pulmonary artery diameter would increase as a function of altitude.

DR. HORVATH: The newborn shows the same type of right axis deviation, the same type of hypertrophy, the same type of pulmonary hypertension, which tends to disappear as long as it isn't remaining at altitude. I think actually it's the way in which it was measured that is confusing us. I think we all agree there is some shift in the axis. What we can't relate is the change in the diameters that you have measured.

DR. BRAUER: Of course, remember you are at a lower hematocrit than you are in all these other measurements and viscosity-wise, if you will recall, you are in a rather critical zone, because below 45 percent or so your viscosity is quite low and then starts climbing rather steeply as you go above that. It is quite possible that in fact what you are seeing is a demonstration of the fact that, if you stay below a critical hematocrit, you are not going to get the changes that you see at the higher hematocrit.

DR. BLATTEIS: I am impressed with the relatively high incidence of mountain sickness that you have been reporting. I don't have experience personally at Pikes Peak and Mt. Evans, most of mine as you know is in the Peruvian Andes. There I was rather impressed with the other situation, that the incidence of the severe kind of mountain sickness is not so frequent. You are probably aware of reports that the incidence of mountain sickness varies apparently with latitude, and we can even find thereby differences with altitude. One interesting observation we made on our subjects last year was that we had precipitated, or we appeared to precipitate, acute mountain sickness, including fainting, when the subjects in the study were moved from a warm environment into the cold environment. This occurs after approximately – the subjects had arrived at altitude rather rapidly by car – three hours in a warm environment and during all that time they had only very mild symptoms, a little bit of a headache perhaps, but nothing to be very upset about.

DR. BRAUER: But they all suffered from motion sickness if they came over the typical Peruvian road by car.

DR. BLATTEIS: But when they were moved into the cold then these symptoms became severe. We had one subject faint in the cold and it took about

ten minutes to revive him. Have you ever seen any correlation between cold and mountain sickness?

DR. HANNON: We haven't studied cold, but our symptoms of mountain sickness have been fairly consistent under the circumstances we measured. There is a marked difference in subjects according to where they come from. As I mentioned earlier, we had this other study a year earlier on men. It consisted of two groups of eight subjects each, and they came out of a laboratory in Boston. Eight of these went directly to the high altitude site and eight of them went there gradually. They stayed at Denver for a week, Climax for a week, and then to high altitude, Pikes Peak, and there was a marked difference in the symptoms of these people. The ones that went up gradually had very low incidences of symptoms whereas most of the ones that went directly to altitude were very sick. In fact, of these eight, I believe there were three or four of the eight who were so nauseated they vomited at altitude. Again it may or may not be a similar problem to the thing in the chamber, because they were in a small hut there, and it was the first night after arriving and they were pretty sick. We know Denver or Colorado residents have very few problems with mountain sickness, at least in our group.

DR. BRAUER: There are areas in the Andes which are cold, where the incidence is higher than in other areas.

DR. TODA: During the subjects' stay at high altitude, they might experience about two menstrual cycles. Did you find any difference in the strength or severity of sypmtoms in the two menstrual stages, the premenstrual stage and post-menstrual stage?

DR. HANNON: No, we did not.

DR. TODA: The same?

DR. HANNON: Well, there were no differences as far as we could see

between the altitude type of symptoms, the high altitude versus the low altitude.

DR. EVONUK: I talked to an Indian army major who told me that they start their troops at 10,000 feet, spend the night at 10,000 feet, and they walk with their pack up to about 13,000 feet, come back to 10,000 feet to spend the night, then they carry their packs up to 13,000 feet, spend the night, walk to 15,000, work at that level during the day, then they come back to 13,000 and spend the night and go to 15,000. It takes them about a week to do this, there is no apparent mountain sickness, and they can continue to work this way up to 18,000 feet.

DR. CHIODI: Well, another thing is important is the psychological factor. I mean I sometimes saw people who had a story about getting acute mountain sickness, but they weren't sick. I saw people getting sick only because some other people in the train going up started to say that, well, at 4,000 meters – you will be sick. In some cases there is very definitely a psychological factor involved.

DR. BLATTEIS: But in contract you know when they work, that is, when they do mild work such as walking, then the headache disappears for a while.

DR. HANNON: Well, I think exercise certainly does improve how you feel at altitude. I don't know whether it removes the symptom in terms of, say, something like mild nausea.

DR. REYNAFARJE: I think the ambient temperature is very important because these symptoms appear most frequently during winter when the temperature is very low, while in the summer there are less frequent symptoms. This may be reasonable, since as Dr. Blatteis has shown cold increases oxygen uptake, and the subject at high altitude has not prepared all his system for the oxygen supply to the tissues and maybe this is – –

DR. HANNON: I don't think cold was a problem in this particular study because we weren't concerned with comparing the altitude responses with the cold responses, so our subjects were kept indoors where the temperature was essentially the same at high altitude as it was at low altitude. We did make a conscious effort to keep the temperatures equivalent.

DR. WEIHE: When they had these symptoms, did you recommend that they go outside?

DR. HANNON: No.

DR. WEIHE: Because we found usually that when they have the subjective symptoms it's good to recommend going outside, that a warm room is worse. I'm not talking about real cold effects, but it is definitely much better to recommend that these people go outside.

DR. BLATTEIS: If the symptoms become severe and you get pale and begin to sweat, then there is a desire for some coolness, fresh air, but whether the heat is the precipitating factor or not, it is a very important and poorly investigated variable in that.

DR. HANNON: One of the purposes of making these symptom measurements, or attempting to make symptom measurements, is to look at the severity of overall mountain sickness and see how this correlated with the physiological or biochemical changes. The severity of altitude sickness was not apparently related to the CO_2 of the blood, but it was related to PCO_2 in possibly just the opposite direction from what you might expect, the lower the PCO_2 the less sick they were. There was a high degree of significance and correlation.

DR. BLATTEIS: There's work that Steven Cane has done, in which he reports that the administration of diamox to two subjects, I believe in an altitude chamber at 14,500 feet or thereabouts, relieved their subjective

symptoms of mountain sickness. This is using metabolic acidosis, which is the reverse situation of the correlations you are reporting.

DR. HANNON: Yes, that's what makes it strange. I did not make any attempt to try to get an exact measure on mountain sickness but on two subjects the general impression was that the severity was much lower, but this could happen in any two subjects.

DR. DILL: What did these girls think about it when it was over? Did they want to go through it again?

DR. HANNON: Yes, they did, surprisingly enough. They were exceptionally good subjects.

DR. DILL: Any plans for doing that?

DR. HANNON: This question came up: should we use the same girls again or get new girls? I think possibly we will get a new group to go back and pick up a lot of these things we have been talking about. We would like to get a lot of measures of cardiovascular functions and blood-gas changes along with these things and do it during exercise also.

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EXERCISE LIMITATION AT HIGH ALTITUDE*

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The performance of sustained muscular exercise requires the transport of adequate quantities of oxygen to the working muscles. This exercise, while accomplishing external work, also produces heat and metabolic waste products which must be removed. Consequently, work performance will be influenced markedly by such environmental factors as heat, cold, and altitude. For the man living at high altitude, the major stress is on the mechanisms of oxygen transport. In high mountain regions, however, low air temperatures, low humidity, wind, and intense solar radiation present man with added problems of thermo-regulation. This review will be concerned primarily with adaptations of oxygen transport in a thermoneutral hypoxic environment. The added stress of cold then will be dealt with briefly.

Magnitude and Duration of Reduction in Maximum $\dot{V}O_2$ at Altitude

As man ascends from sea level to high altitude, the air he breathes decreases progressively in density as the total atmospheric pressure falls. There is a concomitant decrease in inspired oxygen tension, and, as a consequence of this hypoxia, there is a decrease in the maximum amount of oxygen which he can consume per minute. His aerobic working capacity is, therefore, also decreased. This phenomenon has been documented on numerous mountaineering expeditions, and the results summarized recently by Pugh et al. (1) (Fig. 1). A

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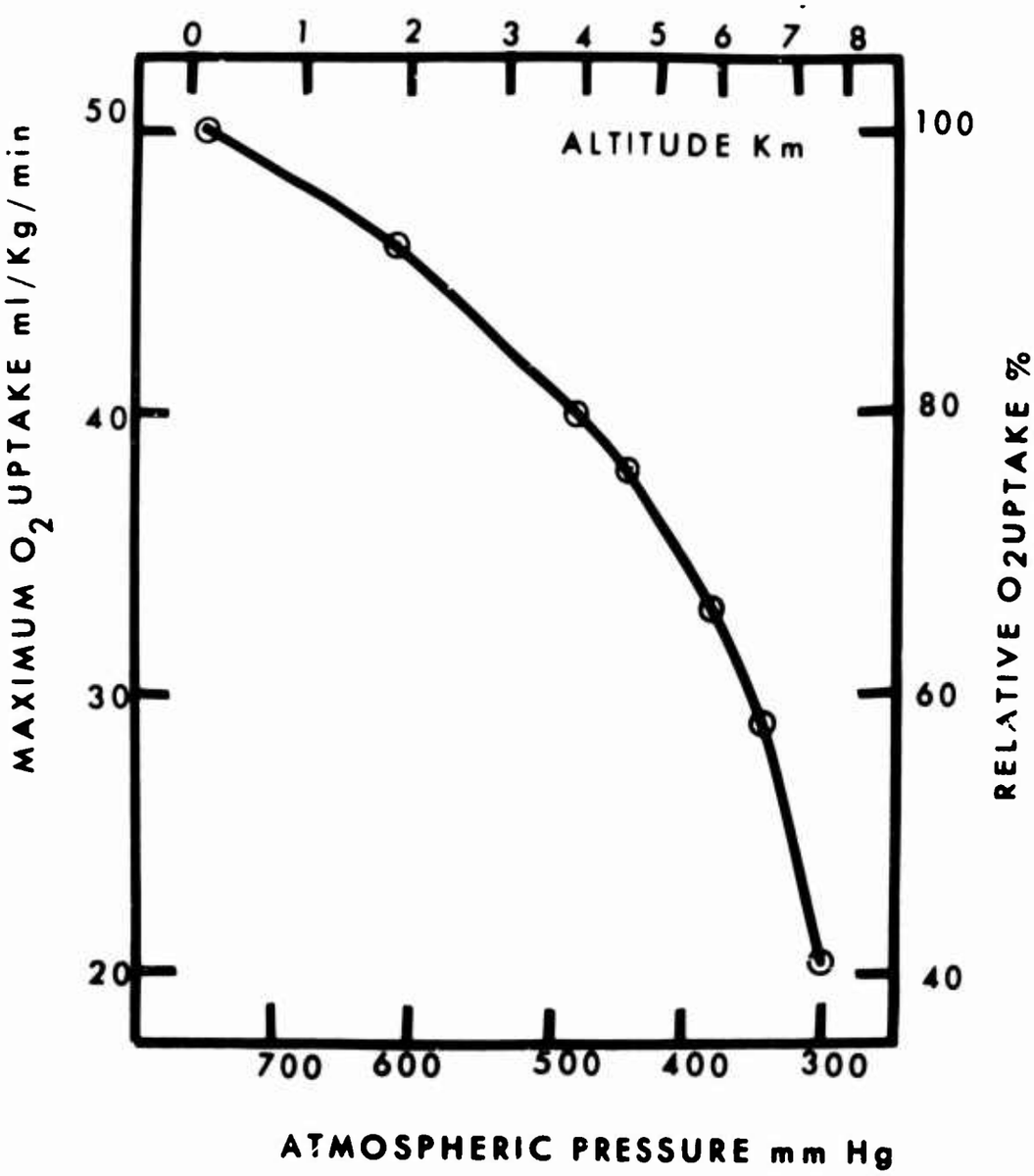


Figure 1
Maximum oxygen uptake of moutaineers decreases with decrease in atmospheric pressure at increasing altitude. O_2 uptake expressed in absolute terms as ml O_2 per kilogram of body weight per minute, and as per cent of sea level value. From Pugh et al (1).

curvilinear relationship exists between maximum oxygen uptake ($\dot{V}O_2$ max) and barometric pressure. This means that a decrease in pressure of 100 mm Hg produces a greater reduction in $\dot{V}O_2$ max at 3000 m than at 1000 m altitude.

Figure 1 is based on the performance of mountaineers, i.e., men in reasonably good physical condition capable of sustained exertion at high altitudes. Such men are not necessarily athletes in the sense of having exceptionally high values for $\dot{V}O_2$ max. The effect of altitude on the working capacity of true athletes is a matter of special interest currently, since the 1968 Olympic Games will be held at 2200 m altitude in Mexico City. Middle distance runners have been studied both at sea level and at 2200 m by Saltin (2), at 3100 m by Grover and Reeves (3), and at 4000 m by Buskirk et al. (4). In each study, $\dot{V}O_2$ max was reduced to a greater degree than one would predict from Figure 1. There is thus an apparent paradox, that men of high working capacity suffer a greater decrement in $\dot{V}O_2$ max at altitude than do men of only moderate working capacity.

DR. HORVATH: Does the athletes' loss of their training edge apply to your figures during altitude?

DR. GROVER: Well, that's a little hard to evaluate. We attempted to maintain the state of training of these individuals and for this we depended pretty much on their coach. We did have them out running every day but how much of a deterioration in physical condition occurred is hard to say.

DR. IRVING: Do you have any indications from time records or from judgment of the coach as to whether their performances were impaired?

DR. GROVER: The actual running times at altitude were determined only on one occasion, at the end of three weeks. We don't have serial measurements.

DR. IRVING: I meant particularly after they had returned to lower altitude.

DR. GROVER: This was not determined, so I can't say that either.

DR. HORVATH: What about this opinion of the coach on their ability to train at altitude? I think it's a very important point. Can people work sufficiently hard at altitude to maintain this rate of performance which is effective down at – or capable of maintaining their peak performance at low altitude, can they train hard enough, intensively enough, at high altitude to maintain this? Do you have any indications as to what the coach from the lowlands felt about the activities at altitudes?

DR. GROVER: Well, I'll be perfectly honest with you; it was the coach's intent in this study to be sure that his boys would win the competition at the end of three weeks, rather than to maintain a constant level of training or work them as hard as he had been working them in Kentucky, and we knew from previous experience that these fellows were better athletes than the ones they were going to compete against – and this was borne out, they won the competition so they weren't under any really great pressure to stay at peak condition. Because of this it is probable that they did not train as hard, and I do know that other coaches feel it is not possible to work a man as hard at altitude.

DR. CHIODI: How many days were they from the peak of their training, when they were at sea level? How many days, because the first day they were still in the peak of training.

DR. GROVER: Yes, that is true. This was less than a week from the time they had won the state competition.

DR. HORVATH: I wonder if I might add just a little. Certainly there is pretty good evidence that the longer the distance the man has to cover at high altitude, the more decrement he shows than one who has to work shorter distances where he depends predominantly on his anaerobic capacity. Were these athletes a mixture in the sense that they ran either short races or very long races?

DR. GROVER: They were a mixture. In retrospect, we could have selected the running capabilities of our subjects a little bit better. We had some who were accustomed to running the 220 yards and others who were accustomed to running the mile, and this is certainly a different type of effort;

however, the actual range of values, physiological values, for these people was very narrow in spite of that.

The reduction in a man's $\dot{V}O_2$ max at altitude is probably permanent. When young athletes from sea level were studied at 3100 m for three weeks (5), and at 4000 m for six weeks (4), $\dot{V}O_2$ max showed no tendency to improve with the passage of time. Furthermore, when Grover et al. (6) compared young athletes native to 3100 m with similar athletes from sea level, the reduction in $\dot{V}O_2$ max was of the same magnitude in both groups (Figure 2), i.e., no less in the altitude residents in spite of acclimatization from birth. It appears that the hypoxia of altitude places a permanent handicap on the oxygen transport mechanisms of the body.

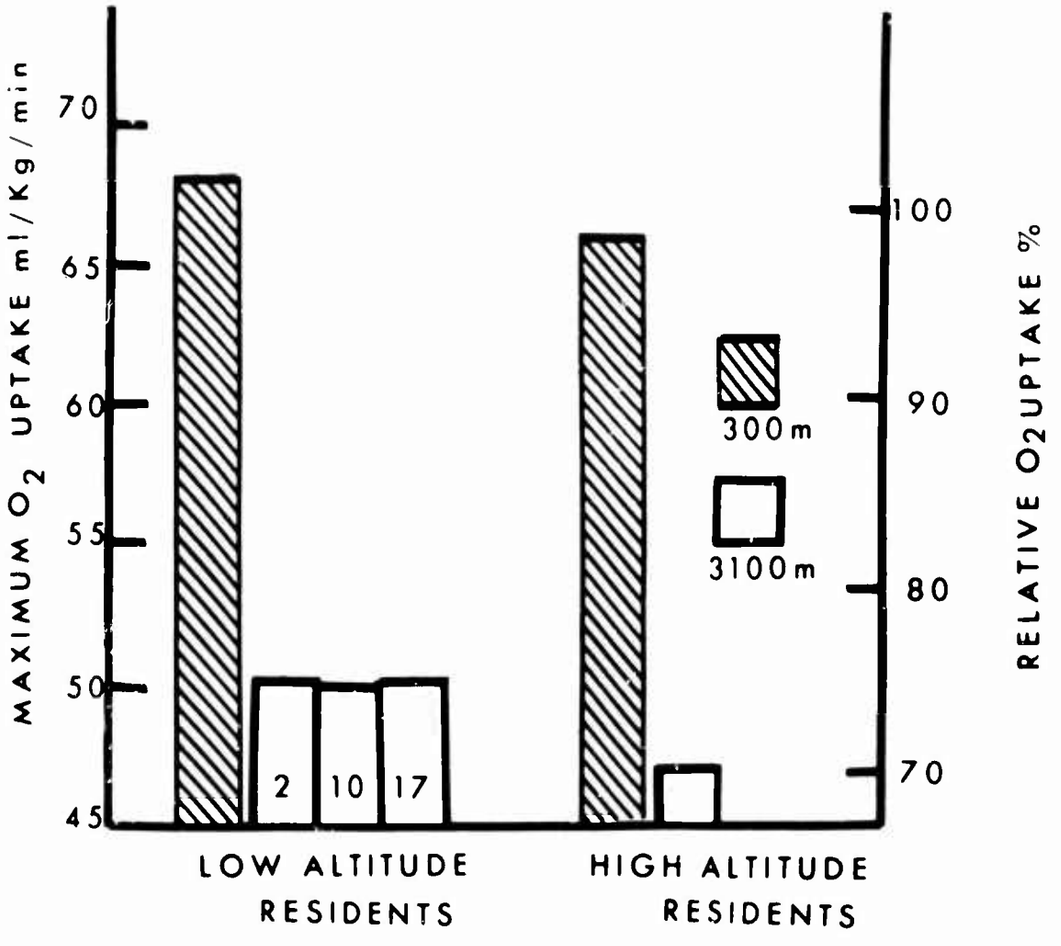


Figure 2
Maximum oxygen uptake of athletes at low (300 m) and high (3100 m) altitude. $\dot{V}O_2$ max of 5 low-altitude residents was decreased 26% after 2 days at high altitude, with no improvement after 10 and 17 days at altitude. $\dot{V}O_2$ max of 5 high-altitude residents was 29% less in their usual high altitude environment than at low altitude.

DR. BLATTEIS: When you took your subjects back to sea level was that the same too?

DR. GROVER: We did not study in detail the ventilation of this group after they had been at altitude for three weeks.

DR. BLATTEIS: And heart rates?

DR. GROVER: Again we didn't do this either. All that was done on the low altitude residents after they returned to low altitude was a Balke test.

DR. REYNAFARJE: The oxygen consumption of the high altitude native and the newcomer is the same, is that so?

DR. GROVER: Yes.

DR. REYNAFARJE: Are they natives or residents? We found low oxygen consumption of the newcomer compared with the native.

DR. GROVER: The high altitude residents are natives, they were born and have lived their entire lives at 3100 meters. The low altitude group was born at low altitude and this was the first time they had ever been to high altitude.

DR. REYNAFARJE: How many hours after they arrived did you test?

DR. GROVER: The first measurements were made within 24 hours after they left low altitude. They were flown to Denver, transferred to cars and driven directly to Leadville, a trip which took most of one day, and then the next morning we began testing.

Adaptations in Oxygen Transport at Altitude

Ventilation. During submaximal exercise, minute ventilation, $\dot{V}_E$BTPS, increases in direct proportion to the increase in $\dot{V}O_2$. Only at maximal exertion is there a disproportionate increase in ventilation (1, 5). When man ascends to high altitude, a given $\dot{V}O_2$ is associated with a greater V_EBTPS. This approximately compensates for the decrease in air density, so that the number of moles of air ventilated, $\dot{V}_E$STPD, at a given $\dot{V}O_2$ is virtually constant and independent of altitude (7). However, as Pugh et al. observed (1), this relationship does not hold for the hyperventilation at maximal exertion. When one remembers that with increasing altitude there is a progressive decrease in $\dot{V}O_2$ max, then a given $\dot{V}O_2$ does not represent a fixed level of exertion but rather a work load which progressively approaches maximum working capacity. Applying this concept, then V_EBTPS bears a constant relation to $\dot{V}O_2/\dot{V}O_2$ max regardless of altitude (Figure 3) (5). In other words, a given work load is sensed in relation to working capacity for that altitude, and $\dot{V}_E$BTPS is regulated accordingly. (There is a similar regulation of other parameters in ventilation, including respiratory frequency, tidal volume, and expired oxygen concentration). This increase in $\dot{V}_E$BTPS at altitude maintains oxygen delivery to the alveoli, but does not offset the decrease in atmospheric pressure. Hence, alveolar oxygen tension (P_AO_2) falls progressively with increasing altitude. An increase in alveolar ventilation counteracts this only slightly. Alveolar hypoxia (a reduced P_AO_2) is therefore inescapable.

DR. BUSKIRK: Could that hypoxia be only a reflection of the perhaps lower maximal oxygen intakes that were found in these people at altitudes?

DR. GROVER: Well, this is true even if you look at the newcomer working at the same altitude. In effect we have attempted to remove the factor you're suggesting by using this device of presenting oxygen as a percent of maximum.

DR. BUSKIRK: Well, what I'm saying though is perhaps the maximal oxygen intake as measured on these natives at high altitude were in fact too low, and therefore your oxygen demand for fixed work load is a relatively greater fraction than it otherwise would be if you had a correct measure of maximal oxygen intake on these people.

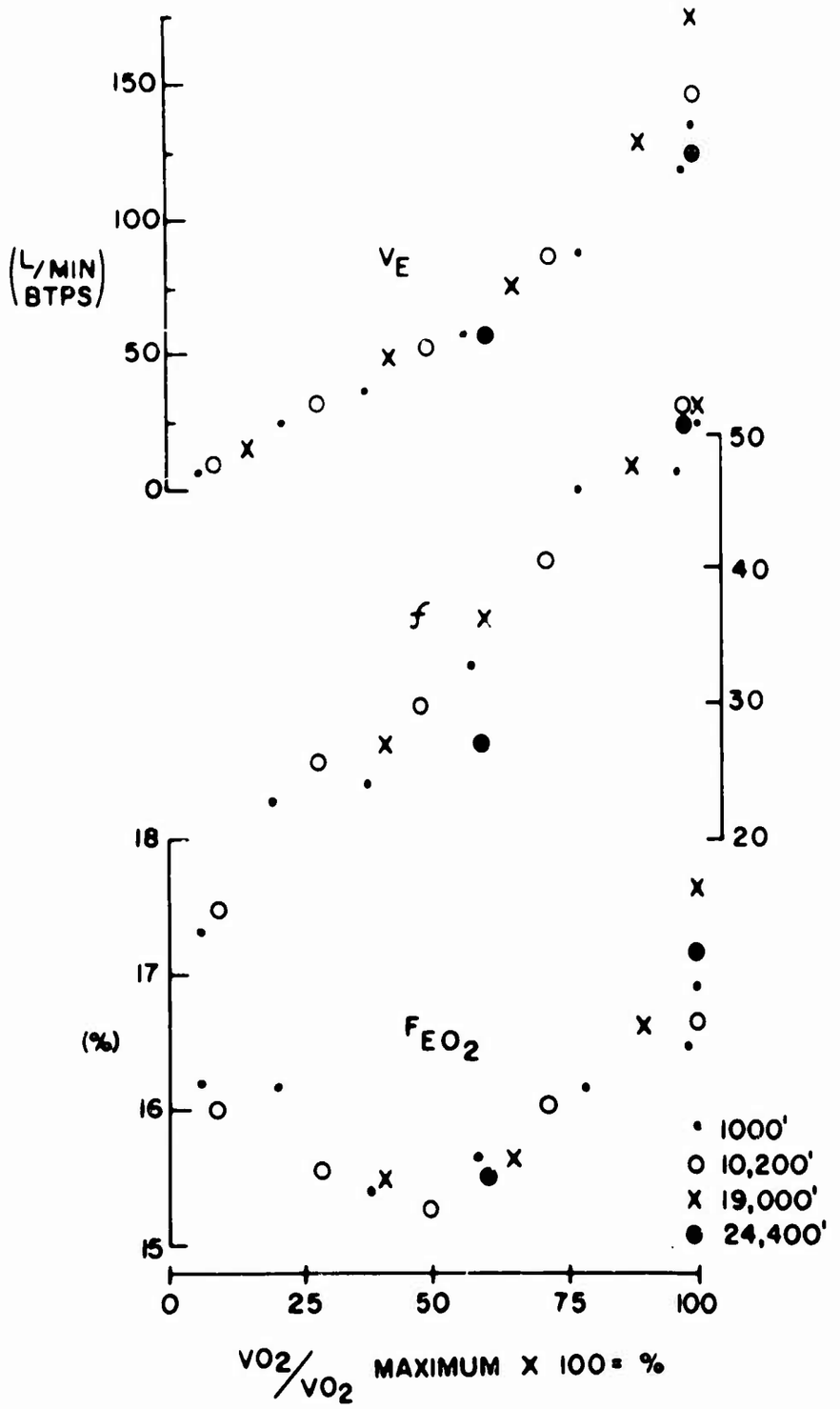


Figure 3

During exercise at altitudes ranging from 1000 ft to 24,400 ft, pulmonary ventilation bears a constant relationship to $\dot{V}O_2$ expressed as a percentage of $\dot{V}O_2$ max for each respective altitude. $\dot{V}_E$ = minute ventilation, liters per minute at BTPS. f = respiratory frequency, breaths per minute. F_EO_2 = fraction (concentration) of oxygen in expired air, per cent. (Figure from Reeves et al [5] reproduced by permission of the American Physiological Society.)

DR. GROVER: Well, this would occur. I can always say that these figures, these maxima, are of the order of 36 to 40 ml per kilo per minute.

DR. BUSKIRK: This is why I asked, because we re-measured some of these people in Minoa and they were all about 50 cc's per kg.

DR. GROVER: Well, by comparison then these are not very high.

DR. HORVATH: They would almost always be on the other curve then?

DR. GROVER: Yes. You mean then, Dr. Buskirk, there was an error in Hurtado's original data?

DR. BUSKIRK: They seem to be kind of low, judging by what the recent experiments have been on these natives.

DR. EAGAN: Were the maximum P_{O_2} measured on the Morococha natives at altitude or at sea level?

DR. GROVER: These data are determined at altitude, yes.

DR. EAGAN: While the maximum P_{O_2}'s on your other group are determined at sea level, or 300 meters?

DR. GROVER: The dotted points are determined at 3100 meters, the solid line is constructed from data all the way from sea level to 24,000 feet. Maybe the whole thing is an artifact as Dr. Buskirk suggests. This data may be in error; if it is not then it suggests a rather fundamental difference in the ventilatory regulation in these particular altitude natives compared to other people, including the subjects we studied who were also natives.

DR. HORVATH: If you had plotted that on an exponential basis you would have a straight line for your Leadville residents, it would appear almost as though the straight line which is appearing for the Morococha residents would fit on that line simply at a low place on the tangent of the curve which you now have, which would strengthen the feeling that the maximum oxygen uptakes were lower, not because of any error in measurement but maybe because of the motivational or some other factors.

DR. DILL: I would like to suggest another possibility – that the Morococha low values are explained by higher resistance in the breathing system. This does make a difference, I know nothing about what their resistance was, but – –

DR. GROVER: They simply could not achieve ventilations of this order because of the great resistance. Well, that would be a mechanism also, of course.

DR. IRVING: Were those Morococha subjects inferior in the amount of work they could put out?

DR. REYNAFARJE: No.

DR. GROVER: On the contrary.

DR. REYNAFARJE: They show longer endurance, they have far longer time.

DR. DILL: What was the maximum $\dot{V}O_2$ per kilo?

DR. GROVER: 36.

DR. DILL: And yours were about 60.

DR. GROVER: Now, this is 36 and 4,500 meters, and our figures were at 3,000 meters, we had 47 to 50.

DR. DILL: Well, 36 is not extraordinary, Balke achieved a higher level at 4,300 meters. I think his was 37 or 38 and he's over 50 years old.

DR. BLATTEIS: The percent oxygen extracted was higher at altitude.

DR. GROVER: In this group it was, yes.

DR. BLATTEIS: So that in effect they are still achieving identical oxygen consumptions.

DR. GROVER: And this is a relatively independent measure. The expired oxygen concentration doesn't depend on how you measure ventilation or anything else, it's an independent measure, and it was lower in these people than in the newcomers.

DR. HORVATH: Well, it could be the PO_2 could be higher at altitude if the resistance in the circuits was greater, because as Dr. Dill pointed out this was quite an important factor. If you're offering a great deal more resistance in the circuit, you will have to extract a certain percentage of oxygen from the expired air in order to make up for that deficit in ventilation.

COL. GOLTRA: Do you have comparisons on lung volumes on those two groups that you're plotting there?

DR. GROVER: No, I don't have the lung volume on this group. Perhaps we want to say simply that this raises an interesting possibility in terms of differences in respiratory regulation and deserves further investigation. The data as it stands shows quite a striking difference, if it's real.

DR. EVONUK: Dr. Horvath, wouldn't an exponential plot of this data give you almost identical slopes?

DR. HORVATH: Oh, yes, just by looking at it I would say it would give you exactly the same slope. It's hard to tell, but this is definitely tangent right now; the Morococha data is tangent right now as you can see to the other, and therefore I would guess it would be the same slope.

DR. EVONUK: Which would reveal a consistent difference.

DR. HORVATH: Yes, if there is one, I think it should have been plotted as an exponential so we could take a look at it.

DR. DILL: I would like to add a comment to this when you publish it, to the effect that this is clearcut evidence that the Balke formula is not intended to be used for estimating maximum oxygen uptake. The Balke formula which is based on the relation between oxygen consumption, rate and grade, applies within the aerobic range but this is what can happen – that the last two or three minutes are accomplished with an increasing proportion of anaerobic metabolism.

Diffusion. An inherent property of the lung is its capacity to oxygenate blood. Oxygen passes from alveolar gas to pulmonary capillary blood by virtue of the difference in oxygen pressure between air and blood. This diffusion of gas is restricted by the tissues separating blood from air, the so-called "alveolar capillary membrane" (although it is well established that the diffusion of oxygen begins quite proximally to the true capillaries [8]). When man exercises at sea level, systemic venous blood returns to the lung with a low oxygen tension. Since P_AO_2 is high, the difference in oxygen pressure from air to blood is large, which favors rapid diffusion. At high altitude, however, P_AO_2 is markedly reduced, so that the pressure difference from air to blood is less, thereby limiting diffusion (9).

If the pulmonary diffusing capacity were to increase at high altitude, then more oxygen would diffuse per minute with a given oxygen pressure difference. This theoretically useful adaptation apparently does not occur, however. West (10) found no significant increase in total lung diffusing capacity for carbon monoxide (D_LCO) in men from sea level who lived for five months at 5800 m. We have measured the pulmonary capillary blood volume (V_c) and the membrane component (D_M) of the pulmonary diffusing capacity in newcomers and residents at 3100 m (11). Neither V_c nor D_M changed in men from sea level during six weeks at altitude. However, in the high-altitude residents, D_M was

twice as great as in comparable sea-level residents, whereas V_C was the same (Figure 4). This should give the high-altitude native an advantage in blood

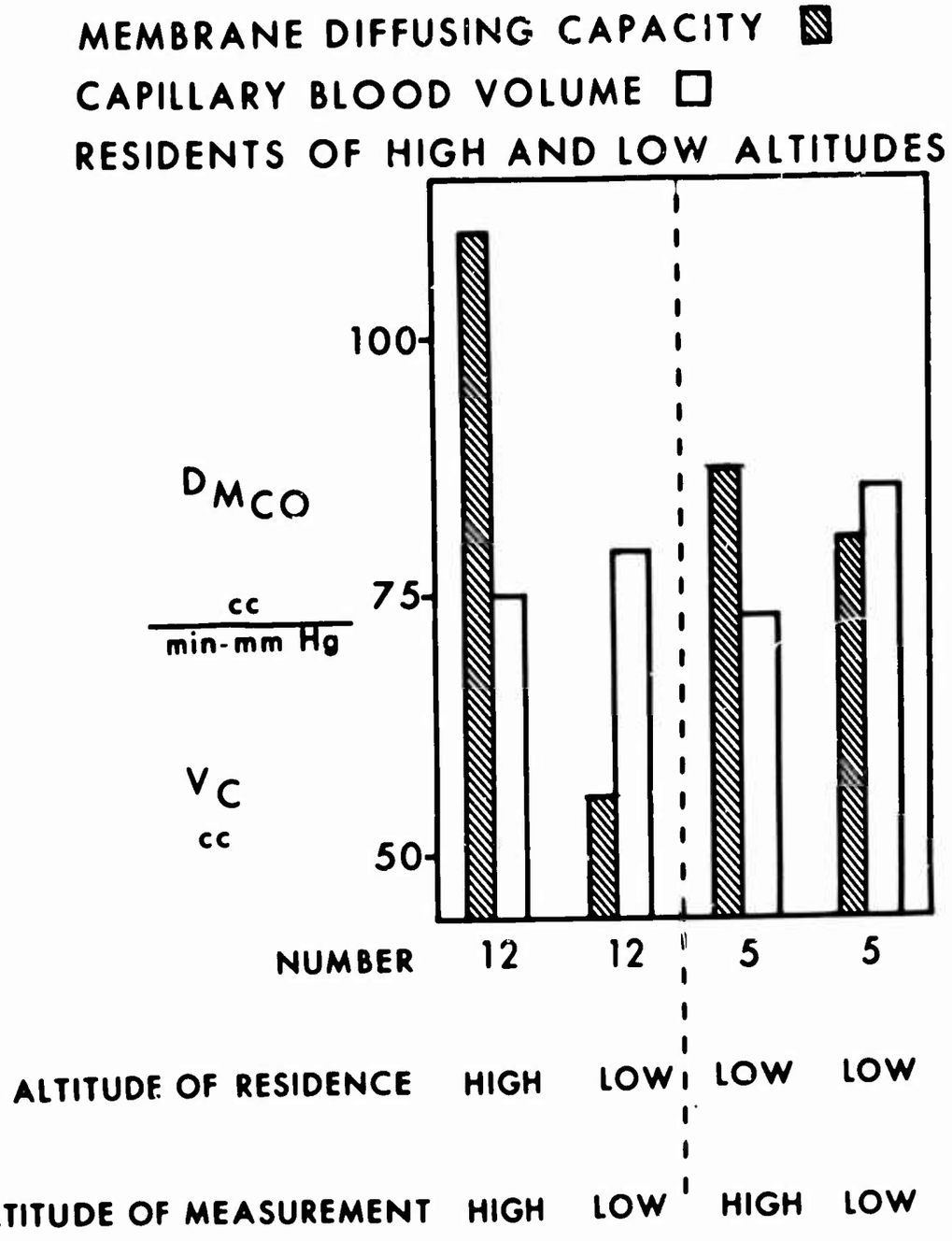


Figure 4

Pulmonary capillary blood volume, V_C and membrane component, D_M, of pulmonary diffusing capacity. Comparing 12 low-altitude residents studied at 200 m, with 12 high-altitude residents studied at 3100 m (left half of figure), D_M is twice as great in the altitude natives, whereas V_C is the same in both groups. When 5 other low-altitude residents were studied at 200 m, and again after 6 weeks at 3100 m (right half of figure), high altitude produced no significant change in either D_M or V_C. (Figure reproduced from Effects of Hypoxia on Respiration and Circulation, D.W. Hatcher, ed., New York/Basel, S. Karger, 1966, by permission of S. Karger.)

oxygenation. Such a potential advantage has not been demonstrable using direct measurements of arterial blood gases. In both altitude residents and in newcomers, the reduced P_AO_2 is reflected in a lowered arterial oxygen tension (P_aO_2). When man exercises, blood passes through the pulmonary capillaries more rapidly, thereby reducing the time available for the transfer of increasingly large quantities of oxygen from air to blood. When this increase in blood velocity is combined with the smaller difference in oxygen pressure between air and blood, complete equilibrium does not occur. Blood leaves the lung less well oxygenated than at rest, the A-a oxygen difference increases, and P_aO_2 falls with an associated decrease in saturation (S_aO_2). (10, 12))See Figure 5.)

DR. DILL: If it has that effect on the saturation of the blood as it leaves the lungs, it will also have an effect in the same direction on the venous blood as it leaves the tissues. I think you should plot a dissociation curve, which you can with these two temperatures if you have them, and see what happens to both venous blood and arterial blood. You have the cardiac output, haven't you?

DR. GROVER: Not on these individuals, but we have it in our subsequent studies.

DR. DILL: Well, at least you can calculate how much unloading there will be for a given venous oxygen tension with a given change in temperature. It's easy enough to re-plot an oxygen curve at the other temperature, the higher temperature.

DR. GROVER: Well, you're perfectly right, it would apply to the venous blood as well.

DR. EVONUK: Are you sure that this effect is not strictly one of pH?

DR. DILL: Yes, that is something you have to take into account in plotting also, but here you have a very different field, between arterial and venous blood.

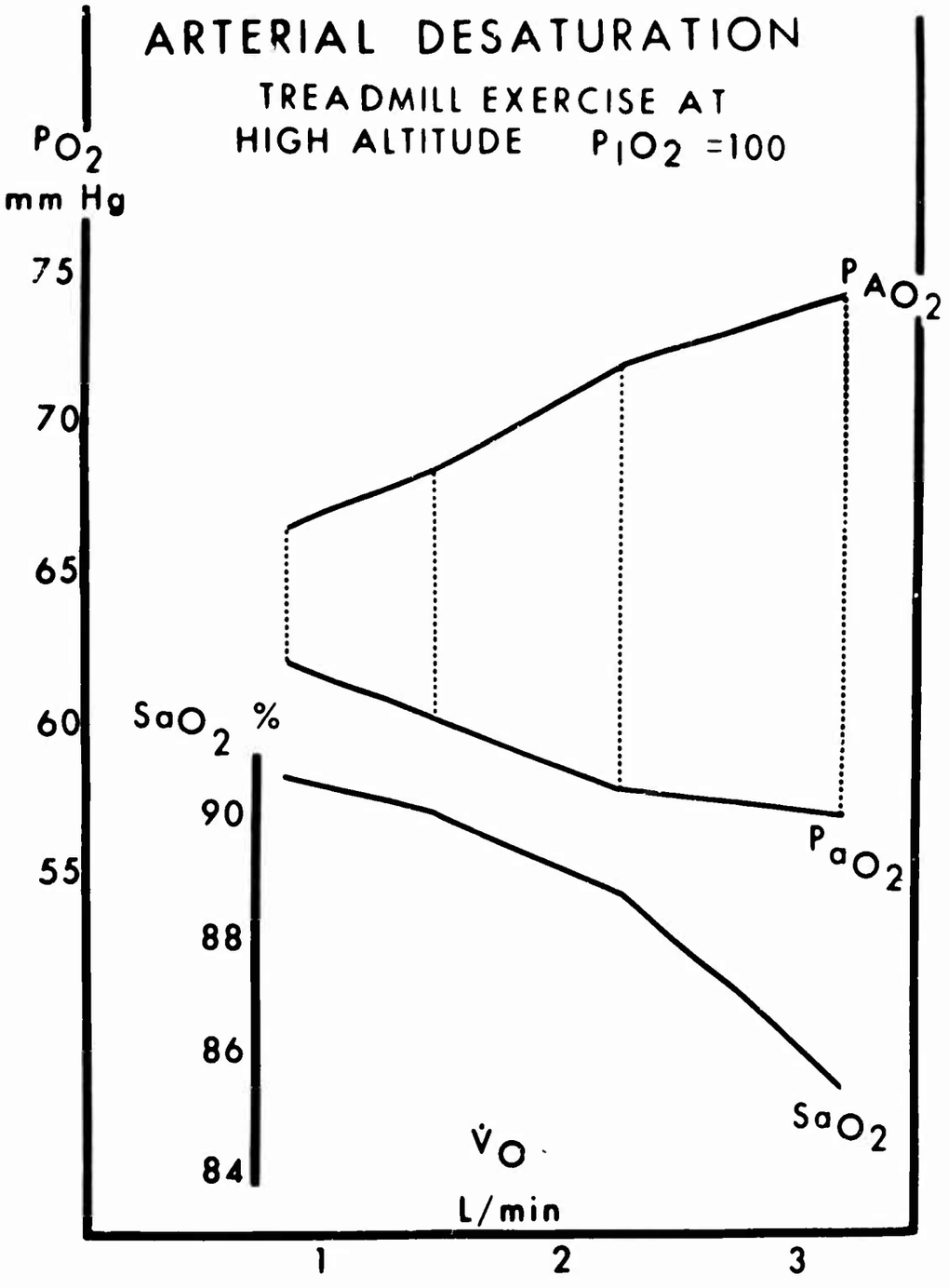


Figure 5

Limitation of pulmonary diffusion during treadmill exercise at 3100 m altitude. As $\dot{V}O_2$ increases in proportion to increasing work loads, alveolar oxygen tension (P_AO_2) rises but arterial oxygen tension (P_aO_2) falls. Hence, the A-a O_2 difference widens progressively, producing a fall in arterial oxygen saturation (S_aO_2). The subject, CW, was an 18 year old male athlete native to 3100 m. (P_AO_2 and $P_aO_2$measured directly at 37.0° C using Radiometer PO_2 electrode; S_aO_2 determined from blood O_2 content and O_2 capacity measured by the method of Van Slyke and Neill).

DR. BRAUER: How about lung temperatures at these ventilation rates? Would you get enough cooling to measure?

DR. GROVER: Well, that's the temperature you would like to have.

DR. BRAUER: Yes, I know. What I'm asking is might the lung temperatures not actually be lower under the conditions rather than raised?

DR. DILL: This is very easy to calculate and it amount to – how much – you've done this, haven't you, Dr. Horvath? It seems to me at the most it can't be more than a tenth of a degree.

DR. HORVATH: That's right, there isn't any great drop.

DR. DILL: Because you have twenty or more liters of blood going through there. If it were cooled a degree you can easily figure what this would do to the body temperatures.

DR. BLATTEIS: What about the speed of the cells as they pass through the lung capillaries?

DR. GROVER: It's suggested that the speed is such that there is not time for equilibration to be achieved, and hence with the increasing speed, the blood leaves progressively less equilibrated with the alveolar gas. That would be in keeping with this decline in arterial tension and widening of the A-a gradient, and it would give a fall in saturation as well.

Cardiac output. Oxygenated blood is delivered from the lungs to the rest of the body by means of the cardiovascular system. With exercise, the muscles are supplied with increased amounts of oxygen by increasing blood flow and by increasing extraction of oxygen from this blood. An increase in muscle blood flow is achieved primarily by increasing cardiac output, and secondarily by

diverting blood away from non-exercising tissues (13, 14). For a given cardiac output, oxygen transport to the body will be reduced if S_aO_2 is lowered. Compensation for this might be anticipated through an increase in cardiac output. When man ascends to high altitude, cardiac output is indeed greater during the first few days. However, this response is only transient, and after 7-10 days, cardiac output is slightly less than at sea level. (15).

Cardiac output, the volume of blood pumped per minute, is determined by stroke volume and heart rate. For any given work load, heart rate is faster at high altitude than at sea level. Maximum heart rate remains unaltered at 3100 m (6), but it significantly reduced at 4500 m in newcomers though not in natives (16). We have determined stroke volume (from measurements of cardiac output by the direct Fick method for oxygen) during steady state submaximal supine exercise in the same individuals at both sea level and at 3100 m (Figure 6) (17). With moderate exercise requiring $\dot{V}O_2$ of 1200-1600 ml O_2 per min, stroke volume was consistently reduced about 10% in both newcomers (10 days) and residents (<3 years at high altitude). Similar findings have been reported using the acetylene and CO_2 rebreathing methods at higher altitudes (15, 18). This reduced stroke volume is not offset by the faster heart rate, so that during submaximal exercise, cardiac output for a given $\dot{V}O_2$ is consistently less at 3100 m (17). Extrapolation of these results to maximal exercise is not justified. Vogel et al. (19) found that both stroke volume and cardiac output were greater at 4300 m than at sea level during maximal upright bicycle exercise. It appears, therefore, that cardiac function in delivering oxygenated blood to working muscles is impaired at high altitude under certain circumstances, as manifest by a reduced stroke volume and/or a reduced maximum heart rate.

Blood oxygen carrying capacity. Hemoglobin concentration determines the oxygen-carrying capacity of blood, each gm of hemoglobin being able to bind 1.34 ml of oxygen. When arterial blood is nearly fully saturated, as is normally the case at sea level, then the actual oxygen content approaches this potential capacity. At high altitude, however, S_aO_2 is reduced, so that the actual content may well be less than 90% of capacity. An obvious compensation for this reduced S_aO_2 would be an increase in hemoglobin concentration.

When man ascends to high altitude, there is an acute shrinkage in plasma volume, producing an increase in hematocrit ratio and hemoglobin concentration. With man's continued residence in the hypoxic environment, red cell production is stimulated and total red cell mass increases. This, together with partial restoration of plasma volume, leads to an expansion in total blood

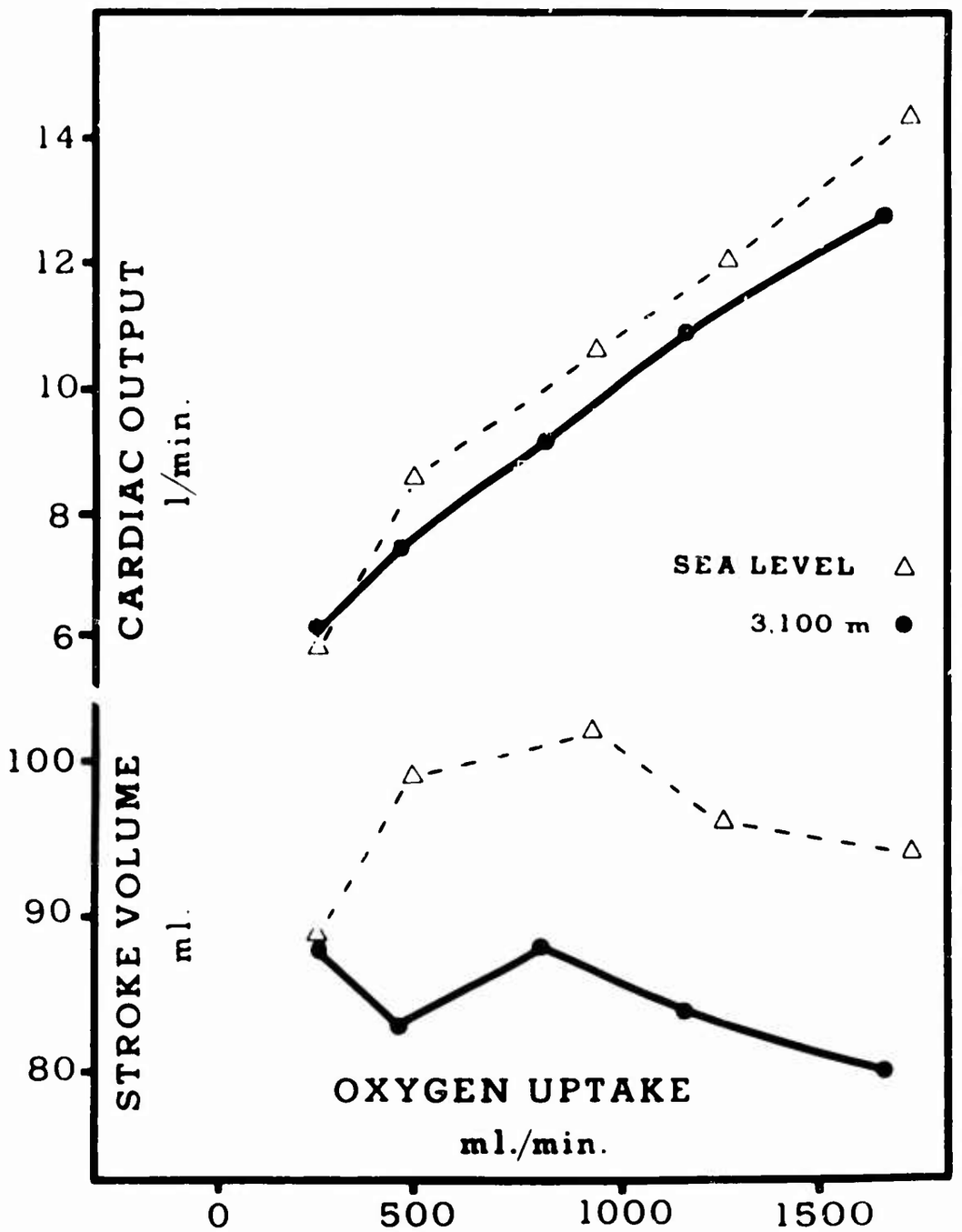


Figure 6
Cardiac output at rest and during four levels of submaximal supine exercise. The same 5 individuals (residents at 3100 m) were studied at high altitude and again after 10 days at sea level. For a given $\dot{V}O_2$, cardiac output (liters per minute) was consistently less at high altitude as a consequence of a significant reduction in stroke volume (ml per beat).

volume reaching about 10% in excess of the original sea level value. After several months of man's acclimatization to 5800 m, the mean hemoglobin concentration was 20.5 gm %, which is an increase of 41% over the control values at sea level (20). This is of the same order of magnitude as seen in native residents at 4540 m, where the hemoglobin concentration was 19.4 gm % (21). Blood oxygen-carrying capacity it thus increased sufficiently to maintain systemic oxygen transport (ml O_2 per minute transported by systemic arterial blood) both at rest and during moderate exercise (Table I). The steepness of the hemoglobin-oxygen dissociation curve then permits the transfer of adequate quantities of oxygen to the tissues, i.e., a normal arteriovenous oxygen difference, in spite of the reduced P_aO_2 (18, 21).

Table I

Systemic oxygen transport in sea-level residents and high-altitude natives. From Banchero et al (21).

	Altitude (meters)	Hb (gm%)	HbO_2 cap. (ml/l)	Arterial O_2 saturation (%)	Arterial O_2 content (ml/l)	Oxygen Uptake (ml/min-m^2)	Cardiac Index (ml/min-m^2)	Systemic Oxygen Transport (ml/min-m^2)
Rest	150	14.8	198	95.7	190	153	3.97	756
	4540	19.4	259	78.4	202	161	3.97	803
Exercise	150	15.4	208	94.9	197	719	6.83	1350
	4540	20.1	269	69.4	186	779	7.70	1430

An increase in hemoglobin concentration to 20 gm % necessitates a rise in hematocrit to 55-60%, which is presumably high enough to increase blood viscosity significantly. While this increase in viscosity should reduced circulatory efficiency, there is no reflection of such an effect in the foregoing measurements of oxygen transport by the circulation in man acclimatized to high altitude. Experiments in dogs, however, indicate that systemic oxygen transport is less than optimal when the hematocrit is increased acutely above 40% (22).

Tissue oxygenation. Sustained exercise requires a continuous supply of oxygen to the contracting muscle cells. This all-important phase of oxygen transport and utilization is poorly understood. Capillary dilatation increases the supply of oxygenated blood to the muscle itself, and the increased blood volume permits the filling of large dilated vascular beds. An absolute increase in capillary density has been observed in the skeletal muscle of some animals residing at high altitude (23). This would reduce the length of the diffusion path for oxygen from blood to within the cell. An increase in muscle myoglobin concentration (24) would further augment oxygen transport. Finally, enzymatic adaptations may occur within the muscle cell, thus altering the pathways for oxidative metabolism in the presence of chronic hypoxia (24).

Thermoregulation

The maintenance of a normal body temperature requires a balance between heat production and heat loss. In a cold environment, the major problem is excessive heat loss. To prevent this, man insulates his body to conserve heat. In so doing, he insulates his body from the environment and creates a warm artificial environment next to the skin. Consequently, "a man in a cold environment is not necessarily a cold man" (25).

When insulation is adequate, then resting metabolism and heat production are not increased. However, if insulation is not adequate, or is removed (as in experimental studies of naked subjects in the cold), then heat production must be increased, and $\dot{V}O_2$ will be well above basal levels (26).

Muscular exercise increases heat production, which contributes to the preservation of heat balance in a cold environment (27). When the work intensity is sufficiently high to prevent a fall in rectal temperature, then the $\dot{V}O_2$ for a given work load is the same whether the environment is cold or neutral (26). In other words, cold per se does not modify the metabolic cost of muscular work.

Work in a cold environment is usually performed with the subject wearing insulated clothing which is often bulky and may be of significant weight. Working efficiency is consequently reduced, and, for this reason, a given work load requires a greater $\dot{V}O_2$. If the cold environment includes snow, the man's efficiency is reduced even more (28). These conditions often exist in high mountain areas where the problem of reduced working efficiency is compounded by a lower working capacity. At great altitudes, the accomplishment of even minimal external work requires exhausting effort.

A significant factor in thermoregulation at high altitude is the intense solar radiation. On clear days, this radiation is very effective in warming the body even when the air temperature is low During the 1960-61 Himalayan Expedition when a party spent the winter months at 5800 m, they realized that because the sun remained well below the zenith, solar radiation fell obliquely and warmed a much greater portion of the body surface area. In addition, the sun was seldom obscured by clouds during those months. A paradoxical situation therefore existed; winter rather than summer was the more comfortable season in the Himalayas in spite of lower air temperatures due to the warmth of solar radiation (29).

While the effects of hypoxia on the performance of muscular work have been studied extensively, there is little information on work performance when hypoxia and cold are combined. Observations in species other than man indicate

that these two stimuli do indeed interact. The cardioacceleration produced by hypoxia in the rat in a warm environment is abolished at 10° C (30). Cats tolerate hypoxia very well if the air temperature is warm and comfortable (31), but they die when the hypoxic environment is also cold (32). Obviously further investigation of man is indicated, for it may well be that while the human threshold for stress can be exceeded by individual factors such as severe cold, severe hypoxia, or severe exercise, stress may also result when these factors are combined, even though each alone is of subthreshold intensity.

DISCUSSION

DR. SALTIN: I want to ask about these Leadville athletes, do they train at sea level or do they perform all their training at 3100 meters?

DR. GROVER: Well, they were at sea level only one week.

DR. SALTIN: Oh, but I mean before, before in their life?

DR. GROVER: They had never been to sea level before.

DR. SALTIN: It's very surprising that it's possible to train at that altitude and reach a maximal oxygen uptake of 45 milliliters, 45, 46 or somthing like that, and then go down to sea level and get 66 milliliters, because when you train at altitude, then you train heart circulation and perhaps distribution of fluid to the muscle, but you don't train the last part of this link of transportation of oxygen, I mean in the muscle cells, mitochondria. They have never before reached that high?

DR. GROVER: As far as we know they never have, and this is not a single measurement. We had several measurements on each individual and we were surprised at getting 66 at sea level, because these were just high school kids who engaged in sports. They were drawn from a relatively small pool of individuals, it wasn't a highly select group, and yet those figures for oxygen uptake are of the

same order of magnitude as the track team from Italy that participated in the Rome Olympic Games.

DR. BUSKIRK: But the picture in mitochondria could still be the same. Why would that have to be different? I don't understand your point here.

DR. SALTIN: My point is that the muscles have never used so much oxygen before, and that's very substantial. It means that it is possible to get a better performance capacity without transporting the maximal amount of oxygen through the whole system. The point is to try to explain why they are lower when they come back to sea level. I found the same in my athletes too, when they came to Sweden they were 5, 6 percent lower than before they had been up at altitude. You may say that the reason is that they haven't performed the same amount of training – that perhaps can be true. If you take a top athlete and measure when he is at peak and when he is out of shape, I think you will find almost exactly the same maximal oxygen uptake; at least that is what we have found in Sweden. Several years ago I tried to compete myself. I had 5.8 liters maximum oxygen uptake, and I trained almost every day; now I exercise once a week perhaps and I have still 5.6 liters. I think other factors are involved to explain the reduction in maximal oxygen uptake when top athletes return to sea level.

DR. HORVATH: I'm glad you brought this point up, Dr. Saltin, because there has been a real difference of opinion as to how much improvement in maximal oxygen uptake one can get. I know that there are people in this country who feel that you can improve maximal oxygen much more than any other facet. It is nice to see that you at least agree with my concept that the major benefit of training per se is the ability to work for a longer period of time at a greater percentage of maximal oxygen uptake. Now, there is of course no question that as man ages the maximal oxygen uptake will decrease and the reason is relatively unknown at present, but within a certain period of time maximal oxygen uptake ought to stay relatively constant. It is the percentage that is being utilized which is important. If a man can walk for over two hours at 93 percent of his maximal oxygen uptake, now that's a terrific performance. I was really glad to hear you say that, because I don't think many of us are thinking in these terms.

DR. DILL: Have you seen the old paper, Robinson and Harmon, a training study on college students where there was an increase – I have forgotten the exact amount; I think it averages between ten and fifteen percent, but it was considerably more than that in a few individuals. Ten or twelve college students were trained very strenuously as though they were out for the mile run over a period of about six months. There was an increase, no question about it. Have you seen the recent paper of Klausen's? He used the indirect Fick procedure on several of us at high altitude, three of us during the 12 days of acclimatization, and there are very considerable changes. At what stage in acclimatization was this man whom you have just reported, just studied here at Leadville?

DR. GROVER: After ten days.

DR. DILL: Well, Klausen found in himself and Phillips, who were roughly the same age, a considerable increase on the second day in stroke volume and a greater increase in cardiac output on the first day, after which the stroke volume returned to sea level values. At the end of ten or twelve days it dropped a little below sea level values. It is important to note the day at altitude.

DR. GROVER: I neglected to mention that, but we deliberately selected ten days to avoid the initial increase that has been found. If you take that into account I think that that data is consistent with what we found.

DR. BRAUER: What do we know about the payoff of the oxygen debt, which I take it is being incurred during the terminal end of the Balke test? Has anybody done lactic acid, blood lactic acid as a function of time at the end of the Balke test during recovery? Have you a report on this?

DR. REYNAFARJE: Not exactly.

DR. BRAUER: I am thinking of recovery.

DR. EVONUK: Have you done any diffusion capacity tests at altitude during work?

DR. GROVER: Yes.

DR. EVONUK: What were your figures?

DR. GROVER: Actually the figures I put on the board were measured at altitude.

DR. BLATTEIS: That was 46 and 47 at altitude?

DR. GROVER: No. At altitude. This is the steady-state method, during treadmill exercise requiring an oxygen uptake about fifty percent of maximum, without any correction for the fact that hemoglobin is not fully saturated with oxygen. These are the figures we got.

DR. EVONUK: They are quite high.

DR. GROVER: They are representative, although we know that diffusing capacity does rise with exercise and there is some disagreement. Some people believe that diffusion capacity is higher in athletes than non-athletes, so I think considering those facts plus the fact that there may be a methodological error for not taking into account the desaturation of the hemoglobin – these figures are deceptive I think.

DR. BRAUER: This might explain why the heart rate did not change – because the altitude was not high enough.

DR GROVER: I suspect it was not high enough.

DR. BRAUER: Yes, because it is amazing that the heart rate did not change.

DR. SALTIN: But that fact takes into account only the maximum heart rate, I mean still it is surprising that the submaximal heart rate did not decrease during this stay at altitude. That is to me one reason why you can think of that they were a little bit more and more untrained during their stay up there, but I don't know really. You don't show any decrease at all in submaximal heart rates; of course that does not depend on the altitude.

DR. BUSKIRK: This doesn't happen in everyone either, does it?

DR. GROVER: Oh, no.

DR. EAGAN: Dr. Grover, was there any change in body weight in either group when they moved from the one level to the other?

DR. GROVER: There were small changes. This was not a factor that we paid particular attention to, so I can't say anything very specific about it.

DR. EAGAN: I wondered if this decrease in $\dot{V}O$ maximal, I'm referring to sea level, might be due to changes in weight factor. It would have to be a considerable change.

DR. GROVER: Well, that was a 15 percent reduction. I am sure body weight wasn't down that much, in fact I would guess, if anything, that the weights would have tended to be lower at high altitude than on return to low altitude.

DR. EVONUK: I have one question: I am trying to equate kilogram meters of work on a treadmill – just to open this up for discussion – and everytime I see a paper referring to kilogram meters of work on a treadmill, the figures are considerably higher than those which you see for a bicycle ergometer. Is this an actual measure of kilogram meters of work per minute on a treadmill?

DR. BRAUER: It's actually underestimating it, isn't it, because on that thing your horizontal motion would show up as zero.

DR. GROVER: Zero work.

DR. BRAUER: And God knows if you walk 18 miles horizontally it's not zero work.

DR. DILL: This is calculated in different ways, sometimes you subtract the cost of standing, other times you subtract the cost of walking horizontal rate, so you get a different answer depending on how you calculate it. Balke's formula gives a fairly good measure of oxygen consumption in his test, which is walking, and the range in efficiency in walking is not very great. It's greater than on the bicycle, but on running it's enormous, it can be plus or minus 20, 30 percent in running on a treadmill. You are jumping up and down: the less skillful the man is, the more he jumps up and down.

DR. HORVATH: I think it might be helpful to recall that old Carnegie publication on the speed of walking, different grades. Most people I think have forgotten it. Do you remember it?

DR. DILL: Yes, Benedict Cathcart is one and the other is H.M. Smith, that's on horizontal and grade walking. This was a Carnegie publication dating back around – one of them, I think, in 1912 and the other 1918. I'll tell you where you will find those, in the introductory chapter I am writing for the book that Johnson and Buskirk are putting out, a new edition of Science and Medicine in Exercise and Sports, and if they accept the illustration – I have an illustration in there of the first treadmill in this country. It is not the first in the world, by any means, because they had them in Germany long ago, but the Carnegie Nutrition Laboratory had the first treadmill in this country which we borrowed in the Fatigue Lab as a model.

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WORK AND OXYGEN DEBT AT ALTITUDE
— BIOCHEMICAL ASPECTS

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During physical work, a large proportion of chemical energy is transformed into mechanical energy. The transformation requires the presence of an adequate amount of oxygen at tissue level; otherwise, the fuel used as a source of chemical energy will be only partially burned and intermediary products will accumulate, leading very soon toward a state of disturbed homeostasis and physical fatigue.

When newcomers work at high altitude, their work endurance is considerably decreased, probably due to incomplete combustion of metabolites through oxidative pathways, since oxygen availability is greatly reduced. In the high-altitude native, however, physical fatigue is delayed and the accumulation of lactate and pyruvate in peripheral blood is far below the level observed in the sea-level resident after the same degree of work.

In this presentation we will show data establishing physiological and biochemical differences between the high-altitude and the sea level native, during work and recovery. Data from men at rest will also be presented as evidence of a different pattern of enzymatic and metabolic activities.

Experiments were carried out in Lima, at sea level, and in Morochcha, at 4,540 m altitude. Human beings and laboratory animals, native to both altitudes, were used as subjects and assayed in their own environments.

Exercise was performed on a motor-driven treadmill. Expired air and blood samples were collected during the entire experiment, but more frequently at the beginning of exercise and recovery. Douglas bags were used for gas collection; Tissot spirometers for volume measurements; the Scholander apparatus for gas analysis; and the methods of Barker and Summerson (1) and Friedmann and Haugen (2) for blood lactate and pyruvate analyses respectively.

Oxygen Consumption during Exercise

The excess oxygen uptake during exercise was, in general, lower in the altitude native than in the sea-level resident. Figure 1 shows that the excess

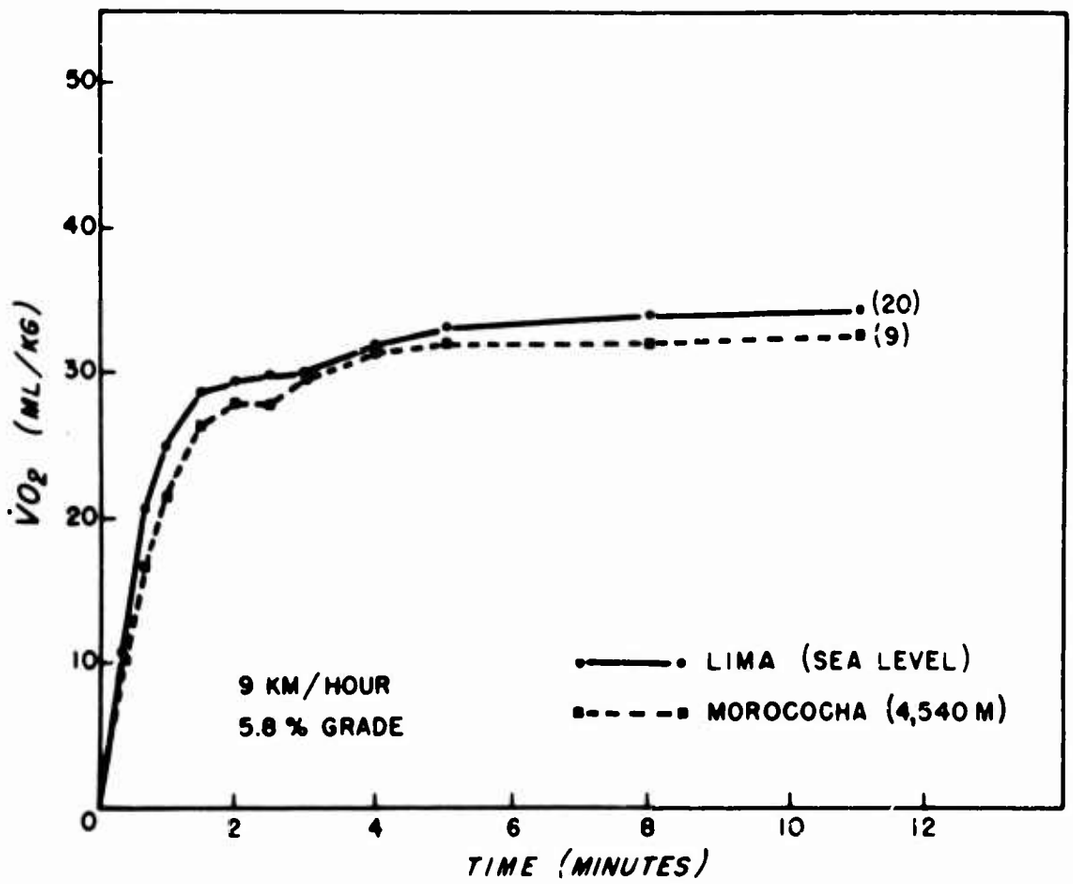
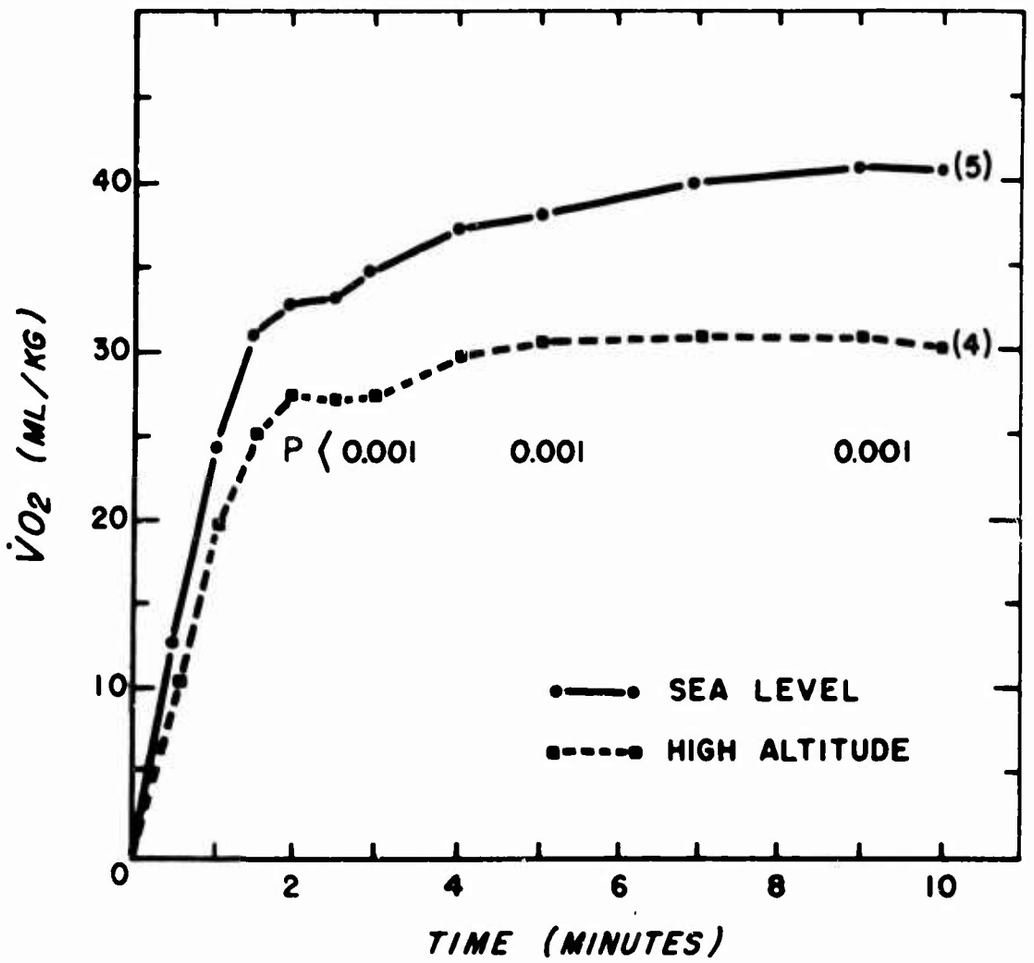


Figure 1
Kinetics of oxygen consumption during exercise at high altitude and sea level. (Figures in parentheses represent number of subjects studied).

oxygen consumption during a run for 15 min at 9 km/hr, on a 5.8% grade, is practically the same in the high-altitude and sea-level groups. It is not infrequent, however, to find groups of high-altitude subjects exhibiting an oxygen consumption significantly lower than that observed in sea-level controls, as shown in Figure 2, after a run at 12 km/hr for 10 min on a 5.8% grade.



12 km/Hour; 5.8 % Grade.

Figure 2

Kinetics of oxygen consumption, in sea-level and high-alitute subjects.

DR. DILL: Was this wholly aerobic for all individuals?

DR. REYNAFARJE: Yes.

DR. DILL: They were in a steady state?

DR. REYNAFARJE: In a steady state, yes. This we will show later based on lactic acid.

DR. BUSKIRK: Is this recent work, or does this go back to others?

DR. REYNAFARJE: No, this is my data. My problem was to establish if the high altitude people really have a lower oxygen consumption, and I was trying to check this, because there was not consistent data, and as you will see in the next slide – we cannot conclude this.

Since the magnitude of oxygen uptake is a function of work load, and the rate of increment in oxygen consumption may not be the same in both groups, experiments were designed in order to measure this rate as a function of work intensity. In Figure 3, the oxygen uptake at the steady state period was plotted

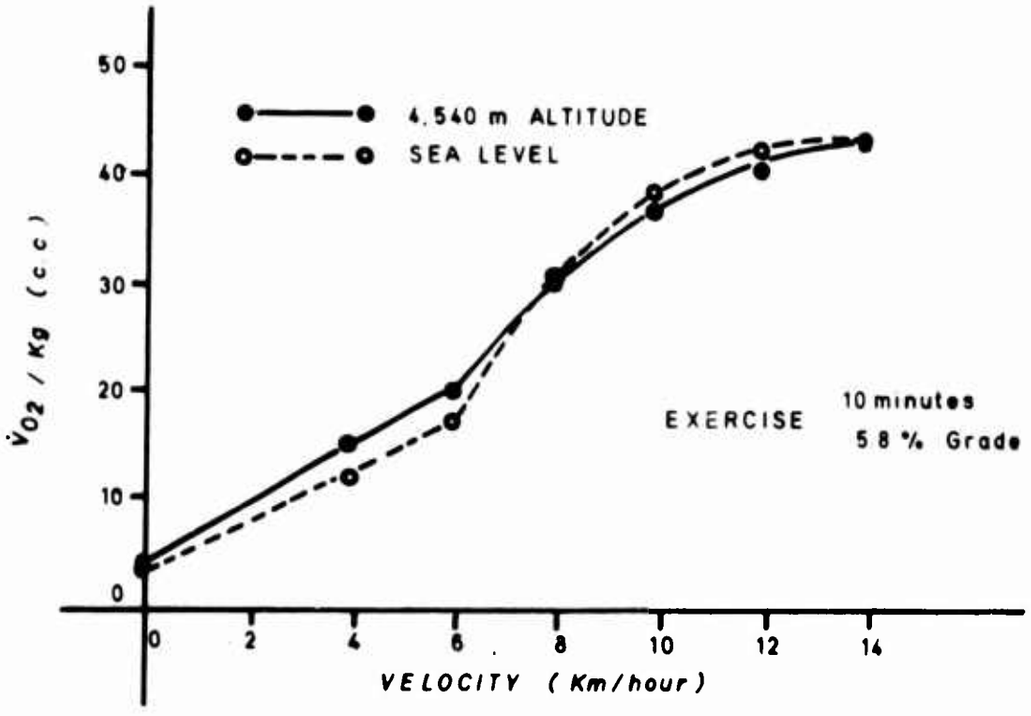


Figure 3
Oxygen consumption (in ml/kg of body weight per min) during the steady state period, as a function of work load.

against the velocity of walking or running, for 10 min on a treadmill placed at a 5.8% grade. Each experimental point represents the average value of at least

eight subjects, except for the exercise at 4 and 6 km/hr, where only four or five subjects were used. It may be seen that at the lower work loads the oxygen consumption is even larger in the high-altitude native, but above 8 km/hr, the amount of oxygen consumed by the native tends to be lower than at sea level, although the difference was not statistically significant.

DR. DILL: This goes up to the anaerobic range, doesn't it, at the end?

DR. REYNAFARJE: Yes, especially for the sea level side, they show a plateau, but in the high altitude there is no evidence of a plateau.

Oxygen Consumption during Recovery

It has been previously reported (3) that the payment of the oxygen debt is slower at altitude. Figure 4 shows the oxygen consumption during the recovery period from the exercise at 9 km/hr. It may be seen that in the sea-level group the oxygen uptake decreases continuously, during the 30-min recovery period, approaching pre-exercise levels. At altitude, on the other hand, the oxygen consumption decreases only during 15 or 20 min. From this moment the oxygen uptake remains nearly as a plateau, but far above the basal level.

Figure 5 shows the same phenomenon after the run at 12 km/hr. It appears clearly that the high-altitude group of subjects comes down to a plateau much sooner than does the sea-level group. If the oxygen debt is calculated, taking as reference the basal level, it would appear that the high-altitude subject has a larger oxygen debt than does the sea-level resident, especially if a prolonged recovery period is considered. Obviously, this procedure of measuring the oxygen debt is not quite correct because it includes the post-exercise increment in the basal metabolic rate, which evidently is much larger in the altitude native. When the oxygen debt is evaluated, taking as reference the end of the recovery period, where the oxygen uptake becomes a plateau, the altitude native has a smaller oxygen debt, and this is paid faster than at sea level. After the run at 12 km/hr for 10 min, at a 5.8% grade, the magnitude of the debt was 2.26 l for the high-altitude and sea-level groups, respectively.

DR. HORVATH: What is the longest period of time that you have followed in recovery?

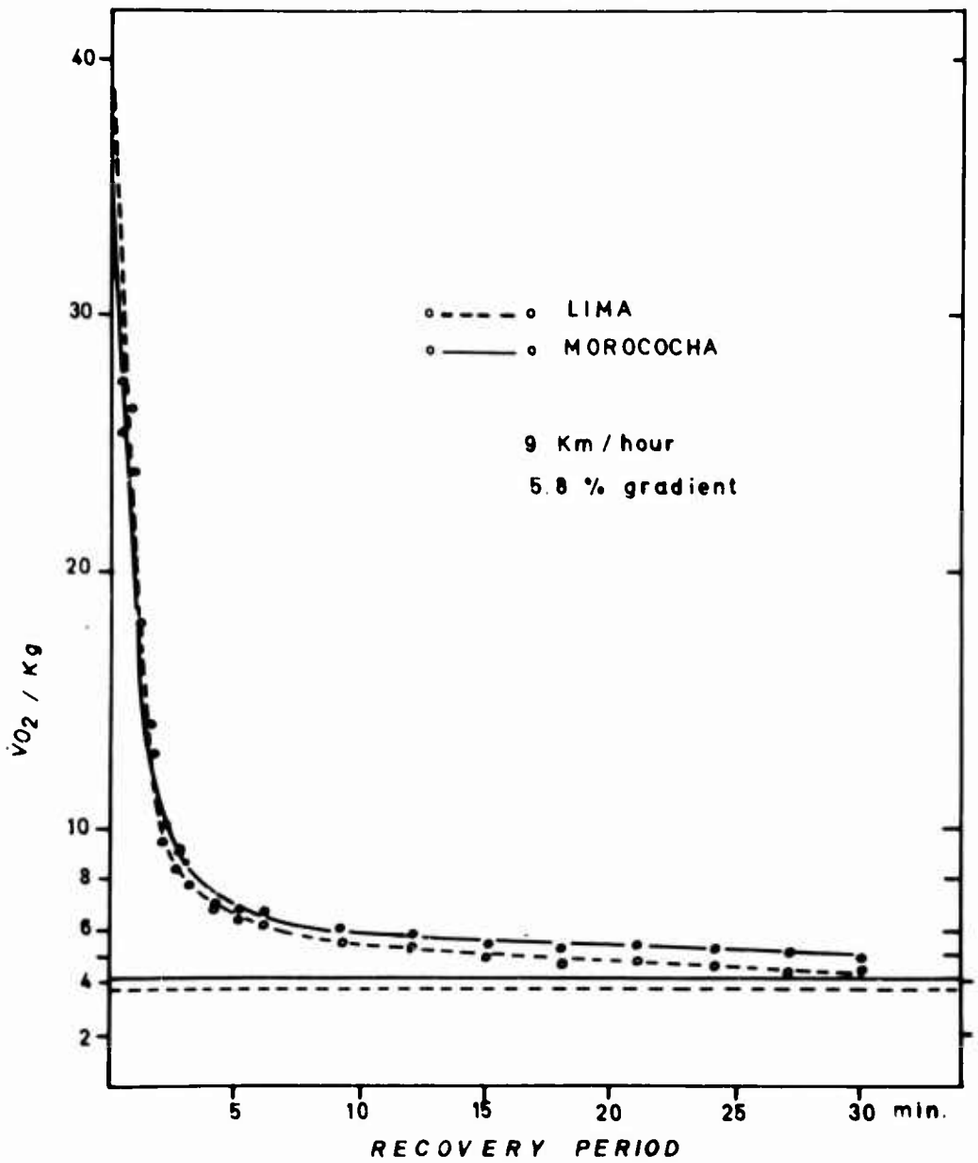


Figure 4
Oxygen consumption during recovery, in 20 high-altitude natives and 9 sea-level residents.

DR. REYNAFARJE: Thirty minutes – which is not good enough – we see that at sea level it is still decreasing. This would be good for high altitude people but it is not enough for sea level people. When we calculate the oxygen debt by integration, when this reaches a plateau, the difference in the oxygen debt is even larger, because high altitude does not show a plateau.

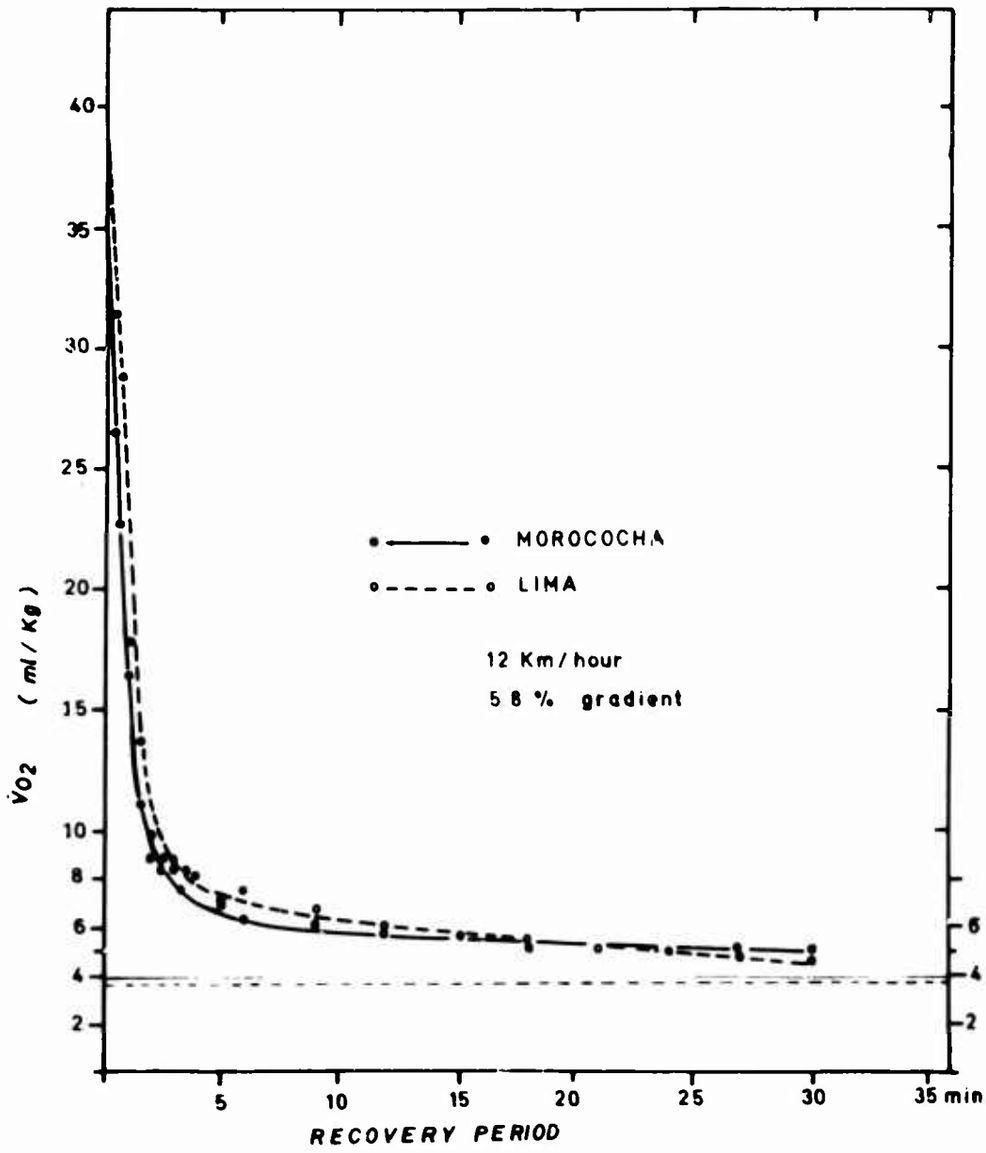


Figure 5

Oxygen consumption in 4 natives from Morococha and 5 from Lima.

DR. CHIODI: Do you have some explanation for that high level of residual oxygen consumption in the natives?

DR. REYNAFARJE: I don't have any, and I would like to ask about

this, because I don't know if the oxygen debt is all this space below the curve, or if it's an artifact. I don't know.

DR. HORVATH: By any chance have you ever measured the basal or standard metabolism of some of these subjects on he day afte; the work period?

DR. REYNAFARJE: We have.

DR. HORVATH: Is it elevated then too?

DR. REYNAFARJE: Well, there is a little difference. The high altitude people have higher oxygen consumption in basal conditions -- and this is significant.

DR. HORVATH: After work, you mean?

DR. REYNAFARJE: No, before work, resting condition, basal conditions.

DR. WEIHE: After work or in general?

DR. REYNAFARJE: After work, no.

DR. HORVATH: I think this would be very interesting if this lasts a long time.

DR. REYNAFARJE: Dr. Hurtado's group has shown for many years that the oxygen debt at high altitude was lower. He computed for only 15 minutes and we take this into consideration, but he reported also that the oxygen debt

was paid in a longer period of time at high altitude than at sea level. We will see that this is not true when we analyze this oxygen consumption during recovery in a little more detail.

Figure 6 shows a detailed analysis of the oxygen debt payment process

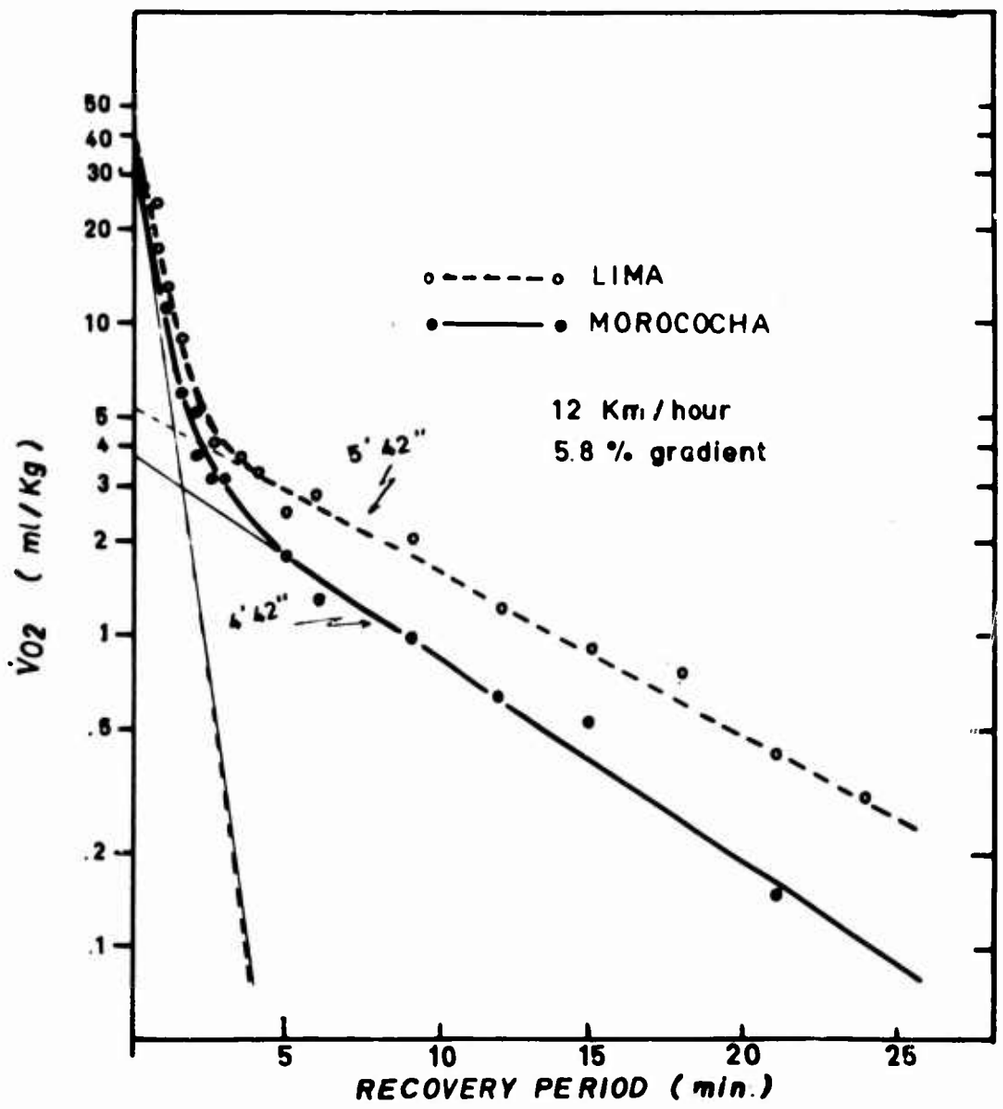


Figure 6
Kinetics of the oxygen debt payment process. (Same data as shown in Figure 5).

when the oxygen uptake at the end of the recovery period (30 min) is taken as reference. It may be observed that the alactacid fraction (4) of the oxygen debt is of the same magnitude in both groups of subjects and it is paid at the same rate. The lactacid fraction, on the other hand, is smaller in the altitude native,

and contrary to what was previously reported, it is paid faster than at sea level. One may conclude from this that any difference between the oxygen debt at sea level and high altitude is due mainly to the lactacid fraction.

DR. BRAUER: I have a recollection that the typical highlands Indian walking has a rather peculiar gait which is quite distinct from mine or yours,a rather more shuffling gait with a minimum of waste motion, and my question therefore is a rather obvious one: would the difference in gait in fact give you rather considerable differences in efficiency between your highlands Indian and the lowland natives?

DR. REYNAFARJE: We have observed the same thing, especially when they run on the treadmill. They almost don't move, they run very smoothly, whereas at sea level they run roughly, and maybe that is the reason for the low oxygen consumption during exercise and recovery. I want to show you this because as Dr. Horvath says, oxygen consumption is not so different at high altitude and sea level, whereas the rate of lactate combustion, its disappearance from blood is much different, as we will see in both groups.

DR. BUSKIRK: Is that difference significant between those two lines?

DR. REYNAFARJE: It is significant and the greater the work load, the more significant is the difference.

DR. BUSKIRK: How many subjects in each group?

DR. REYNAFARJE: There were only five subjects in each.

Changes in Blood Concentration of Glucose, Pyruvate, and Lactate during Exercise and Recovery

The resting level of glucose in peripheral blood has been reported lower at

high altitude than at sea level (5). A considerable increment in glucose concentration after exhausting exercise has been found in subjects at both altitudes, although it is more pronounced at sea level (3, 6).

Figure 7 shows values of glucose concentration in blood after 10 min of

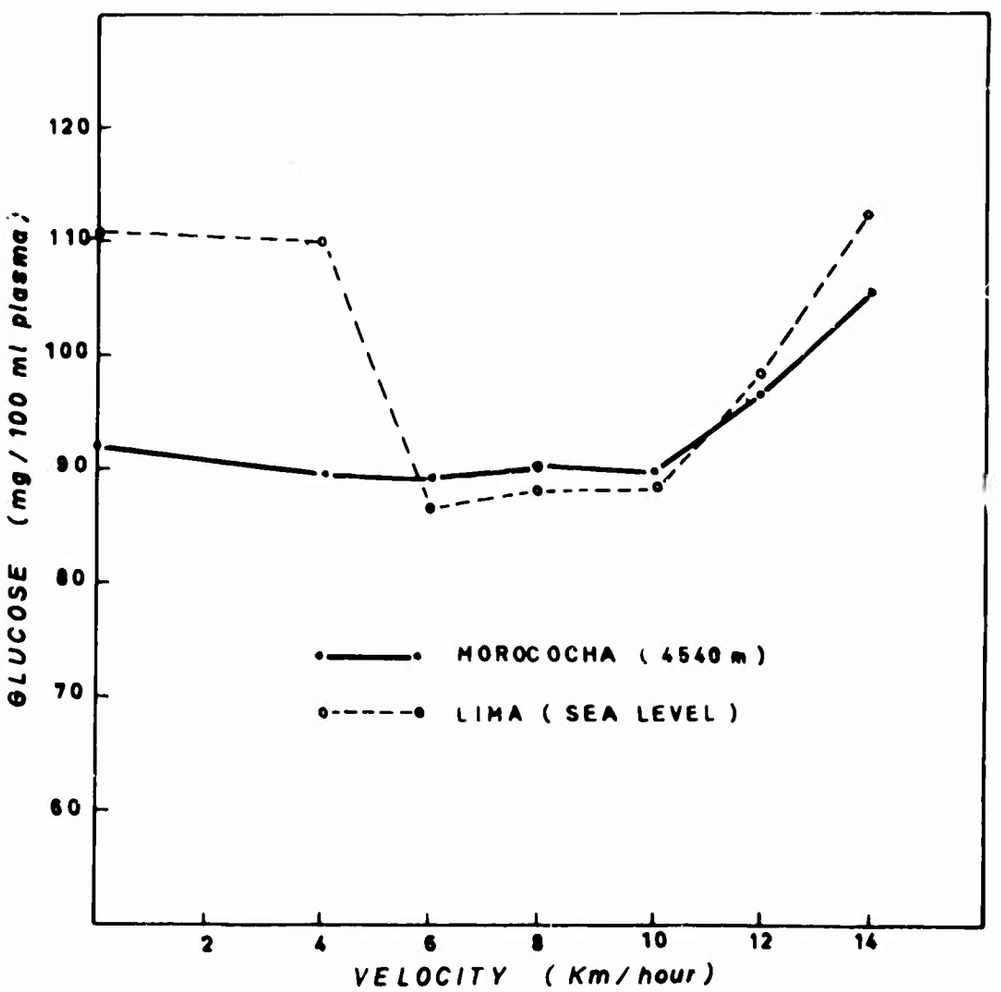


Figure 7
Glucose levels in venous blood as a function of work load. (Same subjects as those described in Figure 3; see text.)

running at different velocities, on a 5.8% grade. It becomes clear that in the high-altitude native, the concentration of glucose is not affected by exercise up to 10 km/hr. After this point the concentration of glucose in peripheral blood increases linearly with the work load.

In the sea-level resident, on the other hand, the change in glucose concentration with work intensity is quite different. Walking at 4 km/hr does not affect the basal level of glucose concentration. Above this velocity, and up to 10 km/hr, the concentration of glucose decreases significantly, becoming even

lower than the level observed in altitude subjects. Above 10 km/hr, glucose concentration also increases as a linear function of work load, but at a faster rate than in high-altitude natives.

DR. BUSKIRK: This difference in resting glucose, I know Picon has documented this too. Have you tried this after giving 200 grams of glucose in the previous meal and putting the people under constant nutrition with respect to tests like this?

DR. REYNAFARJE: I haven't.

DR. BUSKIRK: Well, I am just wondering – I'd expect nothing to happen with respect to the exercise, but I am just wondering about this consistent difference they see in resting glucose and it's marked.

DR. CHIODI: Did you try a longer time? I mean after 20 minutes of exercise do they keep at that higher level or does glucose go down again or what?

DR. REYNAFARJE: During rest?

DR. CHIODI: No, during exercise.

DR. REYNAFARJE: I did it only with one type of exercise, which consisted of running at the same gradient – about six percent – but during twenty minutes.

As far as pyruvic acid is concerned, it may be seen in Figure 8 that there is no increment up to 6 km/hr. For higher velocites pyruvic acid increases at both altitudes, but to a larger extent in sea-level subjects.

The lactic acid accumulation during exercise is probably the resultant of a dynamic equilibrium between its production and its combustion to CO_2 and

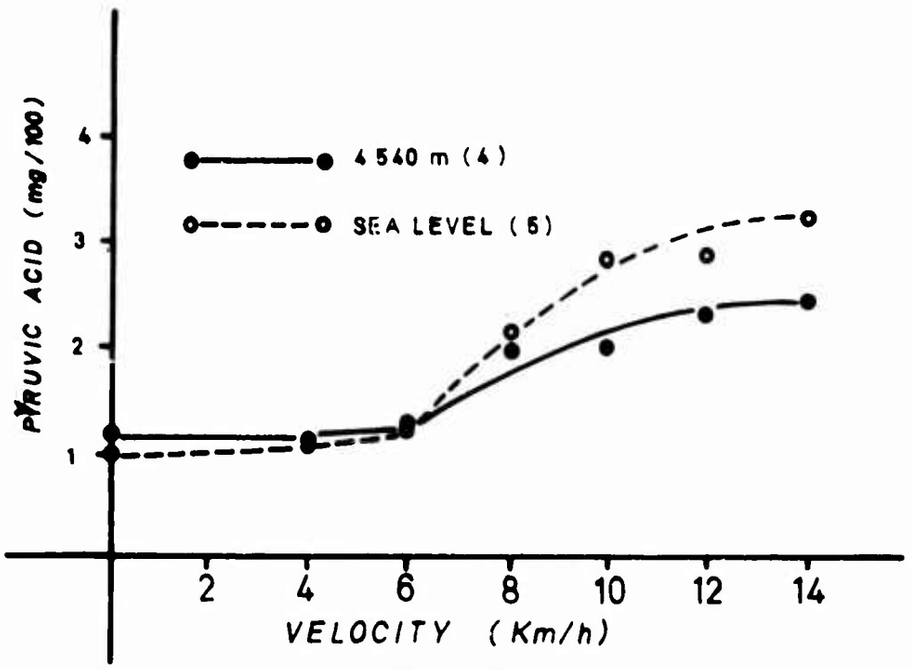


Figure 8

Changes in pyruvic acid concentration during work of different intensities.

water. For a given work load, the rate of lactate production through glycolitic pathways must be constant and independent of oxygen supply (dl/dt = K). In other words, the rate of lactate production during work carried out in anaerobiosis must be linear. In fact, this is what is observed at the beginning of exercise when oxygen utilization at the tissues level is greatly limited by delayed adaptation of the various mechanisms involved in oxygen transport.

DR. IRVING: Do these two groups, the people from sea level and from the mountains, were they both about comparable as far as athletic or activity types are concerned? Were they both moderately accustomed to walking or running?

DR. REYNAFARJE: Well, at sea level they are medical students, and the high altitude native is accustomed to walking the hills so maybe he is better prepared for that type of work. There may be a difference.

DR. IRVING: Was there also a different point in their speed at which the mountain people and the sea level people broke from a walk into a run or

actually changed gait? I suppose at eight kilometers they would just be beginning to exceed walking speed?

DR. REYNAFARJE: Yes, this is a very low workload for them.

DR. SALTIN: What is the maximal oxygen in the sea level group?

DR. REYNAFARJE: Well, it's about the same. We haven't found a great difference in maximal oxygen uptake.

DR. GROVER: When you say there's no difference, do you mean that the medical student at sea level has the same maximum as the altitude native at altitude?

DR. REYNAFARJE: At altitude, right.

DR. CHIODI: Per unit body weight.

DR. DILL: It would appear from this that the Morocochan with this lower lactic acid has a higher capacity for oxygen consumption. Was this the highest rate of work you attempted, 12 kilometers per hour?

DR. REYNAFARJE: Yes.

DR. DILL: Well, it appears to be very close to maximum for those at Morococha. Since the lactate is only 33 milligrams percent, it seems likely that they could accomplish a higher level of oxygen consumption.

DR. REYNAFARJE: But at this work load we haven't found much difference in oxygen consumption.

DR. DILL: I agree, but if you had gone to a higher workload you might have found the ones at Lima had not reached a higher oxygen consumption, whereas the ones at Morococha would reach a higher level.

DR. REYNAFARJE: Right, of course as I say these levels of lactic acid in the blood are the result of dynamic equilibrium, reproduction and combustion.

DR. DILL: Yes.

DR. REYNAFARJE: And we will show later that the combustion in the higher altitude people is much more effective – is much better than in those from sea level.

DR. CHIODI: Did you try exhausting the high altitude men to see how high they could get their lactates?

DR. REYNAFARJE: Well, you see they have reached a plateau here. I want to show on the next slide, this is a type of experiment we have done also, Dr. Buskirk, to show how lactic acid increases at both levels with the workloads. You can see that up to six kilometers per hour there is no increment in lactic acid.

Lactate disappearance through oxidative pathways, on the other hand, must be a function of the amount of oxygen arriving to the tissues ($-dl/dt = K'O_2$). Since this is an exponential function of time, the accumulation of lactic acid must be also an exponential function of time, until full oxygen supply is attained. Figure 9 shows the accumulation of lactate in peripheral blood during a run at 8 km/hr.

This type of exponential curve was found in every subject, at various intensities of work, as can be seen in Figure 10, during a run at 12 km/hr. It should be pointed out that the work load was not exhausting within the time period that it was performed. As for pyruvic acid, the accumulation of lactate in blood is always lower in the altitude native than in the sea-level control, but the difference becomes larger as the work load increases. In Figure 11 the concentration of blood lactate at the end of 10 min of exercise on a treadmill at

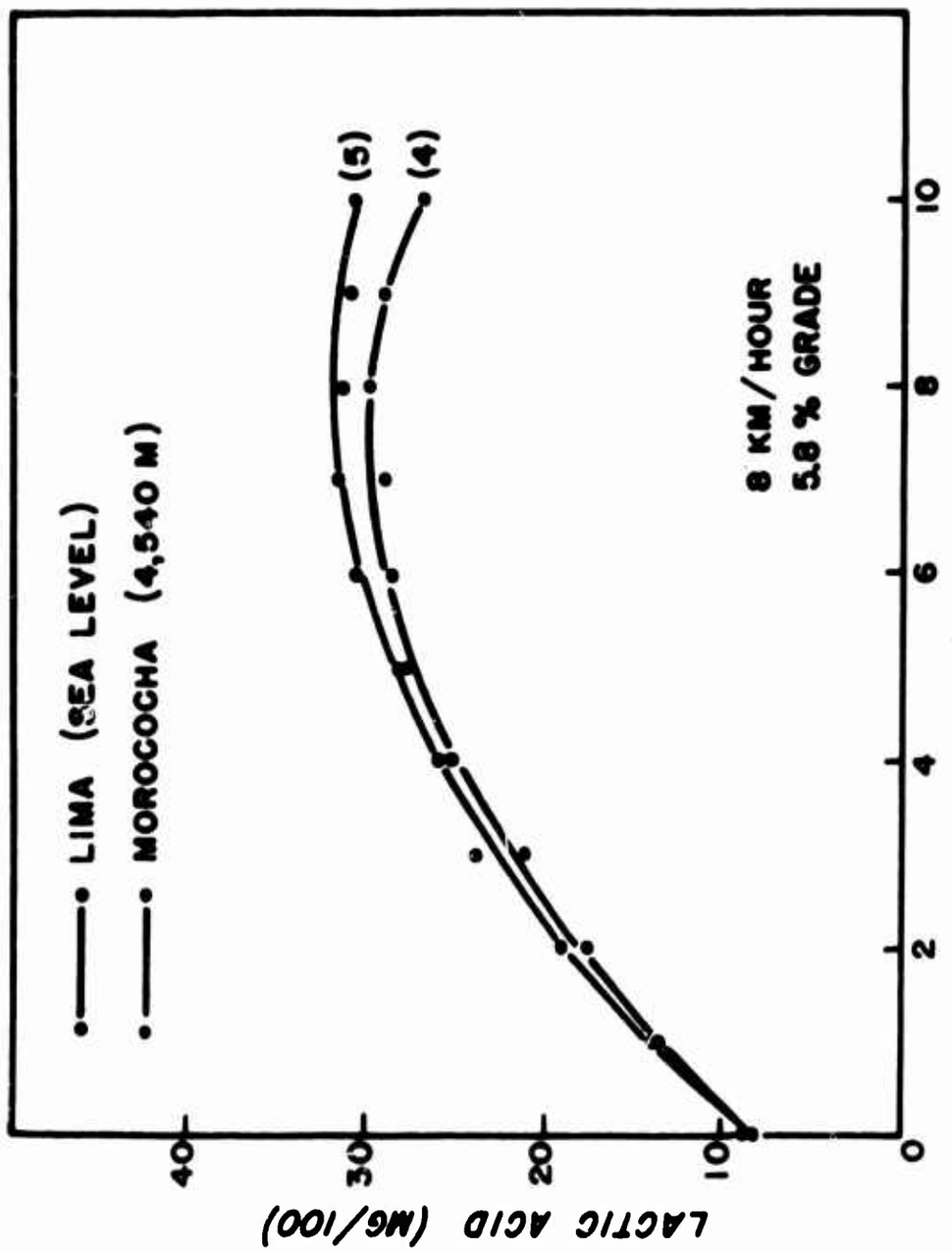


Figure 9
Kinetics of lactic acid accumulation in peripheral blood. . (Upper curve corresponds to 5 sea-level subjects.)

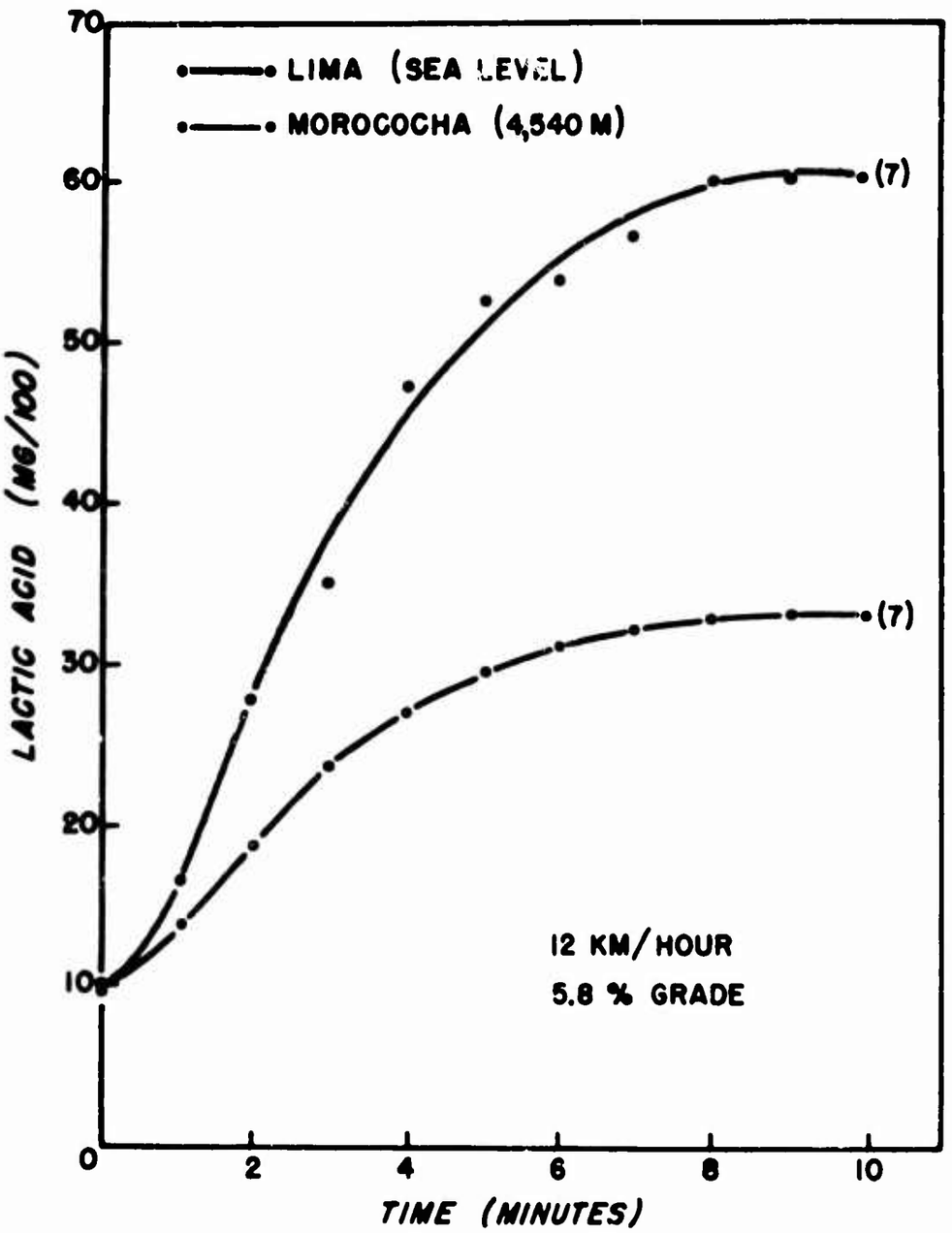


Figure 10

Kinetics of lactic acid accumulation. (Upper curve corresponds to 7 sea-level subjects.)

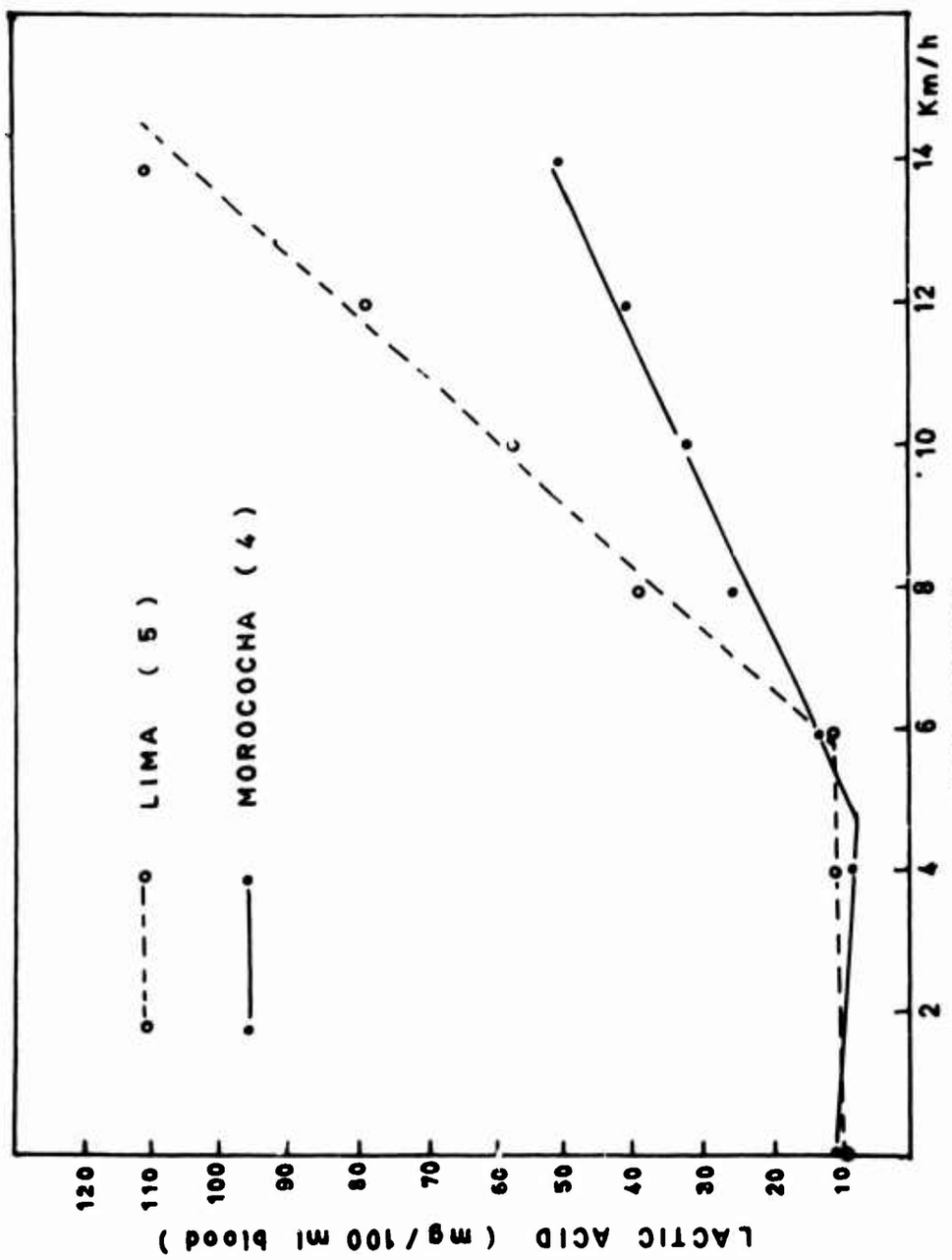


Figure 11
Changes in lactic acid concentration in peripheral blood as function of the work load.
(Figures in parenthesis represent the number of subjects studied.)

5.8% grade was plotted against velocity of running. No lactic acid accumulation is observed until the speed of running is above 6 km/hr. From this point on, lactic acid increases linearly as a function of work load, with a slope which is about twice as much at sea-level as at altitude. Differences are statistically significant above 8 km/hr.

The lower levels of lactate and pyruvate in the blood of high-altitude subjects during and immediately after work could not be explained simply on the basis of reduced production. It is more likely that it is due to greater combustion, as may be inferred from the results presented in Figure 12.

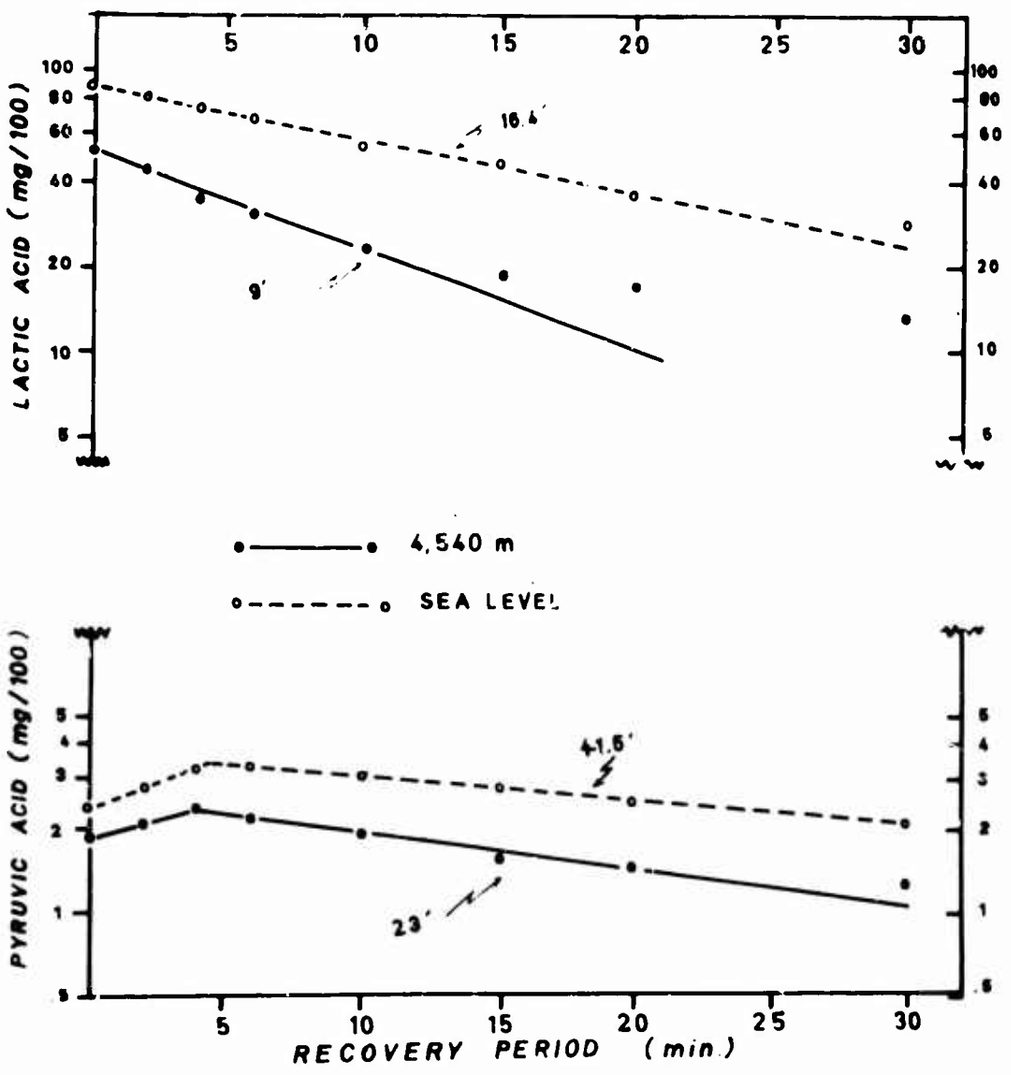


Figure 12
Kinetics of lactate and pyruvate disappearance from arterial blood during the recovery period from an exercise at 9 km/hr. (See text for description.)

DR. BLATTEIS: Could it not be also a better utilization of glucose itself? You won't have lactate accumulation, I mean you will have lactate accumulation if the pyruvate can't enter the correct cycle, so if the pathway is open and all is functioning well, you might not expect that much accumulation of lactate.

DR. REYNAFARJE: I beg your pardon?

DR. BLATTEIS: I am saying that the accumulation of lactate is an indication that all of the pyruvate is not entering into the Krebs cycle, and on to complete oxidation, so you may have simply a better electron transfer system operating.

DR. REYNAFARJE: That's what I mean when I say combustion.

DR. BLATTEIS: You don't mean combustion of lactate, necessarily?

DR. REYNAFARJE: No.

DR. BLATTEIS: You mean combustion of pyruvate?

DR. REYNAFARJE: But lactate has to return through pyruvate.

DR. WEIHE: Did you make determinations of lactic acid in the tissues to compare the concentrations between blood and tissues to see whether the clearance was better?

DR. REYNAFARJE: I didn't do that.

DR. WEIHE: Whether there is a higher increase of lactic acid in the tissues in the Morococha people?

DR. REYNAFARJE: No, i didn't do that.

DR. BRAUER: Do you have any pool size determinations at all on your lactates?

DR. REYNAFARJE: Pool size?

DR. BRAUER: Right, this would answer that question.

DR. REYNAFARJE: No, but we supposed everybody accepts that lactic acid is found in all body fluids, so what we found in the blood is that expression of what we found in intracellular and extracellular fluids, and the body water content of the high altitude people and the sea level people is about the same.

DR. BUSKIRK: How much variation did you have in your high altitude groups? In our series on the Indians last summer, for example, we didn't have a lactic acid below 80 milligrams percent, but all of yours are – well, your average here is 50 at 14 kilometers per hour which I assume is fairly close to maximal oxygen intake for these people.

DR. REYNAFARJE: There was a large individual variation, but at this level there was no overlapping, it is very significant also at this level.

DR. DILL: How long did this 14 km per hour run last? How many minutes?

DR. REYNAFARJE: This was only ten minutes.

DR. DILL: And on the previous curve you showed, I believe it was at 12 kilometers per hour, the lactate had leveled off during the last two or three minutes. Was there the same type of curve at 14 kilometers per hour?

DR. REYNAFARJE: No, no, the previous curve was the concentration of lactate in the blood as a function of time for the same type of exercise. This is the concentration of lactate probably in the steady state. It was leveled off at the end of this curve.

DR. DILL: I understand that, but I wonder if you have a curve for your lactate concentration as a function of time, for this 14 kilometer per hour experiment?

DR. REYNAFARJE: No, I don't.

DR. DILL: Well, my guess is that whereas these men at Lima were right near their maximum, or almost certainly had obtained their maximum oxygen consumption at 115 or whatever it is there, that these men at Morococha could have gone considerably further, and that the reason that you (Dr. Buskirk) got a higher lactate was that your men hadn't gone, for them at least, to a higher level of oxygen consumption. I don't think these Morococha men had reached their maximum oxygen consumption.

DR. REYNAFARJE: I think I agree with you.

DR. DILL: It's a lower slope all right, but it may well continue on out to a hundred or so if you kept them going.

DR. REYNAFARJE: Yes, as the work load is increased the level of the plateau is higher.

DR. SALTIN: You can find exactly the same type of slope if you take a group of untrained, in this case the Lima subjects, and well trained, you find exactly the same. If you then take athletes, you have no increase in lactic acid until they are running 14 kilometers per hour or something like that, so there you more or less have a straight line. So I am still interested to see if native residents at altitude could perform 16 or 18 kilometers per hour, something like that, just as Dr. Dill mentioned.

The concentration of lactate and pyruvate in arterial blood was followed at different intervals of time during the 30 min of recovery from an exercise consisting of running on a treadmill for 15 min at 9 km/hr, at 5.8% grade. Lactic acid disappears from blood as an exponential function of time in both groups of subjects; however, the rate of disappearance is about twice as fast in the altitude subject, as is indicated by the half time constants.

Pyruvic acid still increases in concentration for a few minutes after the cessation of exercise. After this period, pyruvate, like lactate, decreases in an exponential fashion with a speed which is also twice as fast in the altitude group of subjects. The results so far presented suggest that the blood concentration of intermediary products of carbohydrate metabolism is lower at high altitude mainly because their combustion through oxidative pathways is faster or more effective in the altitude-adapted subject.

DR. DILL: Were the men sitting or lying down during recovery?

DR. REYNAFARJE: After running, they were sitting.

DR. EVONUK: What work load was this?

DR. REYNAFARJE: This was 9 kilometers per hour, running for 15 minutes at 5.8 percent grade.

Table I shows the activity of some oxidative and glycolytic enzymes in the

TABLE I

Specific Activity of Enzymes in the Sartorious Muscle of Subjects Native to Sea Level and High Altitude.

	Sea Level		High Altitude		P <
			Whole Homogenate		
DPNH-oxidase	41.38 ± 2.79	(8)	52.09 ± 11.86	(9)	.05
			Mitochondrial fraction		
DPNH-cyt. c r.	57.86 ± 16.37	(9)	65.66 ± 10.15	(7)	N.S.
TPNH-cyt. c r.	0.83 ± 0.29	(8)	1.48 ± 0.39	(7)	.01
Transhydrogenase	1.46 ± 0.61	(8)	2.59 ± 0.97	(9)	.05
			Supernatant fraction		
DPNH-cyt. c r.	97.85 ± 36.55	(8)	104.10 ± 16.71	(7)	N.S.
TPN-ICD	10.99 ± 2.78	(8)	14.78 ± 4.65	(9)	N.S.
L.D.	1358.14 ±79.90	(7)	1321.10 ± 143.10	(9)	N.S.

Values are means ± SD. Figures in parentheses indicate number of cases. cyt. c r. = cytochrome c reductase; ICD = isocitric dehydrogenase; L.D. = lactic dehydrogenase.

sartorius muscle of healthy young men native to sea level and high altitude (7). These data reveal that the oxidative activity of the muscle of men adapted to high altitude is generally higher than that of sea-level residents. The enzymatic change occurred apparently preferentially in the mitochondrial fraction of the cell, suggesting that the respiratory enzymes are essentially involved in the process of acclimation to high altitude. Although an increased activity of the DPHN oxidase system and transhydrogenase had been shown before in guinea pigs native to high altitude, the very large increment in the activity of the TPNH-cytochrome c reductase, as observed in the muscle of humans, was quite unexpected in its magnitude. It is presumed that, in combination with the lower barometric pressure, the ambient cold plays an important role. It has been shown in this connection that the activity of the TPNH-cytochrome c reductase system is significantly increased in the microsomal fraction of the liver of cold-exposed hamsters (8). No appreciable changes were observed in the supernatant fraction. Furthermore, the activity of the glycolytic enzyme lactic dehydrogenase was practically the same in both groups of subjects.

COL. GOLTRA: Did you incubate at 38 degrees?

DR. REYNAFARJE: 28 degrees.

DR. MORRISON: Did you try incubating at body temperature of the individual?

DR. REYNAFARJE: Well, no, in this experiment it was 28 degrees.

DR. MORRISON: I have run those fractions in animals at different body temperatures, and the activity rates are very different. If you're going to work on tissue from an animal and you're going to compare it, if you're going to take the tissue from an animal who is at say six degrees Centigrade and then you homogenize or fractionate and incubate at 38– –

DR. REYNAFARJE: I can't answer that because when I measured activation energy it was the same in high altitude and sea level animals.

DR. BRAUER: Your reference base here is soluble protein or nitrogen?

DR. REYNAFARJE: Beg pardon?

DR. BRAUER: Your figures are given to what reference base?

DR. REYNAFARJE: It is expressed as per milligram of nitrogen, and the content of nitrogen is exactly the same in high altitude as in sea level people.

DR. WEIHE: Is the number of mitochondria increased? Do you know anything about that?

DR. REYNAFARJE: I don't know. This is one of the things that we expected to happen.

DR. WEIHE: You didn't do that?

DR. REYNAFARJE: No, we didn't do anything with that.

We must not conclude from these results that only oxidative mechanisms are involved in altitude adaptation, especially during work. The fact that the activities of glycolytic enzymes and enzyme systems are not different from those of the sea-level control does not exclude the possibility of using different anaerobic pathways, as may be inferred from the following experiment and from a previous one carried out by Picón in the venous blood from the arm (9).

In our studies, four high-altitude subjects and six sea-level residents were catheterized. A 40% solution of fructose was injected through the catheter into the suprahepatic vein in the amount of 1 ml/kg of body weight. The metabolism of fructose in the liver and extrahepatic tissues was studied by taking blood samples simultaneously from the suprahepatic vein and from a brachial artery, at short intervals of time after injection, which was done at a rate of 12 ml/min.

Figure 13 shows the rate of fructose disappearance in extrahepatic tissues.

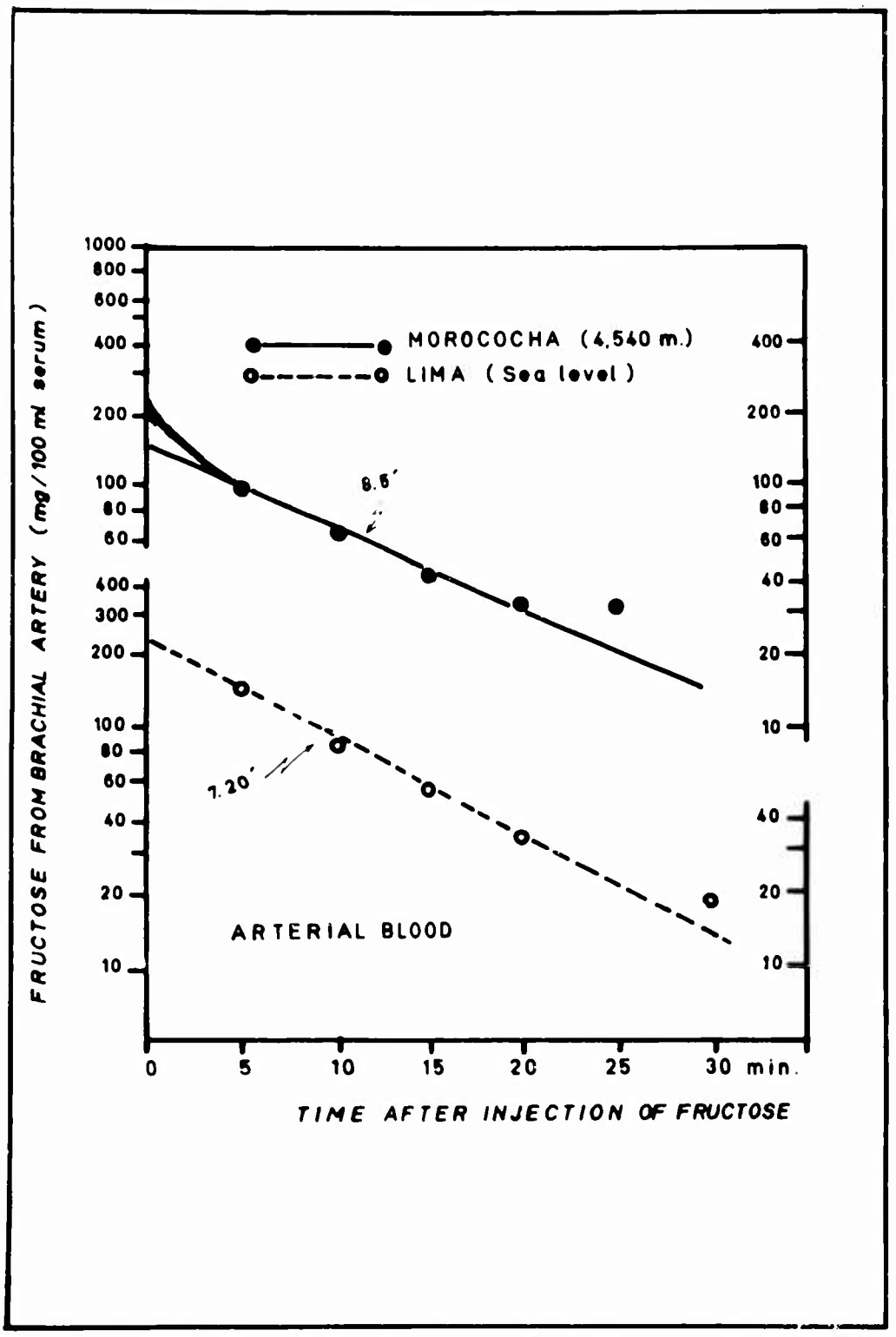


Figure 13
Rate of fructose disappearance in extrahepatic tissues.

It appears that the hexose is metabolized at about the same speed in both groups of subjects and probably follows only one major metabolic pathway.

Figure 14 shows what happens in liver. The rate of disappearance is clearly different in subjects from sea level and high altitude. Whereas at sea level frutctose is metabolized apparently following only one metabolic pathway, or perhaps two, but each one as the same speed, at high altitude the hexose is metabolized following two different pathways, each one at a very different rate, as is shown by the slope of the thinner lines.

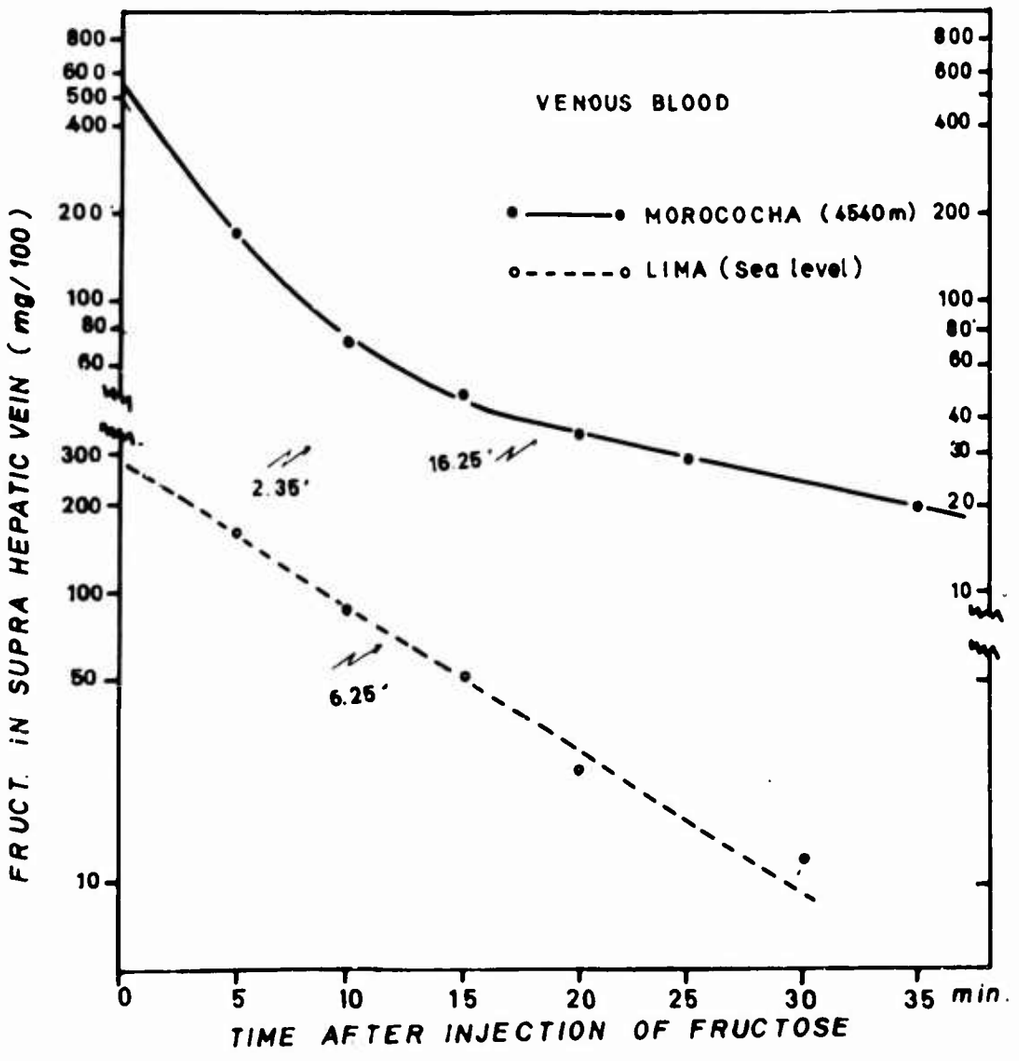


Figure 14
Rate of fructose disappearance in the liver.

DR. BRAUER: The same dose of fructose was injected in both cases?

DR. REYNAFARJE: The same dose, it was a 40 percent solution of fructose which was injected in the amount of one milliliter per kilogram of body weight at the rate of 20 milliliters per minute.

In Figure 15, the rate of fructose conversion into glucose, in liver and extrahepatic tissues, is plotted against time after injection of fructose. At sea-level the glucose concentration over the basal level increases considerably in the blood leaving the hepatic tissue, attaining a maximum value at the 20th min. In the high-altitude native, on the contrary, glucose concentration in suprahepatic blood tends to decrease continuously during at least 35 min.

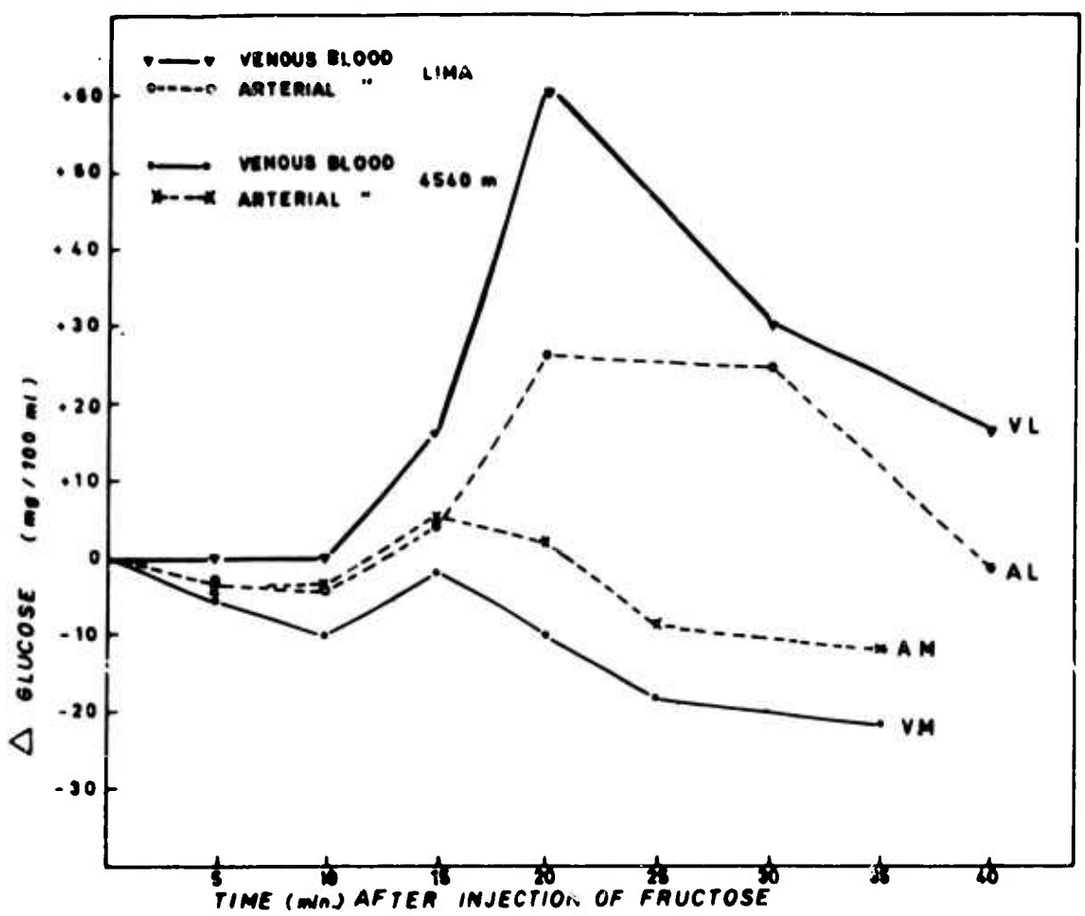


Figure 15
Fructose conversion into glucose in the liver and extrahepatic tissues (V = venous blood; A = arterial blood; L = Lima; M = Morococha).

The change in glucose concentration in arterial blood follows the same direction as in venous blood. However, it is worthwhile to note that while at sea level the concentration of newly-formed glucose is always higher in the vein than in the artery, at high altitude the difference is in the opposite direction. There was always more glucose in arterial than in venous blood.

Lactic and pyruvic acid are formed from fructose, but to a lesser extent at high altitude than at sea level. (Figures 16 and 17). In the sea-level subject, the concentration of pyruvate in venous blood is always higher than in the arterial blood, whereas in the native the reverse is true – there is more in arterial blood than in venous blood. The same phenomenon happens with the lactic acid formed from the injected fructose. We should note that while at sea level lactic acid is still increasing, at high altitude this metabolite is already decreasing, suggesting that its combustion is more effective.

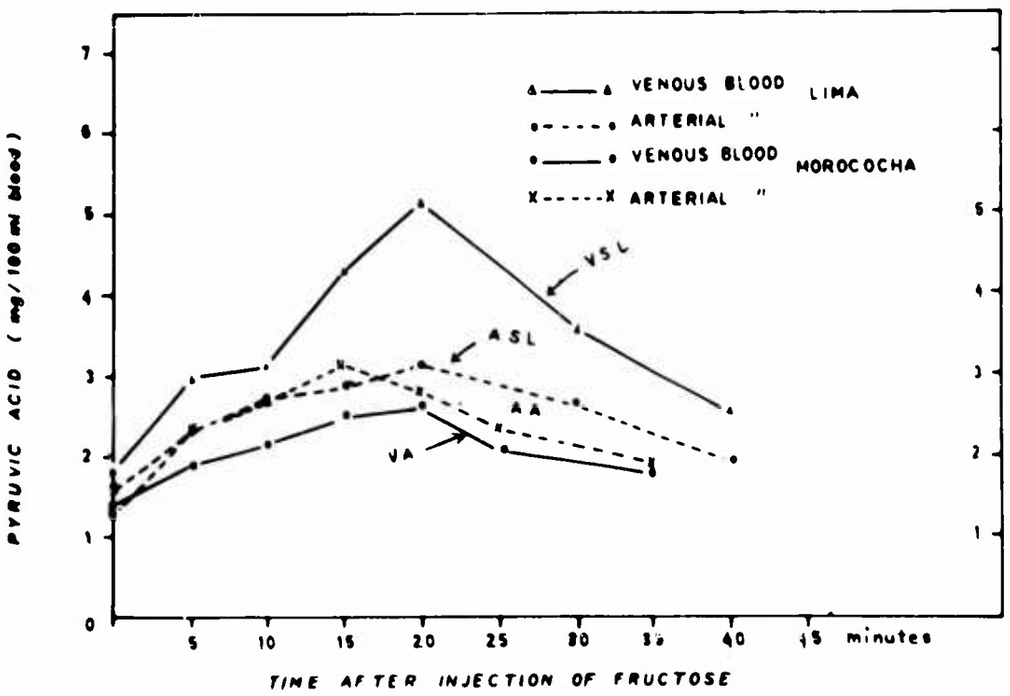


Figure 16
Rate of fructose conversion into pyruvic acid. (V.S.L. = venous blood at sea level; A.S.L. = arterial blood at sea level; A.A. = arterial blood at altitude; V.A. = venous blood at altitude.)

Conclusion

In conclusion, we could suggest that the different physiological and biochemical behavior of the altitude native, during work and recovery, is probably the expression of a different pattern of intermediary metabolism in which anaerobic and oxidative pathways are equally involved.

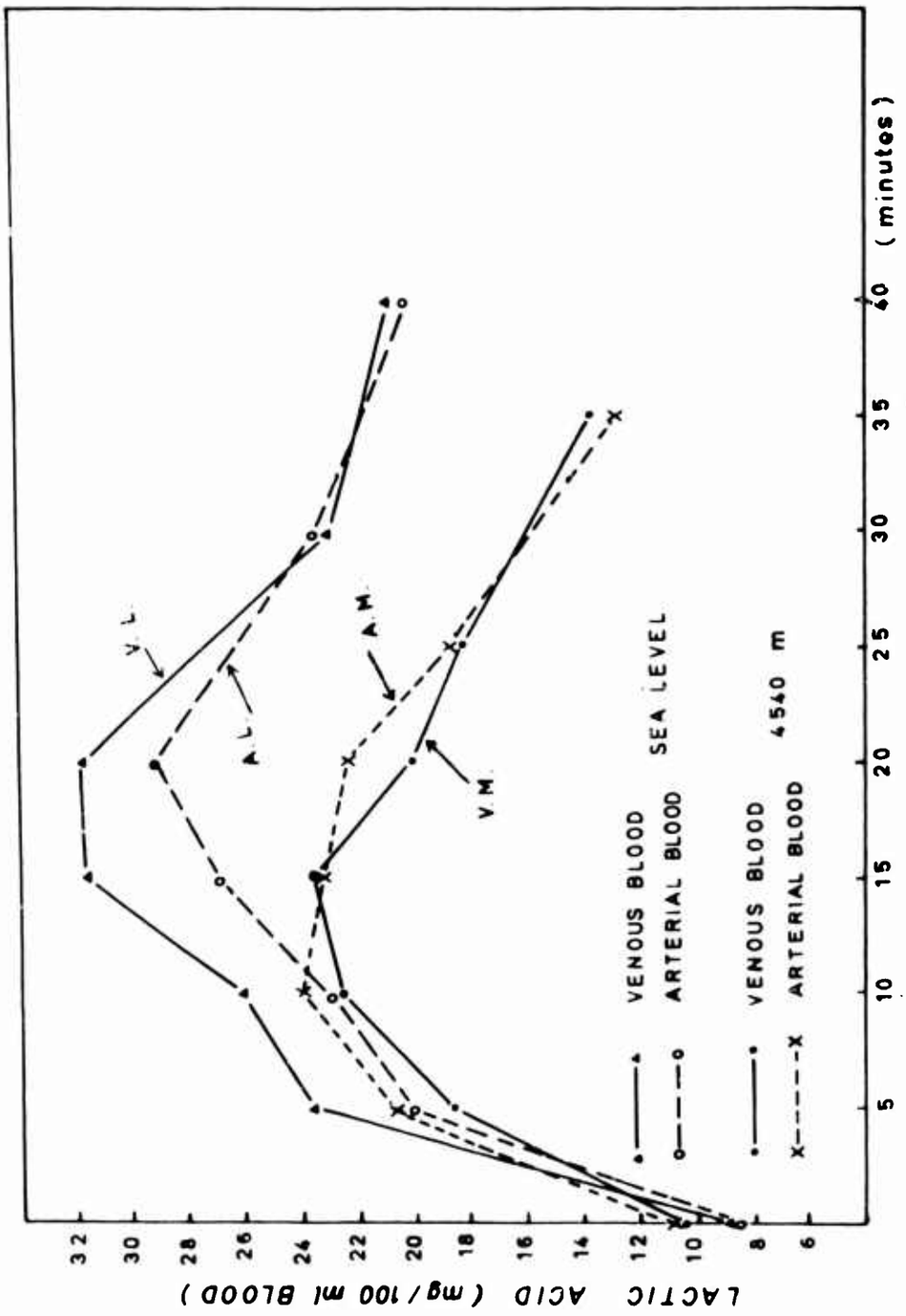


Figure 17

Fructose conversion into lactate. (See Figure 15 for legend.)

DISCUSSION

DR. WEIHE: This faster utilization of fructose, isn't it due to a higher metabolic rate of the liver tissue of your altitude people, when they just need to produce more energy?

DR. REYNAFARJE: I don't know that. We saw evidence that they are using two different metabolic pathways.

DR. WEIHE: I mean the second to the last slide you showed, the utilization of fructose in the liver.

DR. REYNAFARJE: In the liver?

DR. WEIHE: Yes, then in the altitude people, the fructose was immediately burned down while in the sea level people, it was stored away, therefore maybe the liver has just a higher metabolic rate.

DR. REYNAFARJE: They have a higher– –

DR. WEIHE: But this is maybe because as mentioned they have a higher metabolic rate to start with, the altitude people, and this is an expression of cold acclimatization.

DR. REYNAFARJE: Maybe.

DR. CHIODI: Did you try in vitro perfusion of the liver?

DR. REYNAFARJE: No, I didn't.

DR. CHIODI: We saw it in rats.

DR. BRAUER: May I ask something about the catheterization. The same person did the catheterizations in both your high altitude people and your low altitude people?

DR. REYNAFARJE: No, but they use– –

DR. BRAUER: How about the catheter? The same size catheter?

DR. REYNAFARJE: The same size.

DR. BRAUER: The same deposition, how deep did they put it?

DR. REYNAFARJE: Yes, we have x-ray confirmation of it.

DR. BAUER: And were they free flowing or were they wedged? Because what you are getting could be what we have seen when you wedge a catheter, in which case you're going to see abnormally high proportions of the hepatic arterial blood in your catheter samples, the samples – the arterial contribution to the so-called hepatic venous blood under those conditions goes sky high at the expense of the portal venous blood.

DR. REYNAFARJE: No, that's not it, because– –

DR. BRAUER: They are non-wedged?

DR. REYNAFARJE: Yes, we have plates and we can show the same positions in both catheters.

DR. BRAUER: And they were free flowing catheters?

DR. REYNAFARJE: Yes, free flowing.

DR. BUSKIRK: What about nutritional differences in these two groups? For example, what was the carbohydrate picture in terms of the diet of the altitude group versus your sea level group?

DR. REYNAFARJE: I don't know about that, but it has been determined that high altitude people use more carbohydrates in their diet than sea level people do.

DR. WEIHE: Could you say something about the ambient temperature of the two groups during life up there and during the experiment?

DR. REYNAFARJE: During daily life?

DR. WEIHE: Yes.

DR. REYNAFARJE: Well, during the experiment they were in rooms which were about 18 degrees Centigrade, but they live in a very low ambient temperature, about eight degrees.

DR. WEIHE: What's the difference compared to Lima?

DR. REYNAFARJE: Well, it depends on the weather.

DR. WEIHE: I mean monthly mean temperature.

DR. REYNAFARJE: I would say about ten degrees Centigrade, not more.

DR. BLATTEIS: Is it fair to make these comparisons of the last set of data which you obtained on liver and the first set which you got on muscle?

DR. REYNAFARJE: Well, in muscle I show no difference in enzyme activity, and I think that in the glycolytic system there is not much difference in enzyme activity. For example, for fructose metabolism there are two different metabolic pathways.

DR. BRAUER: You haven't done any liver biopsies?

DR. REYNAFARJE: No.

DR. HANNON: I saw an interesting possible relationship in your early slides and your later slides, and this concerns the high post-exercise metabolic rate you see in your high altitude residents. I was wondering if you had measured body temperatures. Possibly you had a higher body temperature in your altitude residents. Could this be related to the increase in the TPNH-cyctochrome c reductase system, the heat generating system? Does their body temperature rise, is it higher or lower or what?

DR. REYNAFARJE: We didn't measure this, we wanted to but we didn't.

DR. BLATTEIS: At sub-maximal workload, we measured it and it wasn't higher and it may have been lower.

DR. BRAUER: What season of the year were these last experiments done?

DR. REYNAFARJE: It was at the end of summer.

DR. CHIODI: What about the animal or human subjects acclimatized to

cold – what will they do with fructose, do you know?

DR. REYNAFARJE: No, I don't know.

DR. HANNON: What's that again now?

DR. HORVATH: The question has to do with cold acclimatization.

DR. WEIHE: And fructose utilization.

DR. HANNON: I don't know of any work that has been done with fructose utilization in cold. One other point I would like to ask about; many of these changes in metabolite levels, fructose or glucose in the blood, could be a function of, or are a function of, rates of synthesis and rates of degradation and in many cases related to blood flow, particularly in the case of the liver. Do you think changes in blood flow could account for any of these changes you observed?

DR. REYNAFARJE: Not in the glucose concentration; it was a very large difference.

DR. HANNON: Well, if you have a constant rate of glucose synthesis in the liver and you half or double the blood flow through the liver, and you're measuring on the venous side, you get a concentration change or an apparent one that is not real.

DR. REYNAFARJE: We didn't.

DR. HANNON: Well, blood flow in the liver is very difficult to measure.

DR. REYNAFARJE: Yes.

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COLD, WORK, AND ALTITUDE: CENTRAL CIRCULATORY ASPECTS

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It is very stimulating to have the opportunity to take part in this symposium and to visit the Arctic Aeromedical Laboratory here in Fairbanks. My task of reviewing–or better, commenting on–central circulation during work, with special reference to altitude and cold, is rather difficult since there is a lack of investigations in many branches of this field. This presentation, therefore, will probably end with more questions than complete answers. During the last years our knowledge regarding circulation during exercise has markedly improved, especially by studies in the United States and Scandinavia. Even the results from circulatory studies at altitude involving hard exercise have been presented in greater numbers during the last years, probably at least partly because of the decision that the 1968 Olympic Games are to be held at an altitude of 2,250 meters in Mexico City. The real problem, however, arises when we turn to aspects regarding the way cold influences the circulation during exercise, or even worse, how cold influences the circulation during exercise at altitude. To avoid being too speculative, I therefore plan to present results from studies of circulation during exercise in upright position at sea level and in optimal climate (18-22°C), and from this platform of knowledge, take some more or less deep glances at altitude and cold.

Circulation during Exercise in Optimal Conditions

During short-term exercise in a normal climate it is of particular interest to study the circulation's ability to deliver oxygen to the tissue, since the rate of transport of other substances and heat with the blood is always more than sufficient when the tissue's demand of oxygen is covered. The cardiac output increases almost linearly with the oxygen uptake from rest up to the maximal level of exercise, as is shown in Figure 1. This figure summarizes individual and

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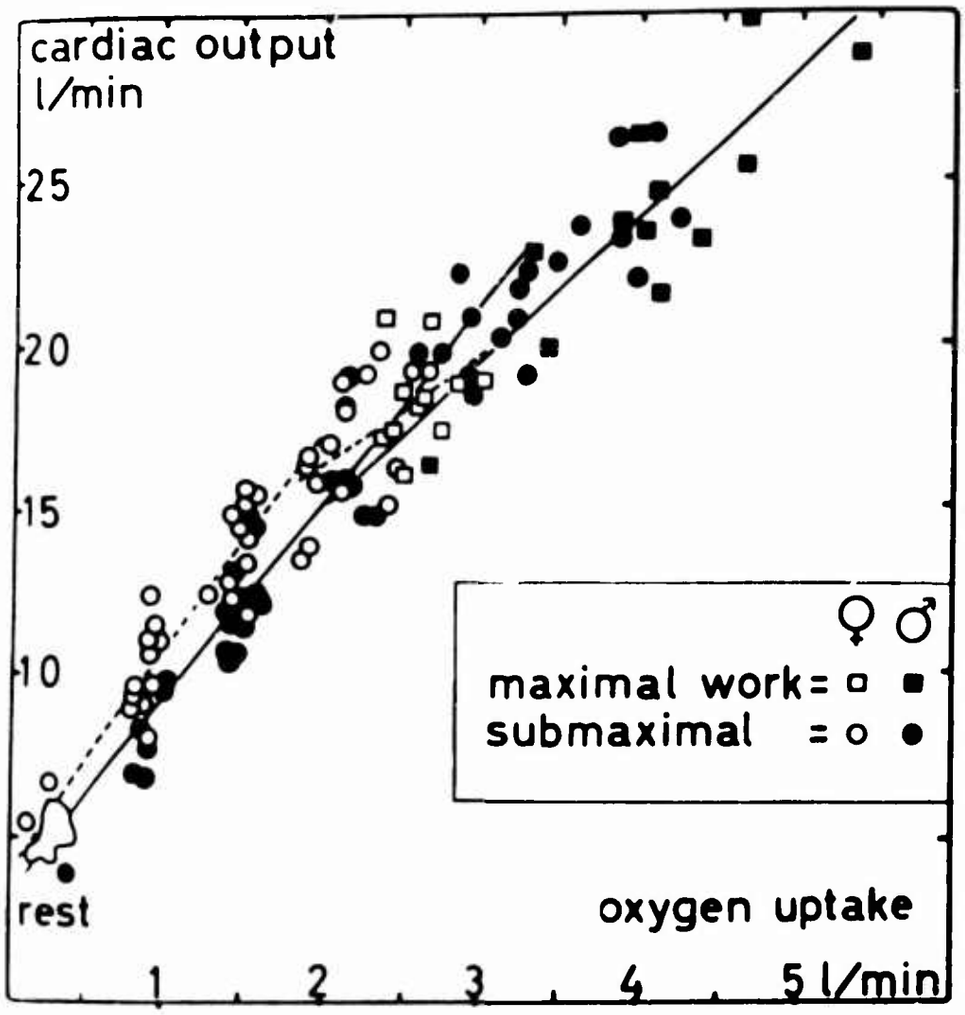


Figure 1
Individual and average values on cardiac output at rest, during submaximal and maximal exercise with 23 subjects sitting on a bicycle ergometer (1).

average data for 11 females and 12 males at rest and performing submaximal and maximal exercise (1). All were somewhat trained, but none in athletic condition. The maximal cardiac output was around 19 l/min for those with an aerobic capacity of 3 l/min, 24 l/min for those with 4 l/min and almost 30 l/min for those with 5 l/min in maximal oxygen uptake. There is a tendency in this material to a declining rate of increase in cardiac output as the oxygen uptake gradually approaches maximum. Any definite breaking point probably does not exist. The relationship between oxygen uptake and cardiac output probably is curvilinear even though there is too little data on the same subject, at very moderate exercise and close to maximal work, for a final validation of this suggestion.

One interesting finding shown here is that the females at a given oxygen uptake had a higher cardiac output than did the males. The probable explanation for this is the lower hemoglobin concentration and, as a consequence, also a lower oxygen content in the females' arterial blood. The sex differences influence the magnitudes of the cardiac output both at submaximal and maximal exercise. Cardiac output per liter oxygen uptake was in both sexes related to the arterial content of the blood. This relationship would further enlarge the sex difference in maximal oxygen uptake, since the females have smaller hearts which makes it impossible for them to attain high cardiac outputs.

The relationship between work load and heart rate is similar to that between cardiac output and oxygen uptake (Figure 2). When the level of exercise approaches maximum, and perhaps also at high levels of moderate exercise, the rate of increase in heart rate is less than observed in between.

DR. DILL: Did you make observations on an individual over the whole range?

DR. SALTIN: Yes, we have over the whole range, and we have compared—though not in this study—the untrained and trained. The untrained has this curvilinear shape up near maximal level of exercise and the trained has a straight line. There is absolutely no tendency to change the curvilinear shape: both untrained and well trained show this.

The heart rate at a certain work load expressed as in Figure 2 in percent of each individual's maximal oxygen uptake is the same for males and females and is independent of degree of fitness. The observed differences between individuals can be explained mainly by differences in maximal heart rate. Interindividual variation within any given age group may be of the same magnitude as the average decrease in maximal heart rate from the age of 10 to 50 years—from 210 to 170 beats/min (2,3). Surprisingly little is known about the genesis of individual variation in maximal heart rate or about its decrease with age. The upper panel in Figure 2 shows the stroke volume in percent of the highest ever attained for each individual. The stroke volume of the subject at rest in erect position is 60% of that attained during exercise. Almost all of the increase takes

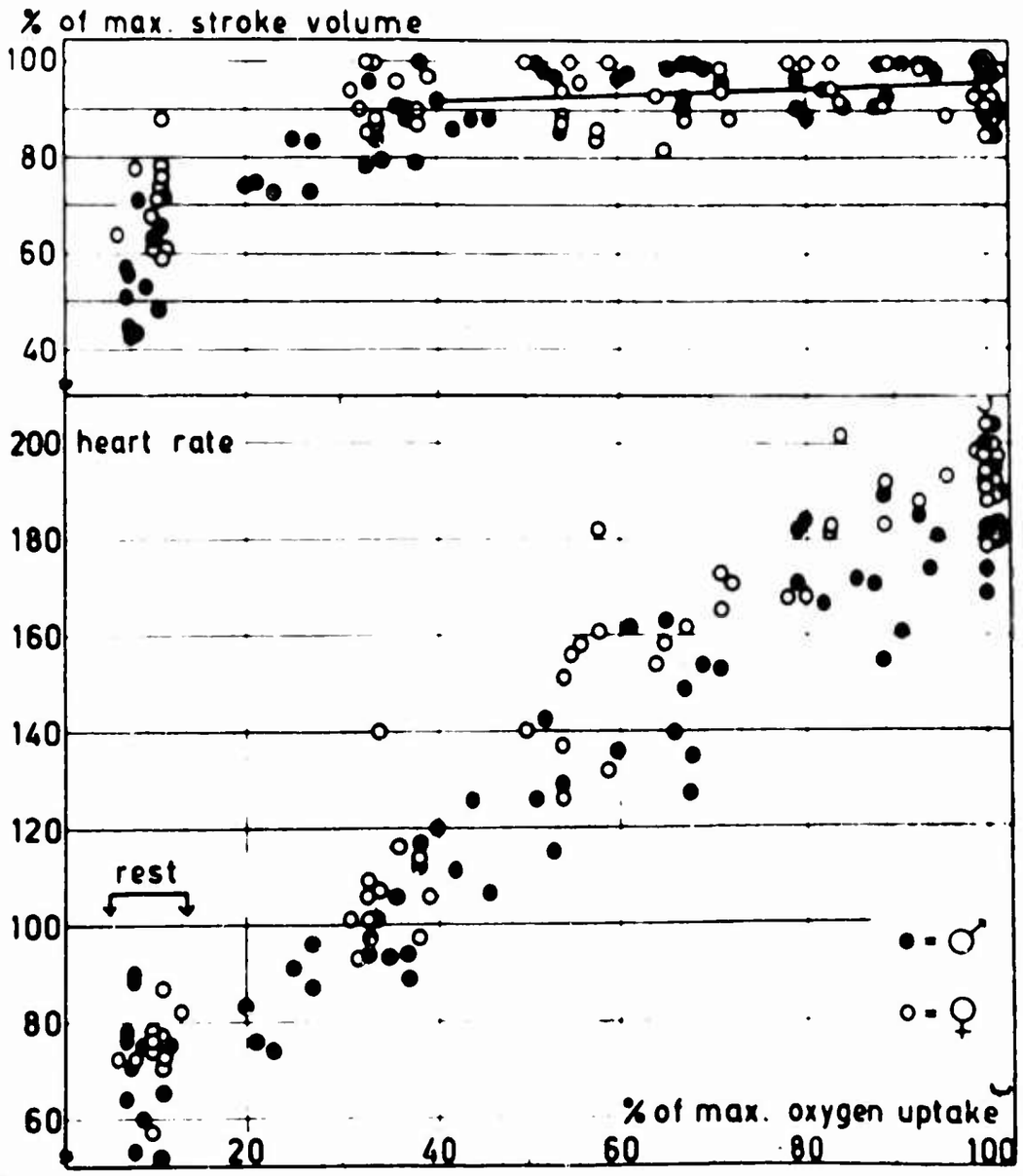


Figure 2

Stroke volume in % of the individual's maximum, and heart rate at rest and during exercise. The oxygen uptake on the abscissa is expressed in % of the subject's maximum. All measurements were done in sitting position (1).

place at moderate exercise, and the stroke volume reaches its maximal value at a 30-50% relative work load. It should be emphasized that there is no tendency to a reduction or increase in the stroke volume at maximal exercise, neither in those with low nor those with a high maximal heart rate. Thus, the time for the diastolic filling of the ventricles in the normal heart is enough to maintain maximal stroke volumes even with heart rates above 200 beats/min.

During the last years there has been an intensive discussion regarding how much the stroke volume contributes to the increase in cardiac output during exercise. All the studies from our laboratory (1, 4, 5) show an almost twofold increase when the determinations are performed on subjects in the erect position, which is in agreement with most other studies using this work position (6). The suggestion that the stroke volume does not contribute at all is based on studies of subjects in supine positions. As can be seen in Figure 3, the stroke volume of subjects at rest in the supine position equals that during exercise in the sitting position, but again at rest in the sitting position, the stroke volume is almost half of that during exercise (7). Studies on old athletes suggest that the increase in stroke volume contributes somewhat more in well-trained than in sedentary subjects (8).

DR. BUSKIRK: What happens if you put the person with his head down slightly?

DR. SALTIN: We don't know, but we plan to do that.

DR. BRAUER: Has this been done with people supine in water?

DR. SALTIN: No, I don't know of any studies with circulatory data other than heart rate, but if you take for example the maximum heart rate during swimming and compare it with that during work on a bicycle or treadmill, you will find a lower maximum heart rate during swimming, occasionally by as much as 10 to 50 beats. We hope next year to have our swimming treadmill, and it will be very interesting to see what the stroke volume is under these circumstances.

DR. EVONUK: This is a dye dilution technique?

DR. SALTIN: Yes, dye dilution.

COL. GOLTRA: I think circulatory studies were done in a hydrodynamic

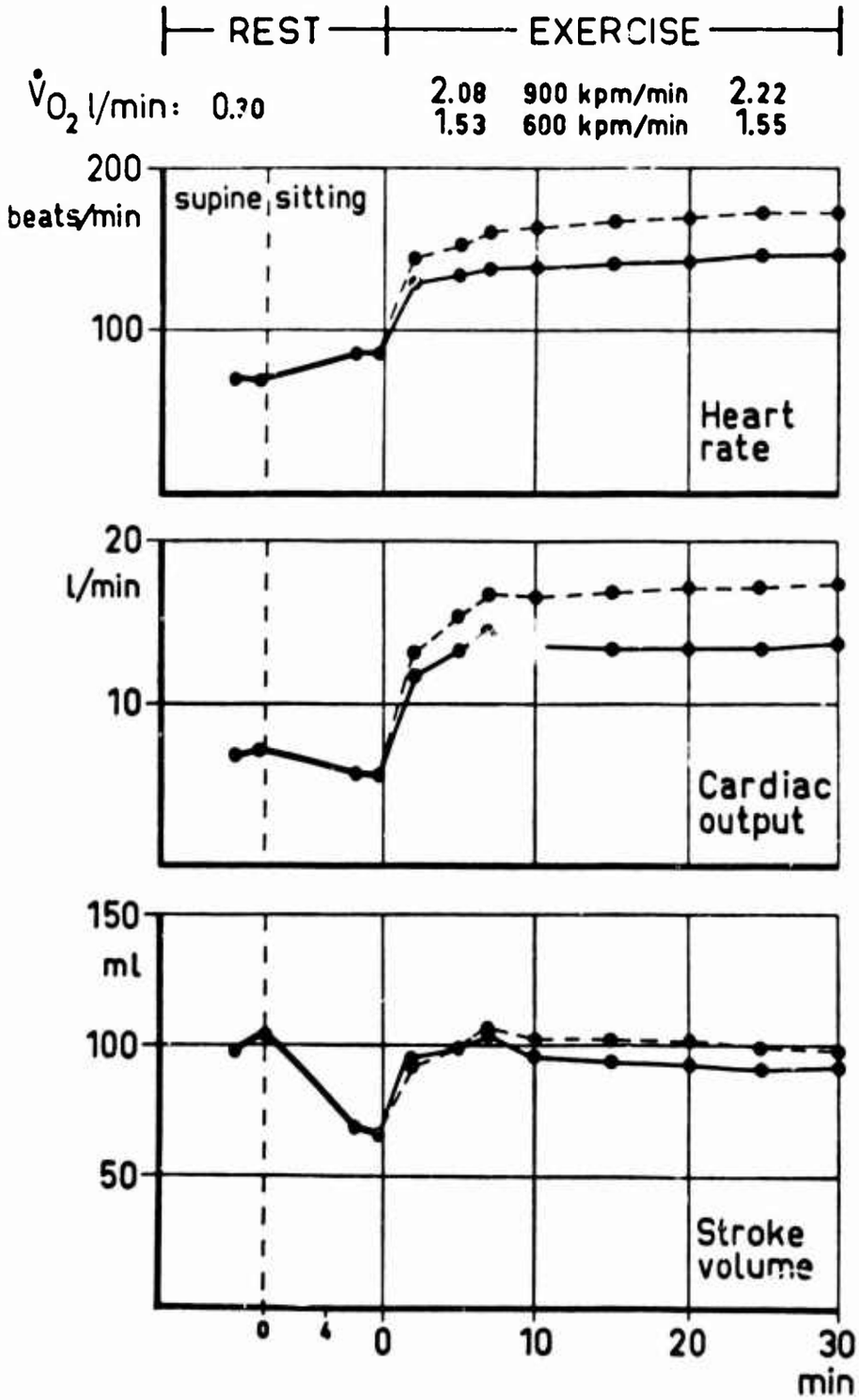


Figure 3

Results at rest supine and at rest and during exercise in the sitting position on a bicycle ergometer. The mean values for six young men at 600 kpm/min (full lines) and at 900 kpm/min (hatched lines), respectively, are given. VO_2 l/min denotes the oxygen uptake measured at rest supine and after 5-7 and 24-26 min of exercise (7).

state at Wright-Patterson Aerospace Medical Research Laboratories including cardiac output and work about two years ago. It's in a technical report now by Dr. A. Hystra.

DR. HORVATH: You don't remember what those values were? Is that Lamb's work?

COL. COLTRA: No, this was done after Lamb left Wright-Patterson.

DR. WEIHE: They would be interesting.

The relationship between cardiac output and oxygen uptake in the same subject is very stable even though the environmental condition is changed. Let us, therefore, for a moment consider just the opposite of exposure to cold. Williams et al. (9) studied two subjects at normal and 97° F. room temperature. No difference was found in their oxygen uptake, cardiac output and a-v oxygen difference during submaximal and maximal exercise in the hot environment compared with the controls. In a larger group of unacclimatized subjects, Rowell et al. (10) found in some subjects a small decrease of 5-10% in the maximal oxygen uptake in the heat, which is in agreement with unpublished findings in our laboratory. In a hot environment, the skin circulation is usually increased. Since the cardiac output is unchanged at submaximal exercise, some other vascular beds must get a reduced flow. According to Williams et al. (9) the muscle blood flow is reduced, but Rowell et al. (10) have shown a lower flow to the splanchnic region in a hot environment. During submaximal work at high temperatures, the heart rate is increased and central blood volume and stroke volume are reduced (11). During maximal exercise of short duration a redistribution of blood occurs, the skin is apparently deprived of its share of the cardiac output, and the circulation behaves as in a normal climate.

Of some interest for further discussion is the fact that after pyrogen-induced fever, there is a higher cardiac output both at rest and during moderate exercise compared with normal (12). An opposite situation, with a lower cardiac output during submaximal work compared with controls, occurs when the plasma volume is reduced by thermal dehydration (4). The

hemoconcentration with higher hemoglobin concentration in the dehydrated stadium probably explains this finding.

Blood Distribution during Exercise

Donald and associates have paid much attention to the distribution of the blood flow both at rest and during exercise (13, 14). They assume that up to 80-90% of the cardiac output is distributed to the working muscles during severe exercise (14). No reliable methods for measuring muscle blood flow during exercise have been available. A promising method has been disclosed, however, using radioactive xenon (Xe^{133}) as an indicator (15). The blood flow can be calculated by injecting small volumes of dissolved Xe^{133} into the working muscle and recording the clearance curve for the isotope. In this manner, Grimby et al. (16) have studied the blood flow in the lateral portion of the quadriceps muscle during submaximal and maximal exercise. There is an almost linear increase in the muscle blood flow from around 3 ml at rest up to 49 ml/100 gm tissue and minute during maximal work. This maximal figure is somewhat higher than that which is found during or immediately after exercise using the plethysmographic technique (17).

DR. BRAUER: These measurements were made by looking at the surface with a counter?

DR. SALTIN: Yes.

DR. BRAUER: How deep are you looking? What is the hardness of the xenon 133 radiation? What kind of radiation is it?

DR. SALTIN: It's a gamma radiation.

DR. BRAUER: Since it is gamma radiation, you are looking presumably quite deep?

DR. SALTIN: Yes, you know we have injected this small volume, say four or five centimeters below the skin.

DR. HORVATH: But doesn't it have the same problems iodine 131 and sodium 22 had, namely that you can't really separate out what is happening in the extracellular fluid spaces?

DR. SALTIN: Xenon is believed to diffuse perfectly through all the tissues, and that's its great advantage compared with all the other substances used. But to be honest, there are problems involved with this method too, though the mean results are very high. I haven't included the standard deviation, but if I do so, we will have a plus or minus seven or up to around ten milliliters.

DR. BUSKIRK: What was the man doing with this muscle group?

DR. SALTIN: He was doing bicycle exercise up to 2,000 kilogram meters.

DR. BUSKIRK: With the counter strapped right on the muscles.

DR. SALTIN: Yes. You have a protector, you put it around his thigh and he can run. He can pedal the bicycle, no problem.

Other vascular beds such as the splanchnic region and the kidneys have their flow markedly reduced during work. The estimated blood flow (idiocyanide-green technique) through the splanchnic region at rest was 1.650 ml. During almost maximal work this was reduced to 400 ml/min (18). This reduction in blood flow was more closely related to the relative work load of the subject than to the absolute work performed. The calculated oxygen uptake for the liver was 68 ml, both at rest and at the severest work load. The flow to the kidney is reduced in the same manner. Grimby (19) found that at a work load corresponding to 75% of the aerobic capacity, the renal fraction of the cardiac output was as low as 3 to 5% compared with 17% during rest.

DR. BRAUER: How did you get these figures? Are these plasma flows or renal flows?

DR. SALTIN: Grimby used dye dilution. This is just published. You can find it in the Journal of Applied Physiology.

DR. HORVATH: But actually isn't there somewhat of a misnomer in using the term percent of the cardiac output, because in essence unless you actually look at the total amount of blood flow through the renal tissue– –

DR. SALTIN: You can see it's related to oxygen uptake, but it's even nicer if you relate it to heart rate.

In absolute figures the renal blood flow at rest, then, is 1.1 l/min and at the highest work load, 0.5 l/min. Wade and Bishop's (20) suggestion that the renal blood flow can be as low as 25% of the resting value during maximal exercise is thus probably right.

The oxygen extraction of the heart muscle is very high even at rest (21). During exercise, therefore, the coronary blood flow must increase almost linearly with the metabolic activity. It has also been shown that during light supine exercise in man, there is a steep increase in the coronary blood flow (22). In dogs the intramyocardial pressure during systole does not inhibit the flow through the coronary arteries, which makes a continuous supply of blood to the myocardium possible (23).

From the standpoint of temperature regulation, the skin blood flow is of special interest. Our knowledge, however, is still based on measurements of total flow to a limb, and measurement of total flow to the forearm and hand during leg exercise is the one mostly used. Figure 4 illustrates the typical response in forearm and hand blood flow during moderate exercise. At light exercise (left panel) and moderate exercise (right panel) there is an initial decrease in forearm and hand flow when exercise starts but during the five-minute work period both flows increase (24). The increase in blood flow to the hand is 10 to 12 times that in the forearm.

DR. HORVATH: If you take into account the amount of skin in the forearm, this would imply that there is practically no change in muscle flow?

DR. SALTIN: They imply that there is a slight increase, indicating again the value of this xenon method. I show this slide mostly because this was done at a normal temperature and we know that this increase is more marked in a hot environment than in a cold environment. I don't know of any direct data during

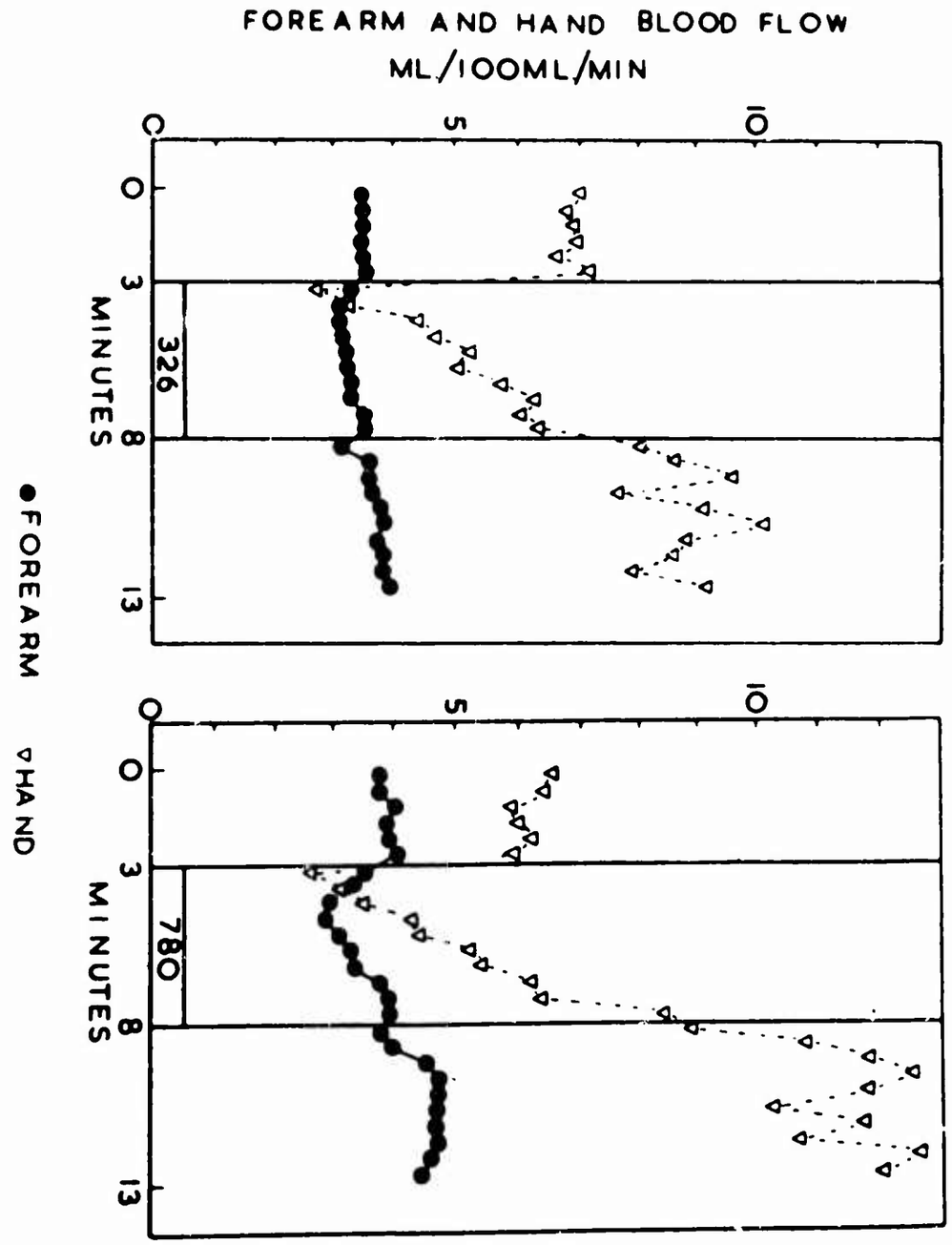


Figure 4

The effect of leg exercise on blood flow in the hand (triangles) and the forearm (dots). Left panel: average result of 19 runs on 3 subjects with an average oxygen uptake of 326 ml/min. Right panel: average result of 17 runs on the same subjects with an average oxygen uptake of 780 ml/min (24).

exercise, but you can expect this to be much lower, and from a circulatory point of view, exercise in a cold environment then means somewhat less stress.

It is concluded that the initial reaction is caused by an increased vasoconstrictor tone predominantly in the muscle, since it is not abolished by blocking the vasomotor fibers to the skin, but by blocking the nerves to the muscles. The subsequent rise in forearm and especially hand blood flow during continuous exercise seems to be caused by an increased skin blood flow, which probably is mediated through vasodilator fibers releasing bradykinin (25). The absolute magnitude of the flow can still only be estimated, but if there is a combination of plethysmographic technique with the xenon method for muscle blood flow, it should be possible to evaluate the exact share of flow to the skin.

Prolonged Exercise

The effect of prolonged exercise on different circulatory parameters is illustrated in Figure 5. The most drastic changes during this prolonged exercise (180 min), loading the oxygen transport to 70-75% of the maximal, are the gradual increase in heart rate and the corresponding decrease in the stroke volume (26). Adolph and associates explain the reduction in the stroke volume after dehydration on the basis of a reduced blood volume (27). This is not a possible explanation when the dehydration is caused by hard exercise, as the blood volume is only decreased to a minor extent (see Figure 5 and ref. [28]). Furthermore, it is possible to attain a maximal stroke volume and the same maximal cardiac output and oxygen uptake even after prolonged exercise when the subjects are pushed to maximal exercise. The conclusion is, therefore, that factors other than the circulation limit the performance capacity during prolonged exercise. One factor may be available–glycogen stores (see later section of "Glycogen Store"), but the water and the electrolyte change at cellular level may also play a role (5, 28).

This short review regarding the circulation during exercise in optimal climate and at sea level has revealed a very precise regulation related to the metabolic demands of the tissue. Environmental factors can influence this circulation to a minor degree at submaximal work, but very little or not at all at maximal exercise. For example, it is impossible to tell from the achieved maximal values on cardiac output, heart rate and stroke volume if the exercise is performed in optimal conditions or in heat or after dehydration caused by thermal heat stress or prolonged exercise (cf. Figure 6). The maximal oxygen

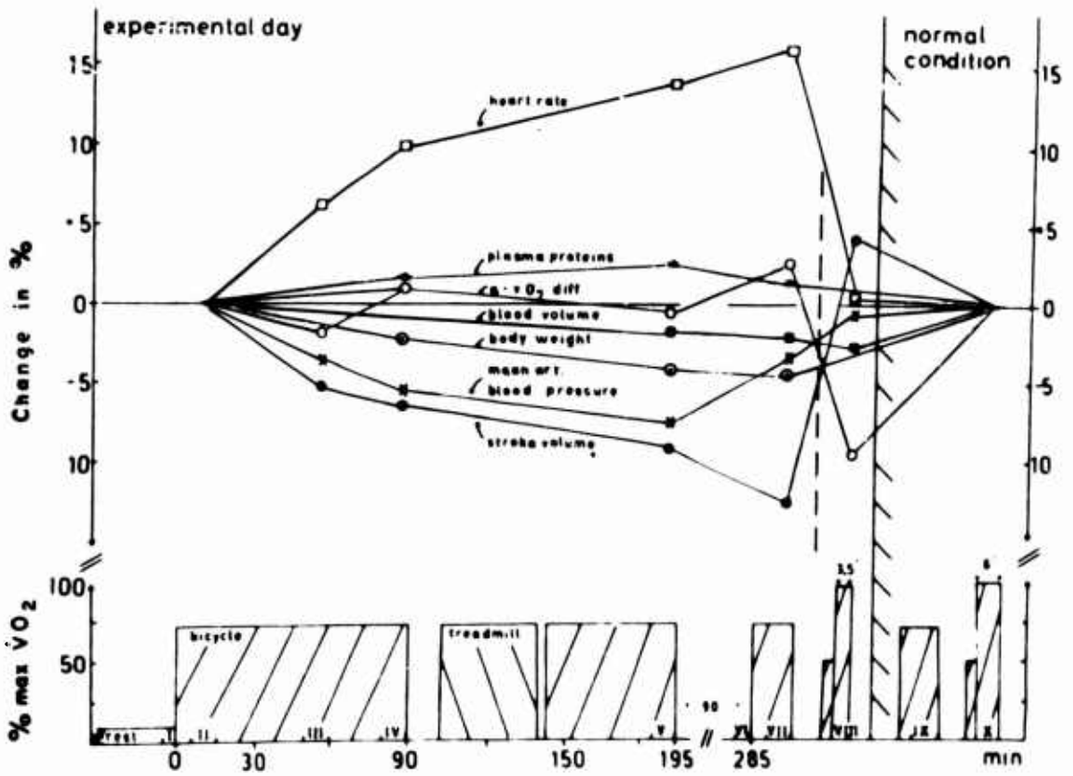


Figure 5

Lower part: Procedure for the experiments both for the experimental day and during normal conditions. The effective work time during the prolonged period was 180 min. Upper part: The % changes in heart rate, plasma protein, a-v oxygen difference, blood volume, body weight, mean arterial blood pressure and stroke volume during the exercise. Notice that for the submaximal work (75% load) the 5-15 min values (II) represent the zero point and for the maximal work the values obtained under normal conditions (X) (26).

uptake is also affected very little in these situations but the performance capacity, measured as work time on the maximal work load, is much more reduced (5).

Effect of Physical Training

An important field of study is to determine to what extent a conditioning program can affect the circulation and improve the maximal oxygen uptake. Most studies show that even a very intensive training program for 1-3 months only increases the aerobic capacity by 10-15% (29, 30, 31). The increase in

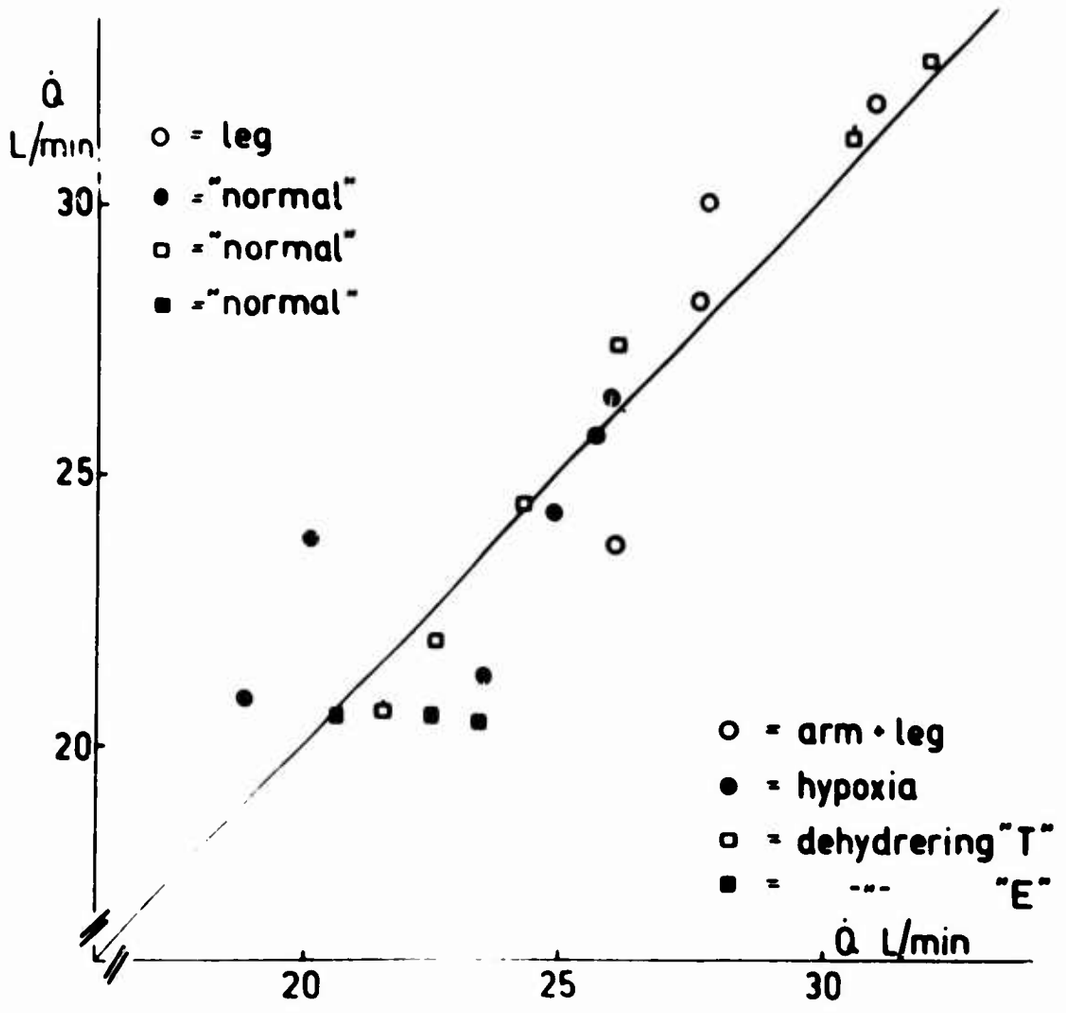


Figure 6
Maximal cardiac output in normal conditions (ordinates) and in different experimental condition (abscissas). The data are from references (4), (26), (33), and (73).

stroke volume and in the cardiac output covers up to 5%, and the rest of the improvement in oxygen uptake then is covered by a widening of the a-v oxygen difference (31). Little is so far known about what happens during prolonged training (years), although it is possible to get some information from cross-sectional studies of athletes.

Degree of training	Material	Age mean range (years)	No. of subj.	Maximal mean values for $\dot{V}O_2$ l/min	Q l/min	Heart rate	Stroke vol. ml	A-V diff ml/1000ml	Heart vol. ml	Hemo. conc. g/100 ml	Height cm / kg Weight
Untrained	Åstrand et al. (31)	23 19-27	8	3.10	22.8	198	(116)* 115	136	796	14.0	179 70
Well-trained	Åstrand et al. + Saltin (1, 4)	25 23-30	6	4.93	28.9	185	(161)* 157	171	1073	14.6	186 77
	Grimby et al. (8)	51 45-60	9	3.56	26.8	171	(163)* 158	133	1060	13.5	173 70

*The highest attained stroke volume during exercise

TABLE I

Anthropometric and circulatory data in a group of young untrained subjects and in well-trained young males and middle-aged still-active athletes.

In Table I are data on two groups of well-trained athletes of different ages compared with students (8). The young athletes are superior to the untrained by a bigger maximal stroke volume and maximal cardiac output as well as a larger a-v oxygen difference. The old athletes keep their big hearts and are also able to maintain the same stroke volumes as the young athletes, but as the maximal heart rate is lowered the maximal cardiac output is decreased. The most important factor for the reduction in the maximal oxygen uptake in the old athletes is, however, the low a-v oxygen difference. No explanation for this is available so far. To what extent genetic factors are involved in the adapting of the athletes is not known. Recent data on young female swimmers suggest that if the training starts before they are full-grown (less than 15 years), a more marked increase in maximal oxygen uptake is possible to obtain compared with swimmers whose training starts later in life (32).

DR. GROVER: So there's a relation between the age at which you train a person and the degree to which he can improve?

DR. SALTIN: We have no systematic studies in this field, but our feelings are strong. If you start to train a ten year old boy or girl, you get an enormous increase comparable to what they really are doing on how they are trained or untrained, and if you do the same when they are twenty, there is less improvement in maximum oxygen output, and perhaps none when they are 40,

45 years of age. We saw it in our study of girl swimmers – I think their improvement in maximum oxygen uptake is not possible to achieve at any other age than just 10 to 15 years. For example, the best female swimmer, 15 years old, had a maximal oxygen uptake of 3.8 liters and that's about the same as the best female cross country skiers in the world, and she obtained this high maximum oxygen uptake in less than two years' training. It's very important when you start to do the training.

DR. BUSKIRK: Don't Jerry Mitchell and Young Won have some evidence that the arterial-venous oxygen differences may actually be smaller in some of their well-trained individuals compared to the untrained?

DR. SALTIN: The Minnesota group performed about the same kind of study that I presented, but they have had some troubles with their maximum cardiac output measurements and they haven't published more than just a figure in the Handbook of Physiology.

DR. BUSKIRK: Now, you would say from your data on the trained and the untrained individuals that these are real differences?

DR. SALTIN: Oh, yes. I haven't prepared to discuss training so I haven't the original data with me.

DR. WEIHE: Do you think even if you start training earlier there are genetical differences?

DR. SALTIN: That is a very interesting point. We don't know that. Earlier we thought there were genetic factors, but if you start training early enough, then genetic factors are not so much involved.

DR. BRAUER: I think this may be a terribly important point for much of the discussion of the failure of altitude adaptation which has gone through the literature as a myth, in which we are comparing the altitude reared people with sea level reared and point out that they don't adapt. I don't know of any experiments in which anyone has actually taken really young individuals and studied their altitude adaptation.

DR. WEIHE: No, but you can see in the mountain Alps in Europe that they start climbing very early. Families take their children up very early, and there is an old belief that they are much better mountaineers than those who come to the mountains later, say at the age of 25.

DR. HORVATH: Is this an impression or is this– –

DR. WEIHE: This is impression – it has not been investigated.

DR. DILL: These values haven't been reduced to unit of body weight or height, have they?

DR. SALTIN: No – you mean milliliters per kilo? But that calculation is easy to do.

DR. DILL: But I would like to say that you can't increase the heart volume of a man who weighs say, 50 kilos up to the heart volume of a man who weighs 80. You certainly have genetic differences in height and weight and I don't see any reason for thinking that you don't also – for a man of a given weight – have considerable genetic differences in the size of his heart and possibly the volume of his blood and his muscular system. I think there must be– –

DR. SALTIN: But in this study we compared the same individuals immediately before and after.

DR. DILL: Oh, yes, I understand that, but I think you're implying that a man by training can increase his heart size up to– –

DR. SALTIN: Oh, no, you have rather big differences in weight, you see.

Circulation during Exercise at Altitude

If we turn our interest to the effect of altitude, it is rather simple to describe its physical side by means of the changes in oxygen tension and density of the inspired air. The biological effects of the drop in oxygen tension are not so easy to quantitate exactly. Here I will first discuss data on the effect of acute exposure to altitude and then the effect of prolonged hypoxia in newcomers and compare them with natives at the same altitude.

Acute exposure. Stenberg et al. (33) have recently studied the central circulation during exercise of subjects at acute exposure to 4,000 meters. The study was performed in a low pressure chamber on six young men with various aerobic work capacities. The results are presented in Figure 7. The hemoglobin saturation of oxygen in the subjects at rest and during exercise fell from approximately 95% to 70%, which gave an oxygen content of the arterial blood of 130 ml compared with 175 ml/l at sea level. At the submaximal work level, there was a relative increase in cardiac output. The mechanical efficiency was unchanged, and the oxygen uptake during the submaximal bicycle exercise was the same at sea level and at altitude. Thus, the a-v oxygen difference was lowered at 4,000 meters altitude. For a given oxygen uptake, the calculated oxygen content of the mixed venous blood was lower at simulated altitude and the concentration of lactic acid was higher.

DR. CHIODI: Do you have arterial oxygen percentage saturations at rest in these subjects?

DR. SALTIN: I don't have them in my mind – I will say they were just not such big differences. They were very stable, and that surprised us very much.

DR. CHIODI: 4,000 meters is a little too low for complete oxygen saturation.

DR. SALTIN: Yes, we know that, but we had another study, six more young male subjects, and they had 65-66 percent.

DR. CHIODI: At 4,000 meters in the mountains, you get around – between 80 and 85 percent.

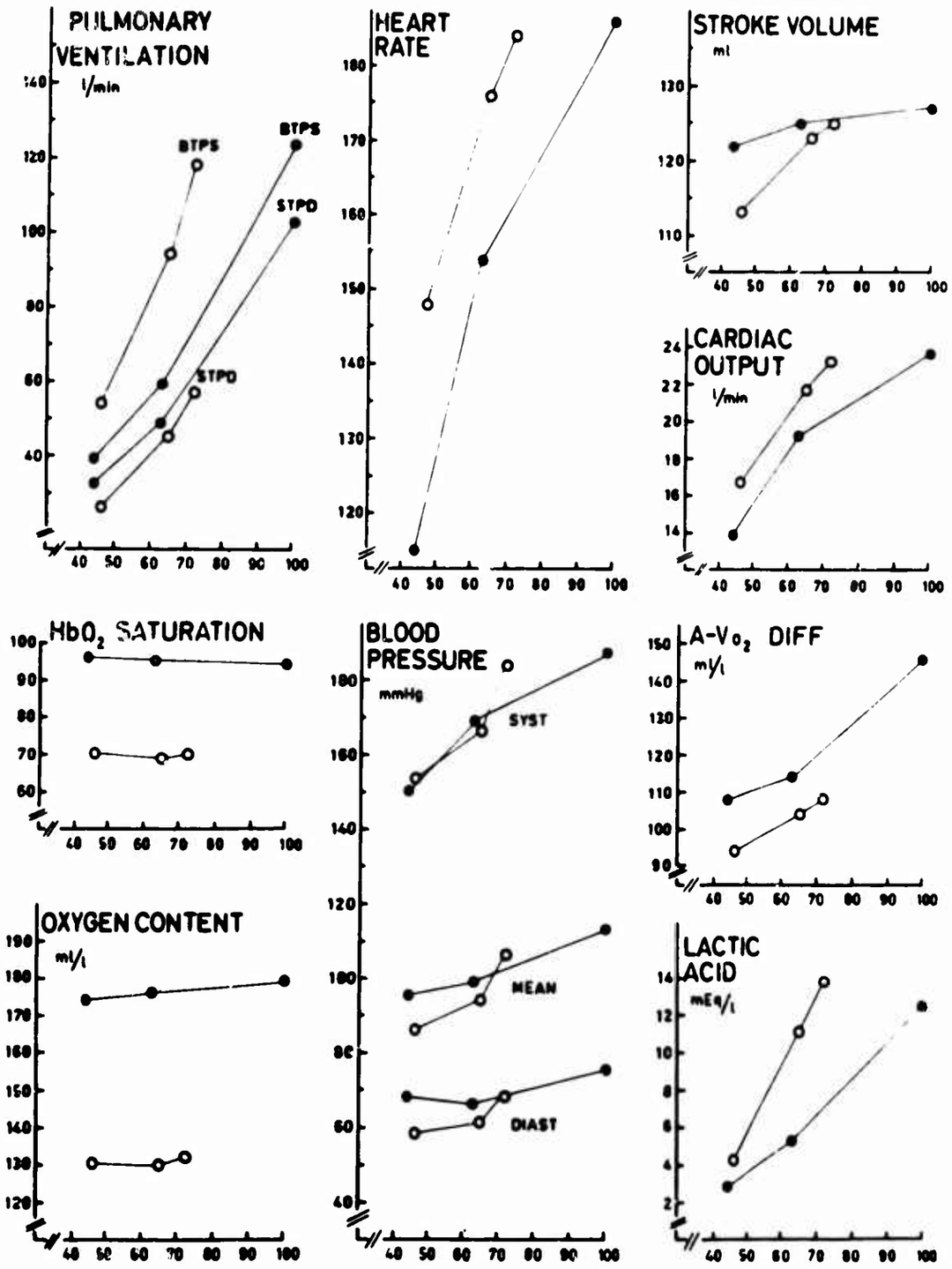


Figure 7

Data from experiments on six young men performing submaximal and maximal exercise at sea level (unfilled circles) and at acute exposure to 4,000 meters (filled circles) (33). For further explanation, see text.

DR. BLATTEIS: But this is just one hour at 4,000 meters.

The stroke volume was somewhat lower at submaximal work at altitude but almost the same at maximal exercise at sea level and at altitude. This means that there was a marked increase in the heart rate at submaximal work levels.

The integrated mean blood pressure in the brachial artery was lower during submaximal work during hypoxia in consideration of the higher cardiac output, which to a lesser degree is valid even for the maximal pressure. During maximal exercise, cardiac output, heart rate and stroke volume are the same at altitude and at sea level, which makes it impossible to tell if the exercise was performed during normoxia or hypoxia (cf. also Figure 6).

DR. HORVATH: Were these very highly trained individuals?

DR. SALTIN: The average maximum oxygen uptake was just about four liters, 3 to 4.5 l. They were slightly trained, all of them, but none of them was in athletic condition.

DR. DILL: What about the ventilation? I can't read those figures.

DR. SALTIN: I haven't prepared that part. There is, of course, a marked increase.

DR. DILL: What was the weight of the individuals?

DR. SALTIN: 71 Kilos.

DR. DILL: I would like to comment on the very large differences between these observations and ours, the weight of our individuals – speaking only of the three young men who range from 19 to 35, the weight ranged from 77 to 90 kilos, so they were larger, but the maximum ventilation ranged from 160 to 200.

DR. SALTIN: At acute exposure?

DR. DILL: At acute exposure, yes.

DR. SALTIN: We have never seen in any of our group at acute exposure to exercise – acute exposure to low pressure, any marked increase in maximal pulmonary ventilation rate.

DR. DILL: No, these didn't increase either, they reached the same maximum virtually without regard to altitude, but it was 160 to 200. We didn't have arterial oxygen saturation, but the blood pressure also reached about the same level, 200 to 210, systolic, and we didn't have any cardiac outputs, but the oxygen consumption instead of being limited at that altitude to about 75 percent was more like 85 percent of the maximum.

DR. SALTIN: But if you take the four liters in maximum oxygen uptake that means that you have more than 40.

DR. DILL: Not much, their maximum oxygen was a little lower for their weight. It ranged from about 3.6 to 3.8, along in there I think, but as Dr. Chiodi says, those are extraordinarily low arterial saturations, and also the results don't agree with Dr. Grover, who showed a decline in oxygen saturation with intensity of work.

DR. BRAUER: How did you obtain the blood samples for the oxygen saturation, were those arterial punctures or– –

DR. SALTIN: Dye dilution technique.

DR. BRAUER: No, I mean the oxygen.

DR. SALTIN: Oh, yes, but the catheter was in the artery; we very seldom see marked decrease in oxygen saturation during even very high exercise levels – say at sea level, none below 93, 94, while at rest they have 96 or something like that.

DR. CHIODI: Did you try to keep subjects longer in a low pressure chamber to see if the saturation goes up? It could be a later response of ventilation of the subject.

DR. SALTIN: Our low pressure chamber is very small, so you can only stay there for a couple of hours; if you are highly motivated you can perhaps stay there overnight, but not more.

DR. CHIODI: That would be enough. I didn't mean a long time, but at least three or four hours. Was there a later response in the ventilation that would increase the oxygen saturation?

DR. SALTIN: Oh, yes.

DR. DILL: Hugo, our exposures were even shorter than his. We didn't pay attention to the resting ventilation, we measured it but the subjects weren't basal. They had been sitting on a bicycle a relatively short time; however, after work started the ventilation was essentially the same, if anything a little higher at altitude than at sea level. In other words there was no lag in attaining a high ventilation rate in exercise. I know there is in rest but there's not in exercise.

DR. SALTIN: In another group of nine athletes who were also exposed to this altitude, this low pressure, we saw a rather marked drop in oxygen saturation. It was lower than expected.

DR. CHIODI: How fast is the circulation of the air through the chamber?

DR. SALTIN: It is absolutely no problem, though I can't give the figure in liters, but you know a tremendous amount of air flows through that chamber and we checked it continuously.

However, in this situation the reduction in maximal oxygen uptake from 4.24 to 3.07 l/min can explain completely the reduced performance capacity. The reduction in maximal oxygen uptake parallels the reduced volume of oxygen leaving the lungs during maximal exercise.

From this data, it must therefore be concluded that at maximal exercise the circulation could not compensate for the low arterial oxygen content either by an increased cardiac output or by a more effective distribution of blood to the working muscles.

Prolonged sojourn, altitude. During a prolonged stay at altitude, there is an increase in hemoglobin concentration. This is initally due to a reduced plasma volume but later there is a true polycythemia as the red cell volume and total amount of hemoglobin also increase (34). During the acclimatization period, the cardiac output at rest and at submaximal work loads gradually returns to sea-level values within 2-3 weeks, even at an altitude of 5,800 meters (35-38). This "normalization" of the cardiac output has been related to the changes in hemoglobin concentration or blood volume. This may be partly true, but other still-unknown factors may also be involved. The heart rate response at submaximal levels of exercise during prolonged hypoxia follows the same pattern as the cardiac output with a gradual decrease in heart rate at a given oxygen uptake (35, 39-42). After 2-4 weeks of acclimatization, the heart rate usually falls in the same range as those recorded under sea-level conditions, but there are big individual differences (34, 38, 43).

At maximal or very heavy work loads, however, most studies have shown that there is a remarkable reduction of 30-50 beats/min in the attained heart rates (35, 37, 39-42). This decrease is not a constant finding in all studies and subjects, but is more common at higher altitudes (over 4,000 meters) and during sojourns longer than 3-4 weeks. The effect on the maximal heart rate when 100% oxygen is breathed in this situation is very fascinating (40). As can be seen in Figure 8, the heart rate increases 20-30 beats/min at the two maximal work loads, when the subject after six minutes of exercise switches over from breathing air to breathing pure oxygen. At 900 kpm/min, which was a submaximal load, the heart rate was lowered somewhat after a transient small increase.

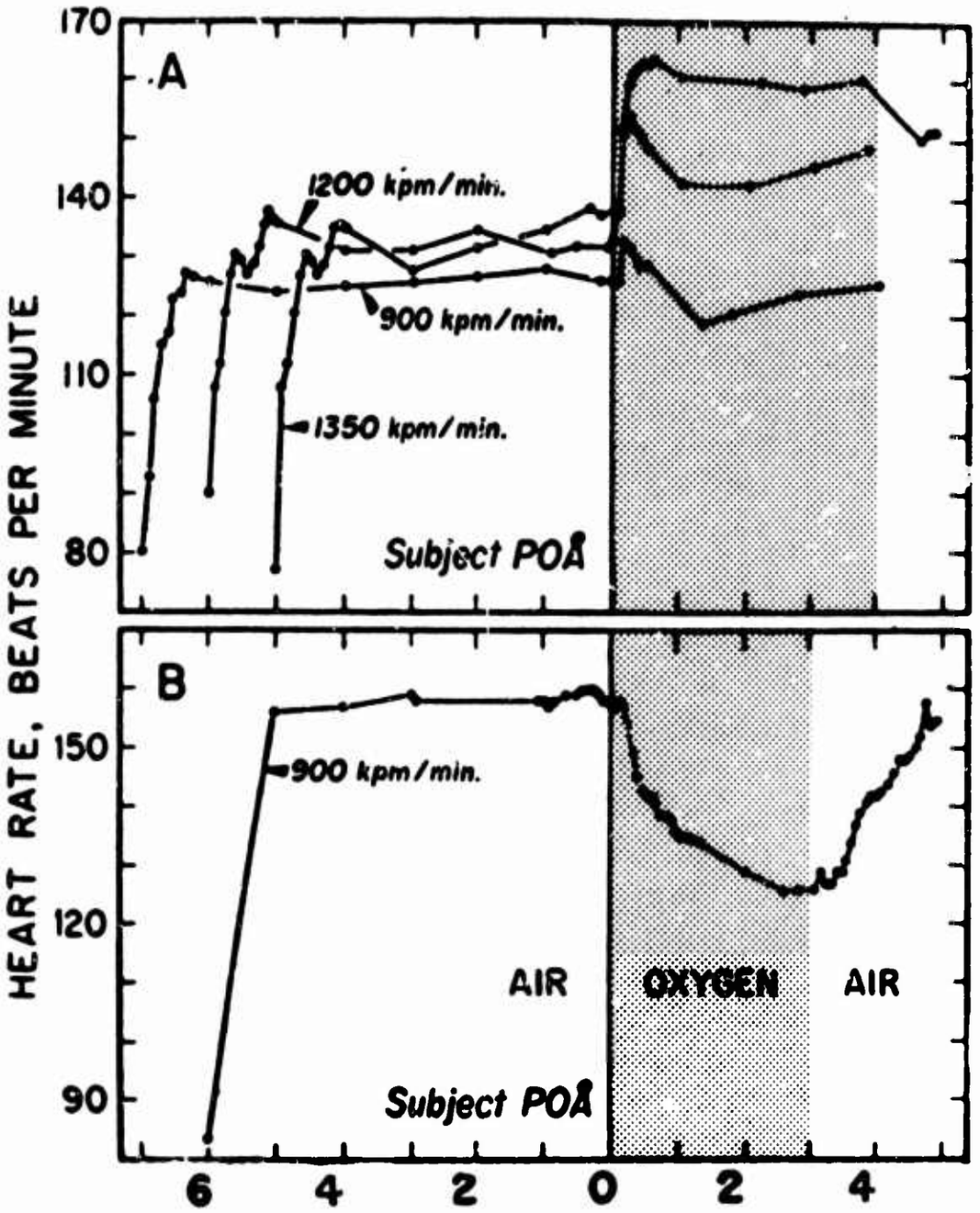


Figure 8

Heart rate and its changes when O_2 is substituted for air, or reverse, during continuous cycling. A is after 17 days at 14,200 ft and B is acute exposure to the same altitude. 1200 and 1350 kpm/min are maximal work loads (40).

DR. HORVATH: Is my recollection correct, that the other subjects who were in this study did not show different response?

DR. SALTIN: They showed – for example, Åstrand's wife showed a slight increase, but the other two didn't show the same pattern.

DR. BUSKIRK: What happens to Åstrand when he does other things? He's got practically a square heart rate response to exercise. This is in itself kind of unusual. What happens when he is exposed to other stresses?

DR. SALTIN: He knows what to do.

DR. HORVATH: This emphasizes the huge problem of individual differences here, and interpretation of results from exceptionally large individual variation.

Pugh (35) found an even more pronounced effect of oxygen breathing after two months at 5,800 meters, with the heart returning to almost the same maximal values as at sea level. It is supposed that the hypoxia could have a direct effect on the heart muscle or the conduction system of the heart, but the question is then why there are no immediate effects (40). A further possibility is arterial chemoreceptor activity. In dogs the chemoreceptors, when stimulated by hypoxia, induce bradycardia (44). This effect is masked in the spontaneously breathing animal by a more powerful cardiac acceleratory reflex elicited from lung receptors which are activated by the hyperpnea also caused by the hypoxia. If this chemoreceptor reflex on the heart rate is the reason for the lowering of the heart rate during acclimatization, it must be presumed that cardiac acceleration in connection with hyperventilation gradually lessens.

Very few data are available regarding maximal cardiac output on newcomers staying for longer periods at altitude. At the extremely high altitude of 5,800 meters, Pugh (35) reported a decrease in maximal cardiac output from 23-25 to 16-17 l/min. The corresponding maximal values for the heart rate were 192 and 144 beats/min, which means that the stroke volume was reduced but only to a minor extent. Vogel et al. (45) have very recently presented data from

a study involving maximal exercise in 16 subjects at sea level and after 1-4 days and 15-18 days at 4,300 meters (Pikes Peak). Some of the subjects arrived at Pikes Peak after one-week stops at intermediate altitudes. Some also regularly performed training during the stay at altitude. The cardiac outputs were determined with the dye-dilution technique. The cardiac output during the first week at altitude increased at rest and at all levels of exercise, including the maximal work load, compared with sea level. There was about the same tendency in the group with abrupt ascent and the group with gradual ascent, even if the absolute amount in increase differed somewhat. With a further acclimatization, the cardiac output returned almost to sea-level values. This was true also for the maximal cardiac output. There was already a small decrease in maximal heart rate between sea level and the first week at altitude, which during the prolonged stay became more marked; the maximal stroke volume was, on the average, 10-15 ml higher at altitude than at sea level.

It is a very interesting finding, indeed, that the circulation would thus have the ability to increase its capacity during hypoxia by increasing the stroke volume when the demand of the tissue for oxygen is augmented. It is, however, very difficult to generalize from the findings in this series. There are many situations where the same adaptation should be of great importance, but no one has been able to present similar data. Furthermore, in the study by Vogel et al. (45) the arterial blood pressure during hypoxic maximal work was not significantly changed from sea-level values. With an unchanged or even higher flow this indicates the same or a higher stroke work of the heart. Thus, the metabolic rate and the oxygen uptake of the myocardium are the same or higher at altitude. One must assume an increase in the maximal coronary blood flow equaling the drop in oxygen content of arterial blood at altitude. Even if I have expressed some astonishment at the increase in the maximal values for stroke volume and cardiac output during hypoxia, Vogel's results should be noted, but I think further studies are justified. If possible, the sojourn at altitude should be prolonged so studies also could be performed when the maximal heart rate has been reduced to values much below sea level values.

Ceretelli (46) has brought up doubt about any benefits of an acclimatization period with regard to maximal oxygen uptake. He states from data in the literature that the net result of a prolonged sojourn at altitude is a further reduction in maximal oxygen uptake during the adaptation period, due to a decrease in maximal heart rate and an increased viscosity of the blood when the hematocrit increases. Judging from studies presented last year by Balke et al. (47), Ikai et al. (48) and Saltin (3), 3-5 weeks acclimatization at 2,000-3,000

meters altitude caused a small improvement in the maximal oxygen uptake. The data by Buskirk et al. (34) and Grover and Reeves (43) show neither a definite improvement nor a decrease in the maximal oxygen uptake at altitudes between 3,000 to 4,000 meters, beyond the initial drop when the subjects arrived at the altitude. DeGraff et al. (49) and Dill et al. (50), however, both found about 10% improvement after, respectively, six and five weeks' stay at this altitude (compare Figure 9). At even higher altitudes a negative effect on the aerobic

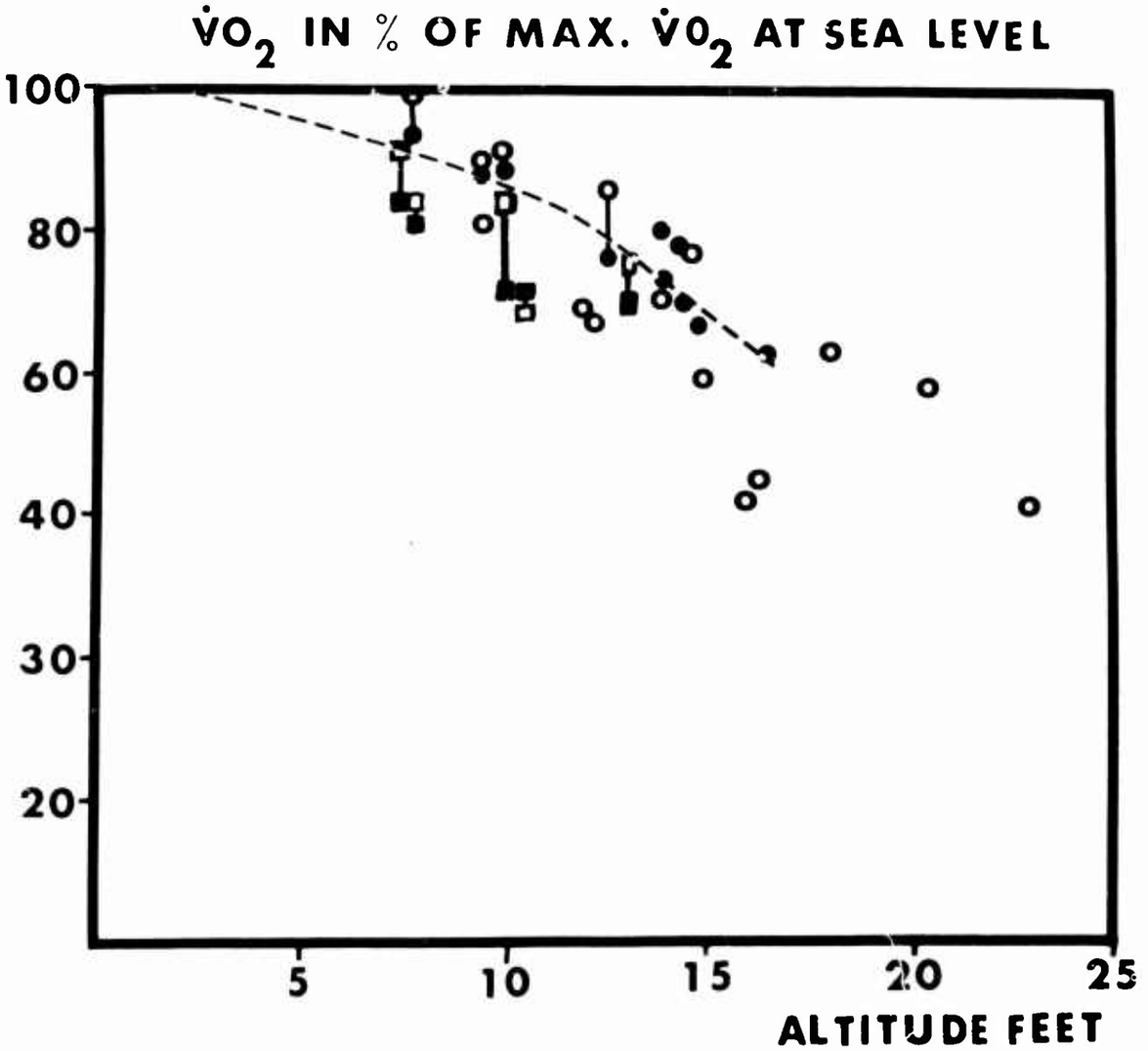


Figure 9
Maximal oxygen uptake in % of sea level values at acute exposure to altitude (filled symbols) and after prolonged sojourn (unfilled symbols). The hatched line denotes average values for acute exposure to altitude. Note that the filled rectangles (athletes) all are below the line. Data are from references (33, 34, 39, 41, 43, 47, 48, 50, 51, 61, 74, 75, 76).

capacity may be more likely as these altitudes cause the most marked increase in hematocrit and drop in maximal heart rate during a prolonged sojourn. However, I do not know of any data directly supporting this view. Furthermore, mountain climbers' experiences are that there is an overall positive effect of acclimatization at this altitude which speaks for no marked decrease in the maximal oxygen uptake (42). More studies are, however, necessary for a final answer.

Natives of high altitudes. Many studies have shown remarkable physical capacities of native residents living in the Himalayas, Rocky Mountains and the Andes. For example, Peruvian natives at 4,500 meters altitude have been found to have 41-50 ml/kg x min (51, 52) in aerobic capacities, which compares well with average values found in sedentary living at sea level. Sedentary newcomers to altitude, therefore, are inferior to the native residents but, as shown by Grover and Reeves (43) and Buskirk et al. (34), sea-level athletes are in general superior even to well-trained altitude residents when competing at high altitude. The situation is somewhat different when top athletes from sea level compete with top athletes from altitude, which was clearly shown last October in Mexico City. In the 140 kilometer bicycle race, the world's best had no chance against the top bicyclists from Mexico, who secured the first eleven places in the race. It will, therefore, be very interesting to see to what extent the sea-level athletes can adapt to medium altitude. A definite answer will be given during the 1968 Olympic Games when sea-level athletes have to compete at 2,250 meters above sea level (m.a.s.l.) against Bikila of Ethiopia and Keino of Kenya who are native residents at medium altitude.

In connection with competition at high altitude, Åstrand (cross-country skiing, Squaw Valley, 1960; 1900 m.a.s.l.) and Saltin (cross-country running, Le Brassus, 1964; 1650 m.a.s.l.) have experience in three cases, with athletes who were striken by "blackouts" when they passed the highest part of the race. In the three cases, the symptoms disappeared after a couple of minutes of rest and the athletes were able to continue to race but with a lower speed. It should be emphasized that none of the the athletes before or later have experienced the same thing. The genesis for this "blackout" is obscure, but hypocapnia is a possibility, since a low CO_2 tension influences the cerebral blood flow (53).

The study by Elsner et al. (52) revealed a maximal heart rate of the native Peruvian Indians to be between 180-200 beats/min. Breathing an air mixture corresponding to sea-level oxygen tension did not increase the maximal heart rate, but a simulated altitude of 6,400 meters caused a marked decrease in maximal heart rate. Thus, the situation is that sea-level natives have no or a very

small decrease in maximal heart rate at acute exposure to altitude but develop a pronounced decrease during a prolonged stay at high altitude. Native residents reach, in accordance with their age, the expected level for maximal heart rate when exercising at their accustomed altitude. They experienced, however, in contrast to sea-level residents, a reduction in maximal heart rate at acute exposure to an altitude higher than they are adapted to. In fact, it is a complex situation.

Another striking finding in native residents of altitude is the pulmonary hypertension and the right ventricular hypertrophy. The elevation of the pulmonary pressure in subjects at rest is related to altitude. As reported by Vogel et al. (54) the mean pulmonary pressure is 15-16 mm Hg in those persons living at about 2,000 meters altitude, and 25-28 mm Hg for men living at 3,800-4,500 meters altitude compared with 13 mm Hg for men at sea level. As can be seen in Figure 10, the pulmonary artery pressure at rest is elevated in this group of

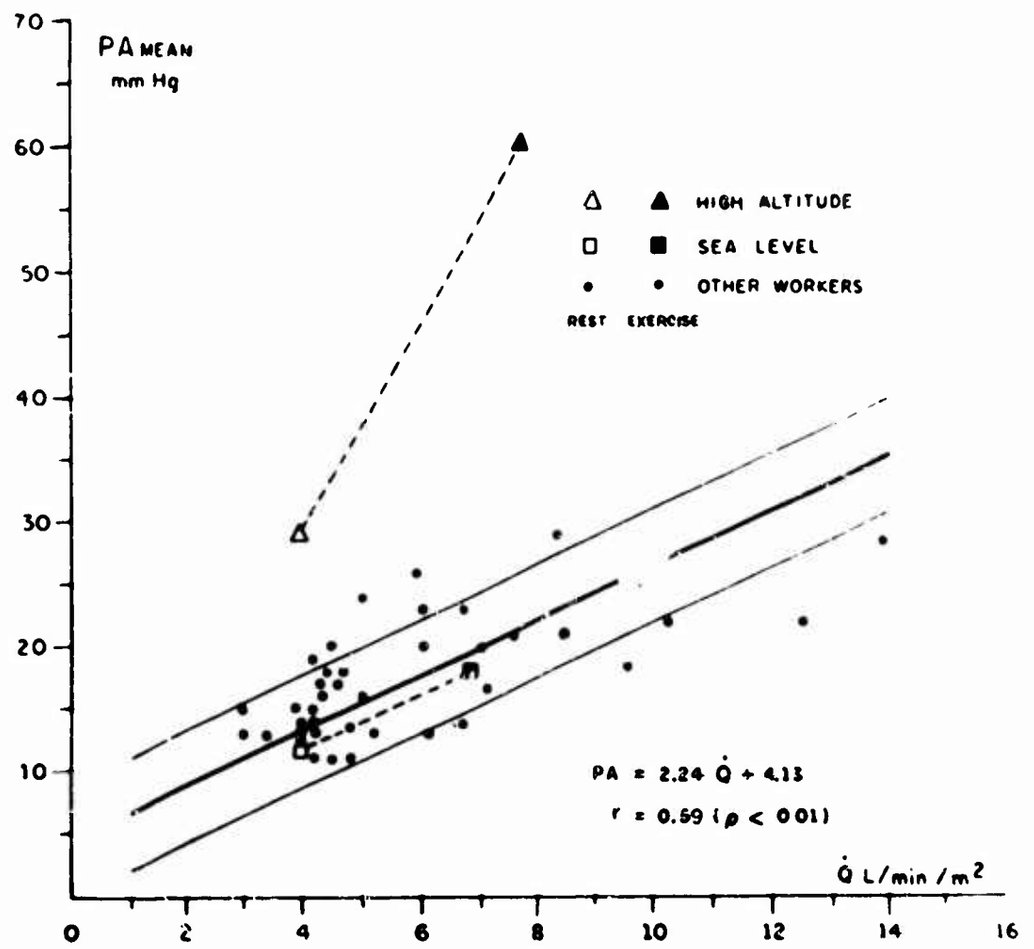


Figure 10

Pulmonary pressure in a group of native residents at rest and during exercise at altitude to 4,540 meters (triangles). The regression line (±ISEE) denotes different material of sea-level residents investigated at sea level (56).

Morococha natives and during light supine exercise the increase is almost incredible (55). Also, sea-level natives slowly develop a pulmonary hypertension during prolonged exposure to hypoxia. Rotta el al. (56) reported that in six sea-level men, after they had lived 12 months at 4,500 meters altitude, the mean pulmonary arterial pressure at rest was 18 mm Hg, compared with 12 mm Hg for sea-level men and 24 for native residents of Morococha. There is also ample evidence that the hypertrophy of the muscle cells of the lung precapillary vessels found in native residents of altitude is associated with the increased pulmonary resistance. Reeves et al. (57) have presented data from experiments with calves indicating that a low airway O_2 tension caused the pulmonary hypertension and not the low oxygen saturation of the blood. This could be expected, since the oxygen content of mixed venous blood during exercise is decreased, and no evidence for pulmonary nypertension is found either in people whose jobs involve heavy physical labor or in athletes in endurance events. The still unsolved problem in connection with pulmonary hypertension at altitude is if it is a consequence of hypoxia without any benefits for the acclimatization process. Grover (see 58) has expressed an opinion that the elevated pulmonary pressure improves the perfusion ratio of the lung. If Grover is right, it is a very high price to pay for the very minor improvement that can be achieved, as it normally is an almost uniform distribution of the lung during exercise.

In this connection, it is worth remembering the occurrence of pulmonary edema with no evidence of left heart failure in native residents of an altitude of 3,000 meters or more when they return to altitude after at least 10-14 days' stay at sea level (59). The same is true for sea-level residents who several times have been partly adapted to higher altitudes. Its genesis and how often it happens in high-altitude and sea-level natives is not known.

The electrocardiogram in newcomers. The electrocardiogram of subjects during submaximal and maximal exercise shows no pathological changes at acute exposure to 4,000 meters (60). In this study the arterial oxygen saturation during exercise at altitude was 70% and the O_2-tension around 40 mm Hg. After a three-weeks' stay at 4,300 meters altitude, Åstrand and Åstrand (40) have reported S-T segment depression and ectopic beats during exercise, which almost disappear when breathing oxygen. Pugh (42), however, could not find any abnormalities in the ECG at rest and at exercise after more than two months at 5,800 meters.

The Effect of Cold on the Circulation

Finally, some aspects of how acute exposure to cold influences the cardiovascular system will be mentioned. In Table II, data at submaximal and maximal work in +20° C and in −5° C are given for two subjects. The work experiments in the cold started after the subjects rested nude 10 min in the cold environment. At the end of the 10-min submaximal work period their oxygen uptake, heart rate and arterial lactic acid are the same in the normal and the cold climate, but the puimonary ventilation is somewhat higher in the cold. At the maximal work load, the values for oxygen uptake, heart rate, arterial lactic acid and work time are also the same in the cold as compared with the normal environment, but again the same slight tendency to a higher pulmonary ventilation is found in the cold. That the overall maximal respiratory and circulatory capacity is unchanged in short-term cold exposure is also shown by cross-country skiers, who during maximal work on a bicycle ergometer in room temperature got 4.90 l/min in oxygen uptake compared with 5.02 l/min during maximal skiing in 20° C below zero (61).

TABLE II

Submaximal Work A and B = 750 kpm/min.

	$\dot{V}O_2$,l		V_{BTPS},l		Blood lactate		HR	
	A	B	A	B	A	B	A	B
20° C	1.81	1.80	57.7	44.7	8.1	7.6	152	128
5o C	1.93	1.77	68.7	44.6	9.0	6.7	155	130

Maximal Work A = 1350 kpm/min. B = 1500 kpm/min.

	$\dot{V}O_2$,l		V_{BTPS},l		Blood lactate		HR		Work time sec	
	A	B	A	B	A	B	A	B	A	B
20° C	2.55	2.99	105.2	110.7	11.6	12.1	192	180	95	205
5° C	2.52	2.96	113.2	116.2	12.0	11.5	191	181	102	190

TABLE II

Data from submaximal and maximal exercise of two subjects in +20° C and −5° C.

DR. DILL: These figures here, in Table II, A and B, B is about double A in work time.

DR. SALTIN: This is work time of maximum workload and A performed this and B performed this.

DR. DILL: Oh, B is maximal. Yet the heart rate and lactate are about the same, aren't they?

DR. SALTIN: Oh, yes, but my way of expressing it – the maximum oxygen uptake of 2.5 liters means that he can't do more than 95 seconds because he is not fit from a physical fitness point of view.

COL. GOLTRA: How are these people clothed? In other words, what kind of stress would there be?

DR. SALTIN: You mean the cross-country skiers? They wear very light clothes, they have a shirt and – they don't wear any gloves, for example.

DR. HORVATH: Probably less than a clo.

One of the very few measurements that is available regarding work at altitude in connection with prolonged cold exposure is Pugh et al.'s (39) data obtained during climbing in the Himalayas (Figure 11). The reduction in maximal oxygen uptake is almost that expected from the reduction in inspired O_2-tension at the different altitudes. The mountaineers, however, seem to keep the same climbing speed at all altitudes up to 6,000 meters, which means that the relative work load was 50-60% of that at 1,000 meters altitude but the maximal oxygen uptake was 90% of that at 6,000 meters. Thus, it is obvious that the cold per se does not affect either the maximal oxygen uptake or the performance capacity. Below -25° C no competition in cross-country skiing is allowed in Scandinavia. This is mainly because of troubles of the respiratory tracts, but frostbite in the feet and in the face can also occur sometimes at this temperature.

During exercise in cold, the surplus of heat in the core of the body is

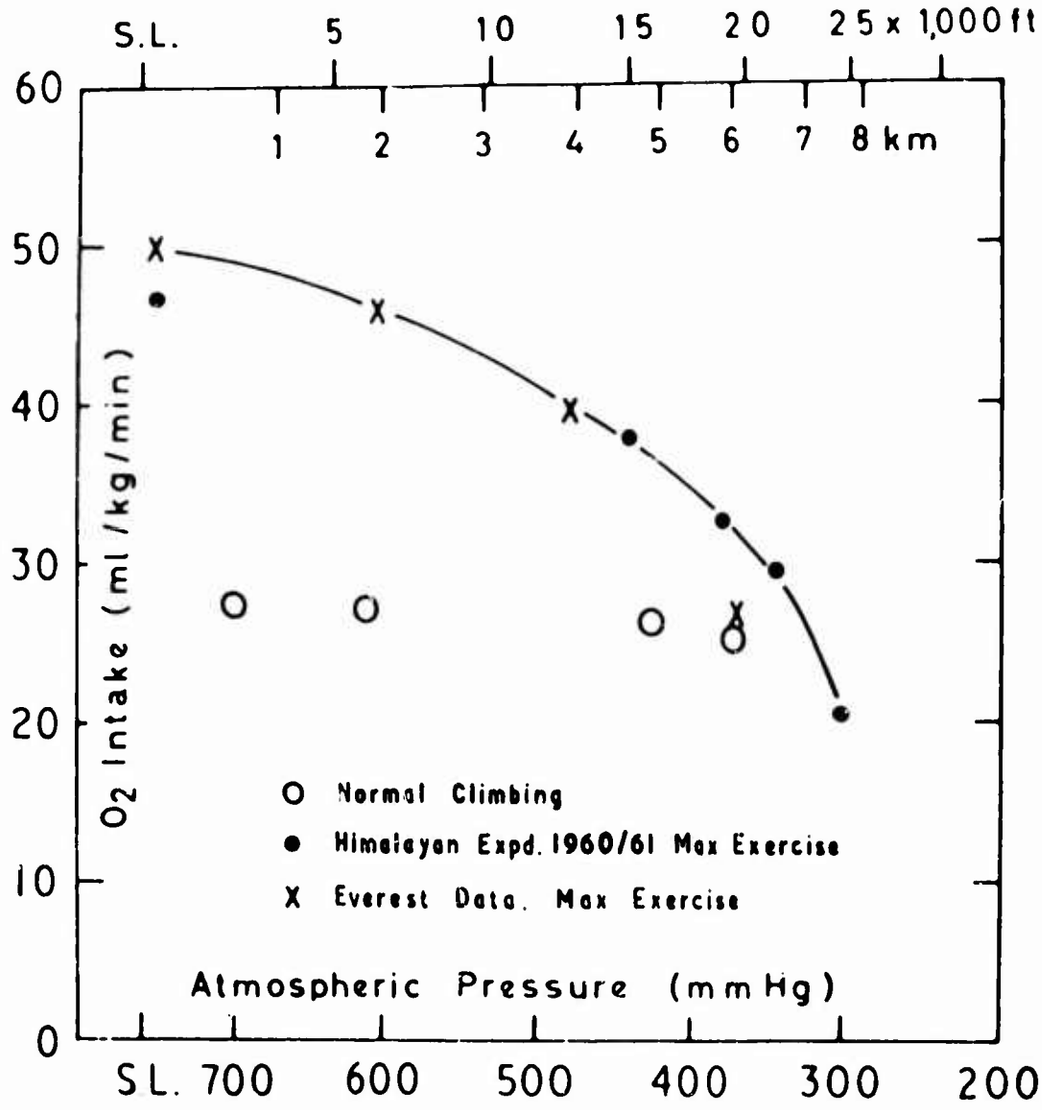


Figure 11
Relation of maximum oxygen uptake to atmospheric pressure and altitude. Also shown are average values for oxygen uptake of men at their habitual climbing pace (39).

essential, since it facilitates vasodilation in peripheral vascular beds; thus the subject can maintain higher peripheral temperatures, as has been shown in groups of lumberjacks, fishermen and students (62). During exercise (300 kpm/min) of subjects in a warm environment, the fingerpad temperature after a transient

decrease is in most subjects in all groups around 35° C, which is the same or somewhat higher than at rest. In the 5° C environment, during rest there is a steady fall in the fingerpad temperature, and no load exercise (oxygen uptake around 0.45 l/min) is not enough to bring the temperature back up to 30° C. In subjects performing 600 kpm/min in the same climate, a skin vasodilatation occurs as the fingerpad temperature increases, after the initial fall, to almost the same as in the warm environment. The temperature starts to increase earlier and attains somewhat higher values in the fishermen and the lumberjacks, who are more used to cold exposure than are the students. These findings fit well with he experience that cross-country skiers very seldom wear gloves during competition even when the temperatures are 10-15° C below freezing point (body clothing 1<clo). In this manner, an important part of the heat excess during skiing can be emitted from the hands, thereby reducing the need for evaporation, which nevertheless is as high as 0.5-1.0 l/hr. (63).

The problem with the cold environment arises when the metabolic heat does not cover the heat loss. This is, however, not primarily a problem for the central circulation, but must be solved in terms of more effective thermal insulation which means better clothing in connection with an adaptation to cold if that occurs. One effect of wearing heavy clothes is an increase in energy expenditure, which also causes a stress on the central circulatory system. If the effect of altitude which causes a lowering of the maximal oxygen uptake is added, the aerobic work capacity may be critical in a situation of surviving in arctic and/or high-altitude regions. From the standpoint of circulatory aspects on cold, work, and altitude, the importance of a good physical capacity, therefore, must be stressed. The most important advantage of being in good physical condition in these situations is probably that the ability to work with a higher percent of the maximal oxygen uptake improves during a training period much faster than does the increase in aerobic work capacity.

Adams and Heberling (64) have also presented evidence that a three-week training program can modify the response to a standard cold exposure. In Figure 12, average skin, toe and rectal temperatures are illustrated before and after training of subjects. The skin temperature can be kept on a somewhat higher level after the training, but in spite of a small increase in the metabolic rate, the rectal temperature is 0.5° C lower after the training period. The pattern for response to the cold stress after the training period is similar to the behavior of Eskimos and cold-adapted young Norwegians. Some doubt about the benefits of physical fitness regarding the cold adaptation has been presented (65), but if the positive effects are genuine, it further implies the importance of physical training before entering cold and high-altitude regions.

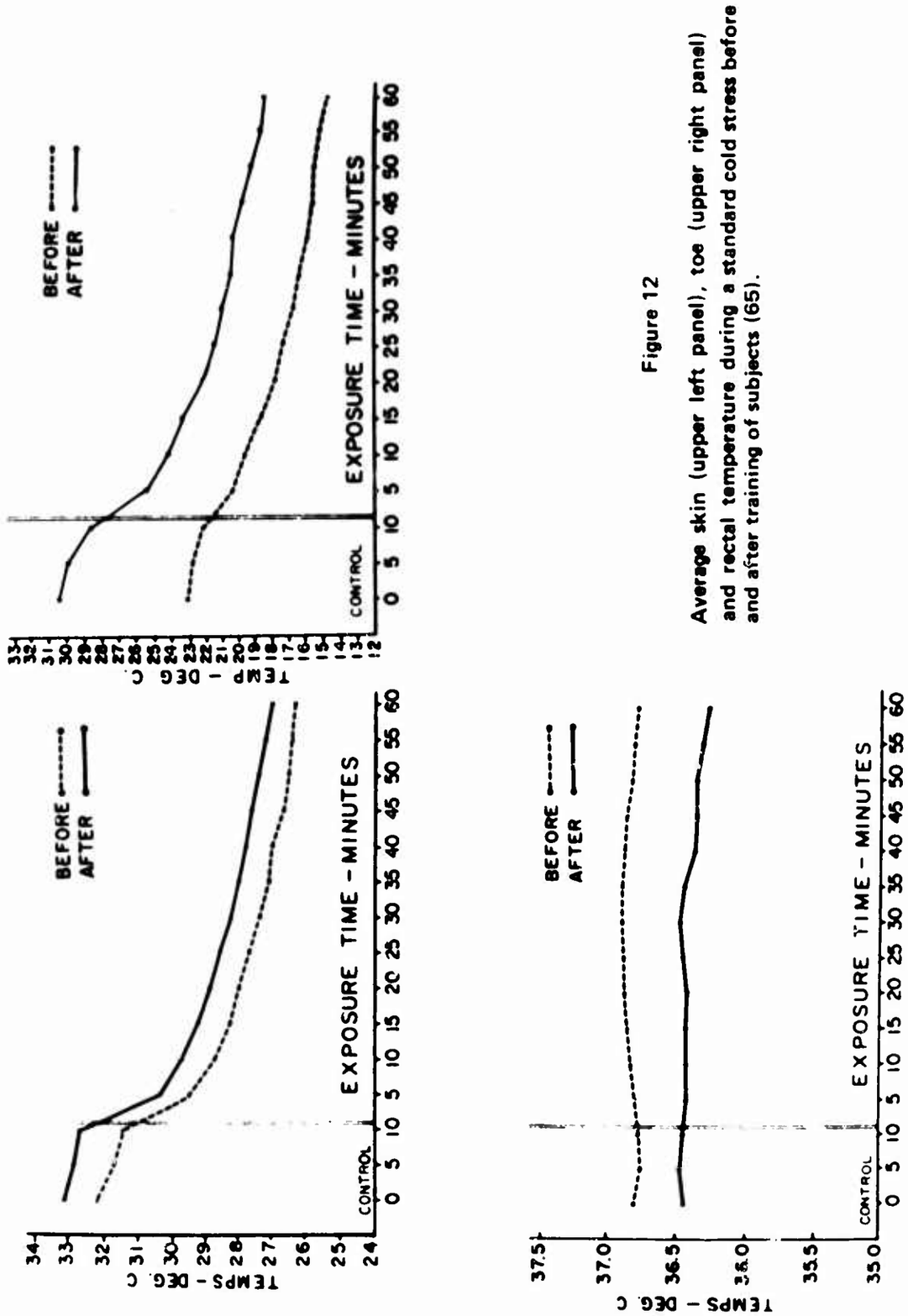


Figure 12

Average skin (upper left panel), toe (upper right panel) and rectal temperature during a standard cold stress before and after training of subjects (65).

Glycogen Store and Ability to Do Prolonged Heavy Exercise

Instead of giving a summary, I plan to present some recent data on the importance of the glycogen store for man's ability to perform prolonged heavy muscular exercise. Since Pettenkofer and Voit's experiment in 1866 (66), it has been known that both carbohydrates and fat are used as fuel for the muscle during exercise. During the last decade excellent work has been done to show the mechanisms of fat mobilization from the depots and the pathways to the muscle during exercise (67, 68). These results have impressed many people so much that they have more or less forgotten the older studies, which definitely also show that fat was used as fuel for the muscle. At heavier work loads, however, the percentage use of carbohydrates increases (69).

The first study (70) that was undertaken consists of repeated 20-min work periods until exhaustion on a work load (bicycle) corresponding to 75-80% of the individual's maximal oxygen uptake. Between each work period the subject rested for 15 min during which time the muscle biopsy was made. Ten untrained and 10 trained subjects were used. Almost all of the subjects were exhausted during the fifth or sixth work periods. At the end of the first work period, the RQ was 0.96 in the untrained and 0.91 in the trained group. During the prolonged work only a small decrease occurred and during the last period the RQ still was 0.91 and 0.89, respectively. The calculated amount of carbohydrates used (from $V\dot{O}_2$ and RQ) was in the both groups 2.7 gm/min, and this figure was almost constant throughout all work periods. At exhaustion, the blood glucose was not lower than 50 mg% and the blood lactate not higher than 5 mM/L in any subject. Figure 13 illustrates what happens to the glycogen content in the quadriceps muscle. The average content of glycogen before the start of exercise was 1.6% of the muscle's wet weight. During the first three work periods there is an almost linear decrease, and when the subject is exhausted the glycogen content is zero or very close to zero in this muscle group. Since the RQ and the rate of carbohydrate used are very little changed in the last periods, the suggestion is that the liver can provide the working muscle with some glucose. Whenever the depot is empty there are no longer any possibilities for the subject to perform this high work level. It should be emphasized that the subjects are able to pedal the bicycle on a lower work load, but, as pointed out above, it is absolutely impossible to continue at the same work load.

In the second set of experiments (71, 72) six subjects were used. Before the first experiment, the subject had had a mixed diet. The work load was 75-80% of maximal oxygen uptake and the subject worked to complete

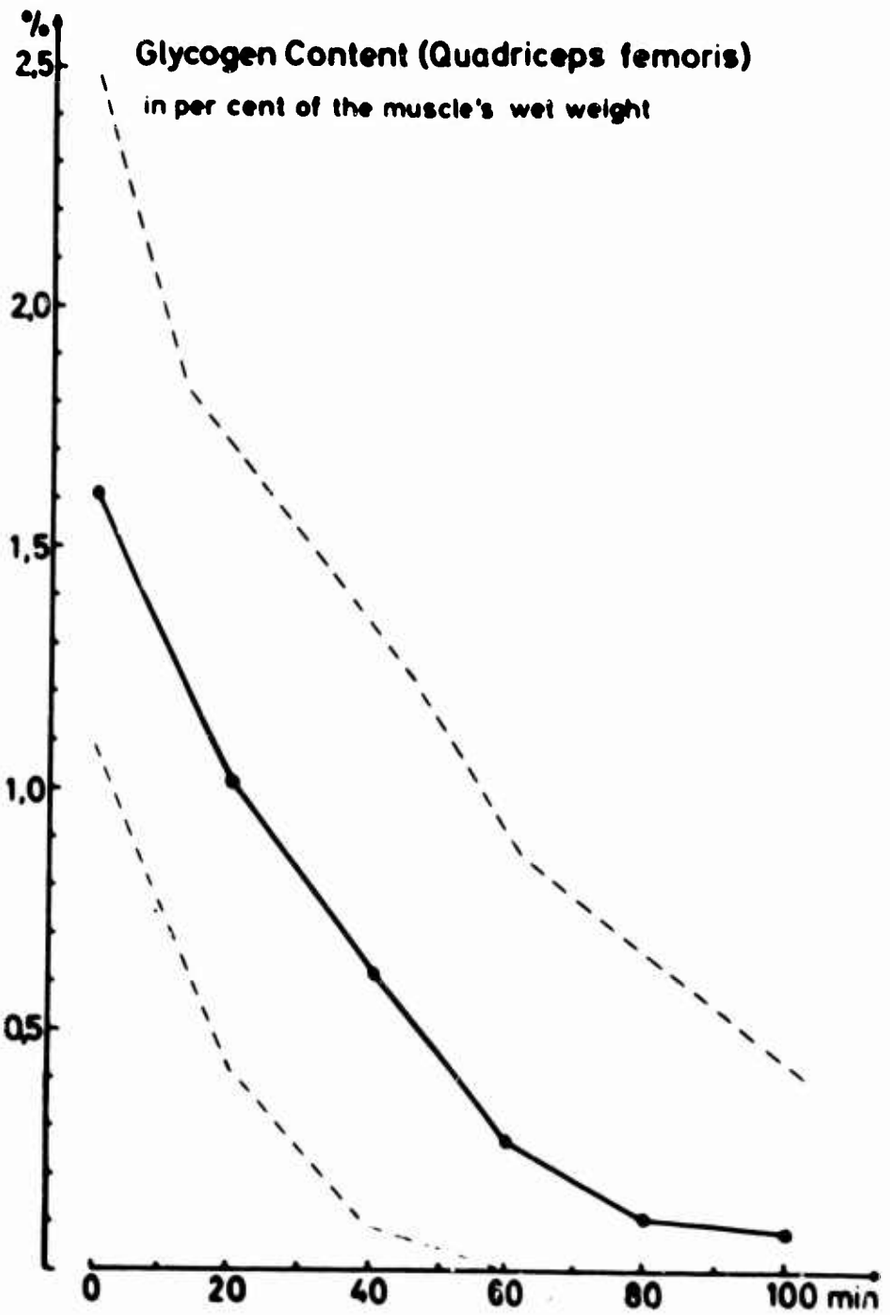


Figure 13

Glycogen content in the quadriceps muscle before and during prolonged heavy exercise (80% of maximal VO_2) performed to exhaustion in a group of 10 subjects (Hultman, Hermansen and Saltin; to be published).*

***Editor's note: By the time this symposium was in preparation, these studies had already appeared. See references 70, 71, 72.**

exhaustion. After this work was performed, the subject had a protein and fat diet for 72 hours, whereafter the subject pushed himself to exhaustion on the same work load. For the next 72 hours, he ate a carbohydrate diet (2,300 kcal carbohydrates and 500 kcal protein) and then the last work experiment followed. The results regarding the glycogen content and maximal work time are found in Figure 14.

I think these results clearly show the importance of available carbohydrate stores for the capacity of a subject to perform prolonged heavy exercise. The reason for bringing up this topic in this symposium is that at altitude and in cold exposure available carbohydrates may be an even more important limiting factor for prolonged work performance. This is because cold exposure may deplete the glycogen store, and because the same external work load performed at sea level and at altitude results in a higher RQ at altitude.

DISCUSSION

DR. BUSKIRK: Let's extrapolate for a minute to the situation of your cross country skiers during a 50 kilometer race: they are working more than 120 minutes and theoretically they couldn't do this on a mixed diet, is that what you're saying? They're working at 90 percent of their capacity, which means according to your slide, they can go from 120 to 150 minutes.

DR. SALTIN: They can go around one hour, one hour and fifteen minutes, without any glucose intake for fifteen kilometers. When they compete over 30 kilometers that takes 145, sometimes 130 minutes, and they sometimes try to go the whole race without any glucose intake but very often it happens that they fail. So the standard formula is for 85 or 90 minute races that they have to take glucose every 15 to 20 minutes.

DR. BUSKIRK: They go for 50 kilometers without eating something?

DR. SALTIN: It is not impossible if they are not interested in speed, but if they want to keep up their speed it is not possible.

DR. BUSKIRK: In the Boston marathon competition, many of the

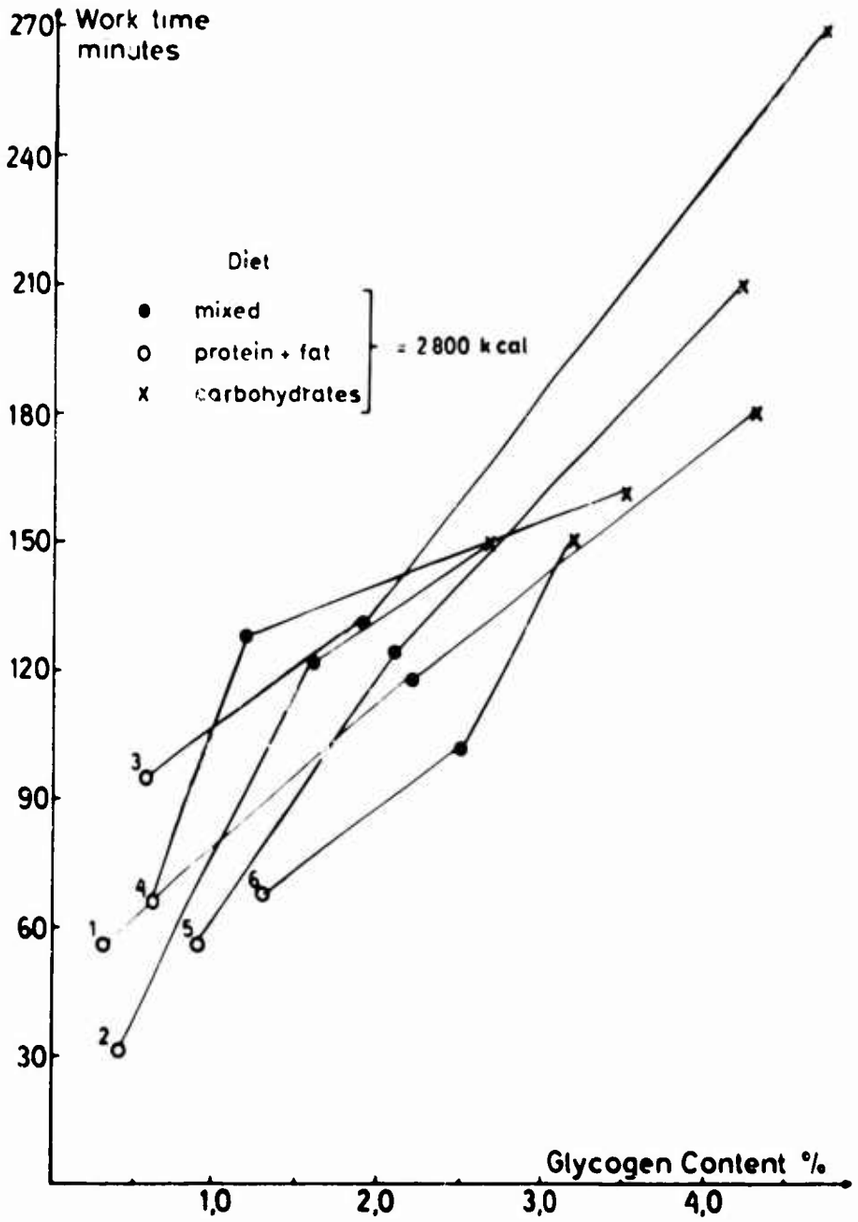


Figure 14

Glycogen content in the quadriceps muscle in relation to maximal work time on a work level loading the oxygen uptake to 80% of the maximal oxygen uptake in 6 subjects. The glycogen content has been varied by having subjects eat a mixed protein and fat and carbohydrate diet. For further explanation, see text. (Saltin, Hermansen and Hultman; to be published).*

***Editor's note: By the time this symposium was in preparation, these studies had already appeared. See references 70, 71, 72.**

competitors, in fact I would say most of them, run it without taking much at all in the way of nourishment.

DR. SALTIN: We have the same in Sweden – they are not interested in drinking anything during the race, but I personally believe they do perform better if they are used to drinking glucose during the race. Perhaps there are practical problems involved. It's much easier to get or to drink this glucose during cross country skiing, they just get it before the downhill slope so they have some time to drink it. We have tried to teach our runners to drink during the marathon run, the 25 kilometer run, but we haven't been successful.

DR. EAGAN: They don't want to drink?

DR. SALTIN: They don't. They say it causes too much trouble with he stomach. One thing more – we studied some people in Sweden performing a starvation march from one city to another. The distance was 500 kilometers, and they covered that distance in ten days and they only drank water. They had no problem covering 50 kilometers per day; we measured the glycogen content before, during, and after, and there was a slight reduction, but they still had glycogen left after ten days without any food at all. That means that it's possible to use fat as a fuel, but then the work rate must be very low.

DR. CHIODI: What about glucose pills, instead of drinking for marathon runners?

DR. SALTIN: It's so difficult to swallow anything during a run.

DR. DILL: I differ with you on that. It's not true in the Boston marathon, nor in – I give you the story of Edelund, whom I mentioned yesterday. He was the winner of the Olympic tryouts in New York City, which were held on a day with a temperature of 92 degrees and with a high humidity, and he won by over two miles. I'm surprised when you say few of them drink, it's standard practice, people all along the line hand them water and fruit juices

and odds and ends, I don't know what-all they hand them, candy – –, and Edeland whenever he was given water if he wasn't thirsty would pour it over him so he kept himself thoroughly wet, and he drank a lot of fruit juices, it's impossible on a day like that not to take a lot of water, and he won.

DR. SALTIN: But in fact, my experiences from long distance runners are just the same as yours.

DR. BUSKIRK: Dr. Gyle and I on two separate occasions followed the marathoners, to see what some of them did take. Johnny Kelly, for example, won't touch a thing, he'll take a little fluid – but in terms of a nutrient – all runners take some fluid, either wet themselves or drink something.

DR. DILL: But they can slow down, of course, part of the time.

DR. BUSKIRK: In general the better the performer the less likely they are to take anything other than simple fluid.

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GENERAL DISCUSSION

DR. HANNON: I have some slides here of Dr. Vogel's studies. These are concerned with changes in peripheral resistance at altitude, during exercise in one case and during rest in another.

DR. DILL: Has Dr. Vogel's work been published?

DR. HANNON: It's a laboratory report now, Dr. Dill. Dr. Saltin probably has seen this data already. This is a subject we haven't touched on yet, other than very briefly. You can see in this slide that the peripheral resistance at all levels of work goes down during initial exposure to altitude, but by the third week at altitude it's back to the same type of picture you see at sea level, except for the maximum work level – where you can see it's still down somewhat.

DR. HORVATH: Is this a true shift in peripheral resistance or is this just an artifact due to the methods of measurement – as far as the work is concerned there is no apparent change in the pattern of peripheral resistance?

DR. HANNON: Yes, this is a function of pressure and cardiac output, and cardiac output is increased at all levels during the initial exposure to altitude. The next slide is from a study on 12 subjects done at Brooks Air Force Base. The middle line is blood pressure, the lower line which eventually crosses it and goes up is cardiac output, and the upper one is peripheral resistance. You see at 11,000 feet – the middle one – there's a tremendous change in resting values; there were no changes over the period of 10 to 40 hours. You can see that resting cardiac output increases markedly, in fact it looks like it's almost exponential in that area, between 11 and 15,000 feet, and the converse happens with respect to peripheral resistance.

DR. BUSKIRK: Does anyone else see this doubling of the cardiac output?

DR. CHIODI: Well, in some ways I would agree with setting a critical point around 3,500 meters – the hemoglobin will start to increase faster at that

elevation. I remember Dr. Grover told us that the pulmonary pressure sometimes is increased at the critical altitude, around 3,000 meters, then starts to go up faster, and it looks as though there is some point which is critical, things going faster than before. It's really an impressive change.

DR. RUSKIRK: Well, certainly as you go to a higher altitude there seems to be – in Pugh's data or in Nevison's, that 19,000 feet, for example, is a little too high even for continuous living in an environment, so there is another critical altitude, too.

DR. CHIODI: Dr. Dill has some data on that from a mining camp at which they were living – the inhabitants tried to live at 54 or 55 hundred meters but couldn't and went down, and that would be the limit, more or less, for permanent residence.

DR. DILL: 5,300 meters is where they lived and they tried living about a thousand meters higher and couldn't survive, or didn't, and Pugh remarks that their attempts to acclimatize at 19,000 feet were a mistake, there was perhaps more deterioration than there was acclimatization.

DR. EVONUK: Tell us, with respect to the forthcoming Olympic games in '68, is it the general consensus now that the athletes would be better off to arrive 15 minutes before they compete, or a week before or two weeks before, in terms of, say, the long distance runners?

DR. SALTIN: This is from my own data. They improved some sixty percent during their three weeks' stay, from a sixty percent reduction in maximal oxygen uptake to around nine percent, so I think it is essential to have an adaptation period of at least three weeks. From another point of view, they can much better pace their speed and so on if they are used to running at altitude. If they don't have any experience at all, it's very difficult to adjust speed, etc. The third possibility, as least with the athletes from Scandinavia, is that they have these blackouts when competing at high altitude. For example, in Squaw Valley one of our cross country skiers blacked out during the relay.

COL. GOLTRA: I am predicting that there will be no world records in Mexico City.

DR. WEIHE: You mean 1,600 meters? That is no altitude.

DR. SALTIN: But I was with them. You know these athletes have run for sixteen years and compete all over Europe and the first time at that altitude (Mexico City) – they arrived the day before and this is what happened. They have larger times for the distance runs, one of them three minutes longer and another five minutes longer time.

DR. WEIHE: Did they repeat this race after a certain acclimatization period?

DR. SALTIN: No.

DR. WEIHE: So you don't know whether this will disappear after some time at altitude?

DR. SALTIN: No. That is one reason more why they need that acclimatization period before they compete at even medium altitude.

DR. WEIHE: But I think you point is much more important, the re-education of the sportsman at high altitude as to the training itself, or the acclimatization needed for the physical acclimatization of the metabolism of the entire body. I personally feel that a well-trained person should be fully acclimatized after two weeks, even less, but re-education is very important because they need to change in how to breathe and how to move, and we heard yesterday that the Indians move entirely differently from another person from the lowlands, and every mountaineer knows that he changes his walking pattern at altitude and I think this is the main part.

DR. HORVATH: Wouldn't it be good to recount the Scandinavian

experiences in the Squaw Valley ski races which were at roughly the same altitude?

DR. SALTIN: This is concerned with the cross country skiing both in 1959 and in 1960 in Squaw Valley. In 1959 and especially in 1960 they had this experience with blackout when they pushed themselves to exhaustion. They told the skiers to maintain just the same speed but in the uphill slow down a little. It's very difficult especially in the relay when there is a lot at stake, to listen to this advice. One Swedish boy and one Russian female, they suffered this blackout in ten minutes up at altitude.

DR. CHIODI: And the others didn't get it? There was some individual variation?

DR. SALTIN: There is some individual variation. The possible mechanism suggested is that they expire carbon dioxide and perhaps that in turn adaptation of the brain lessens.

DR. CHIODI: That would be vasoconstriction and hypocapnia. Didn't you try to measure the difference? There would be some differences in the altitude sensitivity?

DR. SALTIN: Nothing was done, but that is one main reason why Scandinavians in this discussion about Mexico City have their own opinions.

DR. EAGAN: Were you making measurements in the performance of these athletes at their particular sport immediately when they arrived?

DR. SALTIN: No, not immediately, but on one of our runners I have data on maximal oxygen uptake and oxygen debt for the first sixty minutes after completion. I have data after he broke the Swedish record for the 3,000 meter steeplechase at sea level, and after he won the race in Mexico City. If I use my

data and calculate the running time at Mexico City's altitude, I get nine minutes and twenty-two seconds and he won the race at nine-thirty-two.

DR. DILL: What is your estimate of the percentage difference in oxygen consumption? Was there any difference in oxygen consumption for these two times?

DR. SALTIN: In this particular case it was eleven percent.

DR. DILL: That was nine minutes and a difference of ten seconds out of about– –

DR. SALTIN: No, the Swedish record for the 3,000 meter steeplechase is 8.32.4. When I refer to 9.22, it was the expected running time from the physiological data, so there was one minute time difference.

DR. DILL: That's a much greater difference, isn't it, than was seen in the 5,000 meters for example?

DR. SALTIN: Oh, no, perhaps if you take 5,000 meters, but not if you take 10,000 meters. 5,000 was a little bit better. This Swedish runner was a little bit in front of the other runners, so he had not perhaps pushed himself exactly the same on the last lap, because he was already 50 meters in front, so that perhaps can explain the five, six, ten second difference, too.

DR. BUSKIRK: I think this whole business of competition at altitude is really a complex one and perhaps if some of you are interested, there's a clipping here, "Bannister Tees-off on Mexico City***" I'll pass this around. It's an interesting article. I know Dr. Dill and I feel to a certain extent that if you fly these people in, and they compete immediately, they're going to do pretty well,

but they really can't do this because the Olympic games are set up so that they have their opening day ceremonies and then they continue their performances, you see, for five days and events are set up so they have preliminaries on a given day and they have to compete in finals on another day, so that any manipulation that we might make with respect to rapid arrival and immediate competition would be pretty tough unless they set up an Olympic Camp in Acapulco as Bannister suggests. However, it would be to everyone's advantage to have the people at altitude for a couple of weeks if possible. Many of the smaller countri - will be bringing their athletes in and they will be competing this way, and I think this is good, because we have an opportunity to learn something then as to what does happen. The smaller countries aren't going to be hurt too much because I think we can look for a victory in the marathon by either the Japanese or the Ethiopians, and I think the performance is going to be pretty well mixed up no matter how well this is planned. I don't see how we can alter this one thing. This is my own view, anyway.

DR. DILL: What proportion of the events are going to be affected unfavorably by altitude?

DR. BUSKIRK: Well, it seems that swimming, all events in excess of 100 meters, and running all events beyond 800 meters; the bicycling.

DR. HORVATH: None of the field events?

DR. BUSKIRK: None of the field events or the sprints will be affected.

DR. DILL: Hurdles?

DR. BUSKIRK: Well, the only one that might be, and that only minimally, might be the 400 meter hurdles, and then it may be only a second or so, and then you would have the decathalon – there is some evidence to indicate that when a man has to compete day after day after day there may be further deterioration.

DR. DILL: Where are the winter events?

DR. SALTIN: In Grenoble, France, 900 meters.

DR. GROVER: Speaking of winter events, the Pan American skiing competition will be in Portillo, Chile, at about 3,000 meters this year.

DR. EVONUK: Are there any studies at all that indicate that there might be a reduction in explosive force as a result of altitude which may affect the field events? Do you know of any studies of this nature?

DR. BUSKIRK: Relative to gravity, you mean?

DR. HORVATH: Previous indications from other meets held there indicate that if anything they're slightly better in the field events at Mexico City, partially due to the slight difference in resistance offered to the flight of objects through the air, but there has been apparently no change in the small instantaneous type of activity; it's borne out too by the fact that in the very short races where you're depending predominantly on anaerobic capacity anyway, that these are not. These if anything might even be a little better.

DR. DILL: I think it might be interesting for someone who has the time and inclination to do it, to look at all the records of all the performances of each individual in the Pan American games at Mexico City a few years back where conditions were essentially the same, and see what the performance of each man is as compared with his best previous performance in relation to the duration of the race and in relation to his experience at Mexico City, whether he's been there a day or a week or three weeks or whether he was a resident there. This might be productive and I suppose the records all exist. You might have to go to these men to find out how long they had been there, but it might be worthwhile.

DR. BUSKIRK: Well, one thing we noticed in having our track boys run at 13,100 is that there was a form reversal for the two-milers. In other words, the fellow who was the best two-miler at Penn State was also the best two-miler

at Minoa, Peru, the second best, however, at Penn State was the third best at Minoa, and the third best at Penn State was the second best at Minoa, and this was an appreciable reversal. When they came back down to sea level, they switched right back again. Others have commented about this possibility too, and Coach Potts from Colorado mentioned that he has seen this in competing with other schools at altitudes in excess of 7,000 feet. There is this problem, as Dr. Saltin mentioned, of education—for example, the swimmers, and the coaches are quite concerned about this. Swimmers must alter their breathing pattern on turns, for example, and they turn out of water instead of under water to get that extra breath on the turn. Well, someone has to tell them this, or they're going to lose a second or so. If they're together at altitude for a short period of time, everybody learns this, and then it's no longer a factor. Certain runners have a distinct breathing pattern with respect to the way they move their legs and there's some indication that they may have to change this a little bit at altitude. They're going to have to go out slower in these longer races than they normally would. If they go out at their regular speed, this means an inferior performance. Some of these factors involving education are going to be quite critical, but I don't know how one can handle this equitably among all the countries. We had two of our cross country men at 13,000 feet and they were able to keep a pace slightly below a six minute mile for a distance of five miles. This is a slightly faster pace than that used by the famed couriers for the Incas. Our boys could not compete in soccer with the Indians until after three weeks. They found that they were running too fast too soon, and they couldn't adapt to the pace of the games until three weeks later. Then they had no problems competing on even terms with the natives. In fact they played on the winning team in the area, they won the championship.

DR. GROVER: Back to the question of how long to spend at altitude. This is not entirely optional, of course, because the Olympic rules committee have set up a maximum time, which the athletes cannot exceed, in going to Mexico City. It's three weeks, isn't it?

DR. BUSKIRK: No, four weeks. They've kind of arbitrarily picked this out.

DR. SALTIN: Still you have that factor. They open the camp in Mexico

City the first of September and the competition starts the 12th of October, the 15th or something like that, so that means that you have almost six weeks to prepare your athletes in Mexico City. That's of course the official Olympic rules.

DR. BUSKIRK: The thing that has bothered Dr. Dill and me, too, is that Dr. Balke has been negotiating with the Olympic Committee with respect to some additional studies at intermediate altitudes on people with high performance capabilities, and there has been an attitude to indicate that this should not be universally distributed to all countries, and I think this is a real mistake. It is certainly not in the spirit of the Olympic Games and it really surprised me.

DR. HORVATH: Or in the spirit of scientific investigation, either. Well, I think we've probably resolved for the moment the problem of the Olympic Games; it looks like the solution to this is you're going to get caught if you don't, and if you do you may not win anyway. I would like in the little time we have remaining this morning to go back to some of the problems raised by Dr. Saltin's talk and I wonder if you have any questions you would like to relate to that specifically, now?

DR. BUSKIRK: This last series of data he had I think is extremely intriguing from a number of points of view. What plans do you have for continuing this sort of work? What are you going to look at next?

DR. SALTIN: What we intend to do is to concentrate on how much comes from carbohydrates and from free fatty acids. The first thing to do is to label the free fatty acid turnover rate, and then we plan of course to use different work levels. Now we are working with eighty percent of the maximal oxygen uptake, and if 3,500 is critical in regard to altitude, I think 75, 80 percent is very critical with regard to percent of maximal.

DR. BUSKIRK: What if a person engages in this type of activity, let's say on a mixed diet, and then doesn't eat thereafter and is in effect on a protein-fat-endogenous diet, and he attempts to run in the next 2, 3, 4, 5 days, can he run?

DR. SALTIN: Of course he can, but not for very long.

DR. DILL: What were the precise conditions under which a man who has exhausted his glycogen stores in a long hard exercise will overshoot and go up four percent in—as I remember—between two and three days? Was that wholly diet or was it related to the severity of the exercise also?

DR. SALTIN: We really don't know.

DR. CHIODI: Have you tried insulin injections?

DR. SALTIN: We have tried. I hope to do more.

DR. CHIODI: Are the subjects aware of the change in diet and do they know when?

DR. SALTIN: I had one bicyclist with me down in Mexico City who had never heard this story before, and he had never heard anything about physiology either, but every day after training he took 400 grams of sugar and put that in a bottle with orange juice and carried that and drank a couple of liters of it in the evening. He tried to convince his younger brother to use it too. That's the only way, if you want to train as hard or compete as hard tomorrow as you have done today. They really do know by experience that glucose is very important.

DR. HORVATH: I think these changes are really remarkable, because they emphasize a fact which has long been neglected. If you put people on a diet, as we had, on a zero protein diet for a period of up to a month, there is no change in their maximal oxygen uptake, in other words, their maximal capacity for work is unimpaired. So you can see diet doesn't change the maximum, but apparently what is most important is that if you work for prolonged periods of time at sub-maximal levels it does change.

DR. HANNON: I think we have to be a little cautious in these diet things, particularly the type Dr. Saltin talked about. When you put a person on a diet of high protein for a period of two days, sometimes he can get pretty sick in response to a diet like this, and this in itself can reduce performance. I think if you extend exposure to the diet to the point where the individual has adapted to the diet itself you may get a different picture.

DR. SALTIN: One remark, the carbohydrate diet was 2,300 calories of carbohydrates, 500 protein. Just to eat a normal diet, more or less, that caused no problem, but of course protein and fat, they didn't like that the first day but the second day they had three chickens for dinner.

DR. HORVATH: What is the proportion of fat to the proteins that you used?

DR. SALTIN: It was fifty-fifty.

DR. HORVATH: Fifty-fifty, half the calories in protein and half in fat?

DR. SALTIN: We tried to have more fat but they won't take it.

DR. HANNON: That sounds like the pemmican diet that Dr. Vaughan here and Dr. Drury worked on.

DR. HORVATH: How long does it take to become adjusted?

DR. VAUGHAN: The third day is generally the peak of ketosis, and then it slows off some and we have gone as long as nine days without a secondary rise.

DR. HANNON: And the exercise enhances this, does it not?

DR. VAUGHAN: Well, I just think it's a caloric deficit. You see, this wasn't a full caloric intake, this was just a small supplement. We have some experiments going now on rats swimming and we're feeding them high fat diets. We only feed for two hours a day, so that in this way we can control the individual variations. We find that on a high carbohydrate diet the liver glycogen is reduced considerably after just an hour and a half of swimming, and these rats are not really working that hard.

DR. BRAUER: Do you put "nodes" on your rats when swimming or do you just let them swim?

DR. VAUGHAN: We swim them three or four in a tank.

DR. BRAUER: So it's an intelligence test—the rat that bloats himself best is the one that has the least work to do?

DR. VAUGHAN: No, not when they're together in the tank.

DR. BRAUER: Why not?

DR. VAUGHAN: Because they push each other down all the time.

DR. BRAUER: In other words, the one that pushes hardest—

DR. VAUGHAN: We have some more aggressive rats, this is true, but it's surprising how uniform our results have been. We find even there that, oh, there may be a rise of about fifty percent in oxygen consumption and that's not very much. They look like they're working harder than that. There may be something about our measurement—

DR. BRAUER: Do you squeeze out the air from them? It makes an enormous difference in endurance.

DR. HORVATH: Just put some Prell in the water.

DR. BRAUER: They will swallow enough air, so their specific gravity—we've put some very heavy weights on them and they will still go. We have rats with a specific gravity well below that of water after the second trial, and investigators usually take much longer to learn.

DR. HORVATH: I somehow feel that we have lost one important point. I would like to take advantage of the fact that I have to close the session, and recall that the increased cost of doing a standard amount of work is something in the neighborhood of 19 or 20 percent when wearing the standard Arctic issue. With that amount of increased work just to carry your clothing around, this is going to interfere markedly with the potential capacity of a man to work at altitude where again you have another decrement. We have ignored the fact that the man at altitude is going to have to be protected against the cold, and the additional protection against the cold adds an additional stress on him. I think this is going to make a considerable difference because it's going to put the man now at the 80 to 90 percent level much sooner, so that the total overall time that the subject can work at high altitude will be depressed, much more than we probably realize.

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BODY FLUID VOLUMES IN RELATION TO ALTITUDE, EXERCISE AND COLD EXPOSURE*

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The material offered on the succeeding pages provides a brief review of the literature on fluid volumes in man, particularly the adult male, exposed to altitude, chronic exercise or cold stress. Since the mechanisms involved in the fluid shifts that occur with exposure are to a major extent unknown, this review will focus on a description of the observed changes. It has been difficult to collect and evaluate the data presented here systematically, because the data were gleaned from various types of publications (proceedings of conferences, etc.) where reporting was either incomplete or only graphic. Data were obtained, for example, by measuring bar graphs. The inaccuracy of this data transfer process adds to the variability observed. In addition, it was frequently difficult to determine who did what to whom when. I apologize at the beginning to those investigators who are slighted because I have attributed their data to another source: review of data from South America makes me particularly vulnerable in this regard. Where it was necessary to reduce a fluid volume to ml/Kg body weight, a native Peruvian was assumed to weigh 58 Kg, and a native North American European, 70 Kg. The age of the subjects was not always provided nor was the occupation or pattern of habitual physical activity.

More space is devoted in the review to discussion of fluid volumes in relation to altitude than in relation to exercise and cold. The latter two areas have been reviewed adequately elsewhere (1, 2) although a brief discussion is provided to assist in the interpretation of the observations obtained at altitude.

The polycythemia of high altitude has been relatively well studied. It was apparently first suspected by Bert (3) and subsequently demonstrated in Bolivians by Viault (4). Various reviews have discussed the many subsequent studies (5, 6, 7). The degree of polycythemia appears to be inversely

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proportional to pO_2 of the environment, i.e., until a critical altitude of perhaps 6,500 meters or 20,000 feet is reached. In contrast, little is known about fluid volume changes, and careful studies of compartmental variation and water and electrolyte balances are rare. Body weight loss at altitude has been a common experience of mountaineers, as well as others who travel to and work at high altitude. Weight loss usually means some body water loss and not necessarily an isotonic contraction of a given fluid volume.

A few references not used in preparation of the tables and figures are listed in the bibliography solely for the convenience of the reader. These references provide information of considerable pertinence, but space limitations mitigated against presentation of their content.

Plasma and Blood Volume

Movement to altitude. Changes in plasma and blood volume on movement to altitude from either sea level or a lower altitude are shown in Table I. Although the procedures used to measure plasma and blood volume varied widely, and some are of questionable validity, e.g., Brilliant Vital Red, the results indicate that plasma volume was usually reduced following arrival at altitude. This reduction in plasma volume appears usually by the third day, and plasma volume may remain at below sea level control values until 150 to 200 days have passed. Apparently plasma volume begins to return toward the sea level value after about six months of residence at altitude and is essentially back to the control volume by one year. Two exceptions to this general trend are apparent in Table I, i.e., the studies by Balke (8) and Dill et al. (9). Plasma volume increased in each of the five individuals studied by Balke (8); however, these results were obtained at the relatively low altitude of 2,300 meters. Dill (9) suggests that in older individuals an increase may be found consistent with movement to altitude. The observations on Dill himself support this view.

While the blood volume is not strictly a fluid volume, it is of interest to investigators studying altitude acclimatization because the fluid portions of blood support circulation of red cells and facilitate O_2 transport to working muscle and other tissues. Blood volume results appear somewhat more variable on movement to altitude than do results for plasma volume. In general, there appears to be either some reduction or no change in blood volume after three to thirty days of residence at altitude. Thereafter, a gradual increase to levels above those obtained at sea level appears. A relative polycythemia develops, and after six months of residence at altitude, the blood volume is distinctly elevated because of the large red cell volume. After one year at altitude, the

TABLE I

Plasma and Blood Volume (ml/Kg) with Respect to Movement to Altitude (Alt.)

All Observations on Men.

Description						Plasma Volume				Blood Volume			
Study	Tech.	Group	$Alt._m$	P_B mmHg	Days at Alt.	B	A	Δ	%	B	A	Δ	%
Asmussen and Consolazio 1941 (16)	CO	n = 2	4,300	460	15					91.3	75.0	−16.3	−18
Asmussen and Nielsen 1945* (30)	CO	n = 1	4,500	450	4½	52.9	30.0	−12.9	−30	77.2	62.9	−14.3	−19
Hurtado et al., 1945 (12)	Vital Red	n = 5	4,540		2-6	42.0	42.0	0	0	79.1	86.5	+ 7.4	+ 9
Merino 1950 (34)	Vital Red	n = 6 Age 20-42	4,540	450	7-21	46.3	39.5	− 6.8	−15	85.0	87.1	+ 2.1	+ 2
Lawrence et al. 1952 (10)	P32	n = 14 Age 21-27	4,500	450	1-10	38.7	32.0	− 6.7	−17	70.7	62.3	− 8.4	−12
Pugh 1964 (14)	CO	n = 6 Age 23-51	4,660 5,800	438	56-196	44.4	39.9	− 4.5	−10	77.9	93.5	+15.6	+20
Balke, et al. 1965 (8)	T-1824	n = 5	2,300		10	42.9	47.7	+ 4.8	+11	78.5	91.1	+12.6	−16
Dill, et al. 1965 (9)	T-1824 or I131	n = 2 Age 34 & 73	3,800	485	7	41.5 42.3	32.5 57.8	− 9.0 +15.5	−22 +38	76.3 76.2	67.0 93.5	− 9.3 +17.3	−12 +23
Buskirk, et al. (11) 1966	T-1824	n = 6 Age 19-22	4,000	474	32	44.2	37.0	− 7.2	−16	80.8	73.4	− 7.4	− 9
Reynafarje 1964 (35)	T-1824	n = 10	4,540 4,540 4,540	450 450 450	~ 45 ~165 ~365	39.0 39.0 42.9	31.0 36.0 40.0	− 8.0 − 3.0 + 1.0	−20 − 8 + 3	77.0 77.0 77.0	75.0 88.0 96.0	− 2.0 +11.0 +19.0	− 3 +14 +25

* Study conducted in Chamber
Tech — Technique or method employed
B = before going to altitude
A = after arrival at altitude

polycythemia is more apparent, which together with the relatively larger plasma volume, produces a significantly elevated blood volume.

Movement from altitude. When men descend from altitude, their plasma volume increases (Table II). This was found in all studies except the relatively short study (1 to 10 days) conducted by Lawrence et al. (10). In contrast, blood volume decreased in all studies except in one by Buskirk et al. (11). In the latter study, blood volume at altitude was still below the sea level value immediately before the men returned from altitude. All the men in the study by Buskirk et al. were track athletes, and three had remained at altitude for 48 days and three for 64 days before returning to lower altitude.

Indigenous groups. A comparison of natives indigenous either to sea level or altitude provides evidence that plasma volume on a per Kg basis tends to be lower and blood volume higher in the altitude population. Results from these comparisons are presented in Table III. The one exception to this generalization is the comparison of plasma volume measurements made by Hurtado et al. (12) using Brilliant Vital Red.

Miscellaneous findings. Newcomers to altitude show progressive changes in plasma and blood volume with time spent at altitude. The initial, but transient, decrease in plasma volume reverts toward normal, and blood volume soon equals or exceeds sea level values. These trends were shown, particularly by the data of Reynafarje et al. (13), in Table I, and the data from Pugh (14) in Table IV.

Data on vascular redistribution at altitude are sparse. Monge (15) cites experiments by Monge Jr. (methods not disclosed) in which a comparison was made between distribution of blood in the lungs and the remainder of the body in natives who resided either at sea level or at altitude. It would appear from Table V, although the data are somewhat equivocal, that the relative percentage of plasma, red cells and blood in the lungs is greater in the altitude residents.

Dill et al. (9) have raised the problem of a different adaptation of plasma volume in older as compared to younger men who travel to altitude. Results on Pugh and Dill are presented in Table VI. Pugh was 51 years old at the time the measurements were made and Dill was 73, and Pugh had spent a much longer time at altitude than Dill. If Dill's contention is correct that there is an age-related difference in the loss of water from plasma on movement to altitude, then it must occur sometime after age 51, or it occurs in different individuals at different ages. Diet, water and salt intake, physical activity, cold exposure, and other gross factors may affect what happens to plasma and blood volume, and thus should be kept as constant as possible in order to detect an age-related change in fluid shifts within the body.

TABLE II

Plasma and Blood Volume (ml/Kg) with Respect to Movement From Altitude (Alt.)

All Observations on Men

Study	Tech.	Group		Alt.$_m$	P_B	Days after Alt.	Plasma Volume				Blood Volume			
		n	Age		mmHg		B	A	Δ	%	B	A	Δ	%
Merino, 1950 (34)	Vital Red	2	21-23	4,540	450	34-38	34.3	42.9	+ 8.6	+25	102.0	96.1	− 5.9	− 6
Lawrence, et al. 1952 (10)	p^{32}	11	19-2	4,500	450	1-10	36.0	36.0	0	0	83.5	80.2	− 3.3	− 4
Monge, 1954 (15)	Vital Red	10	19-23	4,550	446	21	39.5	46.0	+ 6.5	+16	96.2	94.8	− 1.4	− 2
Reynafarje 1964 (35)	T-1824	10		4,540	450	15	34.0	40.0	+ 6.0	+18	90.0	90.0	0	0
		10		4,540	450	~120	34.0	46.0	+12.0	+35	90.0	82.0	− 8.0	− 9
		10		4,540	450	~245	34.0	45.0	+11.0	+32	90.0	82.0	− 8.0	− 9
Buskirk, et al. 1966 (11)	T-1824	6	19-22	4,000	474	15	37.0	44.6	+ 7.6	+21	73.4	83.6	+10.2	+14

All values are for Peruvian Highland Natives except those from Buskirk et al.
See footnotes for Figure 1.

TABLE III

Comparison of Plasma and Blood Volumes (ml/Kg) in Indigenous Groups

Who Reside at or near Sea Level (S.L.) or at Altitude (Alt.)

Description					Plasma Volume				Blood Volume			
Study	Tech	Group	$Alt._m$	P_B	S.L.	Alt.	Δ	%	S.L.	Alt.	Δ	%
Hurtado, et al. 1945 (12)	Vital Red	n = 26 n = 30	3,730	518	47.1	48.9	+ 1.8	+ 4	86.5	108.7	+22.2	+26
Hurtado, et al. 1945 (12)	Evans Blue	n = 10 n = 11	4,540	446	46.2	36.2	−10.0	−22	85.4	100.3	+14.9	+17
Hurtado, et al. 1964 (36)	Evans Blue	n = 20	4,540	446	42.0	39.2	− 2.8	− 7	79.6	100.5	+20.9	+26
Monge, 1952 (37)	Vital Red	?	3,100	518	48.6	44.0	− 4.6	−10	90.0	92.4	+ 2.4	+ 3
Monge, 1952 (37)	Vital Red	?	3,730	480	48.6	47.6	− 1.0	− 2	90.0	106.0	+16.0	+18
Monge, 1952 (37)	Vital Red	?	4,550	446	48.6	45.7	− 2.9	− 6	90.0	120.0	+30.0	+33
Merino, 1950 (34)	Vital Red	n = 9, n = 7	4,540	446	46.4	32.9	−13.5	−29	84.5	100.0	+15.6	+18
Lawrence, et al. 1952 (10)	P^{32}	n = 11, n = 9	4,500	450	38.7	36.0	− 2.7	− 7	70.7	83.5	+12.8	+18

TABLE IV

Average Percentage Changes in Plasma (PV) and Blood Volume (BV) from Sea Level Values. Pugh (14).

	18 Weeks 4-5,800 m	3-6 Weeks 5,800 m	14 Weeks 5,800 m and higher
PV	−29	−20	−19
BV	− 9	− 1	+10
	n = 4	n = 5	n = 5

TABLE V

Lung Blood Volume in Relation to Total Lung Volume at Sea Level and at 4,550 Meters. Monge (15).

Sea Level	Lung ml/Kg			Total ml/Kg			Lung / Total + 100		
	S.L.	Alt.	Δ	S.L.	Alt.	Δ	S.L.	Alt.	Δ
PV	5	8	+ 3	43	34	− 9	13	24	+11
RCV	5	12	+ 7	34	61	+27	16	20	+ 4
BV	10	20	+10	77	95	+18	14	21	+ 7

Values rounded to nearest whole number.

TABLE VI

Effect of Altitude (3,800 M) on Plasma and Blood Volume (ml/Kg) in Older Men

	Pugh Age 51			Dill Age 73		
	S.L.	4,650 m	Δ	S.L.	3,800 m	Δ
PV	50.5	38.3	−12.2	42.3	57.8	+15.5
BV	84.2	79.7	− 4.5	76.2	93.5	+17.3
		after 105 days CO Method			after 7 days T-1824 Method	

The initial marked reduction in plasma volume may serve a useful purpose in that it is associated with a marked increase in the O_2 capacity of a unit volume of blood. This relative increase in O_2 capacity is of advantage to the organism until erythropoiesis and polycythemia are established.

Body Water and Other Fluids

Chamber experiment. If plasma water is lost from the body or redistributed to other body fluid compartments when one goes to altitude, the movement patterns should be apparent from careful studies of body water balance and body fluid volume measurements. Very few studies of this type have been attempted. One of the first and most complete studies on water balance was performed using an acute exposure in a low pressure chamber (16). Table VII reveals that both fasting and acute exposure to a barometric pressure of 450 mm Hg produced a reduction in plasma and blood volume, but that these reductions were more marked at simulated altitude. A greater water loss was experienced at 450 mm Hg than at 760 mm Hg which could be explained partially by a diuresis. Care was taken to match the chamber environment in the experiments at the two pressures; although no mention was made of humidity control, a critical variable, it was assumed that the remainder of the greater water loss at low pressure occurred because of increased evaporation from the skin and lungs. The water loss exceeded the plasma loss by a factor of three, indicating that fluid redistribution within the body had occurred.

Additional work (Table VIII) with fasted individuals included measurements of total postassium and sodium excretion. An estimation was made of the loss of extracellular water (ECW) using the expression: liters of ECW lost $= \frac{Na - 0.425K}{148}$ Na and K represent meq. of Na and K excreted, 0.425 represents the ratio Na/K in muscle and 148 the average meq. of Na in ECW. Intracellular water (ICW) loss was estimated from the formula: liters of ICW lost $= \frac{K - 0.017Na}{112}$ where 0.017 is the ratio of K/Na in extracellular fluid and 112 is the average meq. of K in muscle. The assumed ECW volume was 25 liters. The main portion of the water loss was said to have been derived from plasma; while this statement is supported by the results presented in Table VIII on subject K, it is hardly true for subject L, and water redistribution must have played a greater role in subject L. The difference between "found" and "calculated" blood concentration indices at low pressure was smaller for plasma protein than for red cells, presumably due to loss of protein from plasma. Only one-third to one-half of the hemoconcentration could be explained on the basis of estimations of fluid movement. In addition, marked differences were observed

TABLE VII

Acute Effect of Low Atmospheric Pressure (450 mmHg) on Body Water Loss in One Subject

(Age 25, 70 Kg, 176 cm.)

Asmussen and Nielsen (30)

	BV	PV	Cell Vol. %	Plasma Prot. %	Loss of Wt. gm	Loss of H_2O gm	Total Diuresis	Total Cl $Loss_{meq.}$
760mmHg								
Control	5.93	3.29	44.6	7.09				
Fasting, No H_2O	5.20	2.76	46.9	7.82				
Change	−0.73	−0.53	+ 2.3	+0.73	2,015	1,915	1,125	186.7
%	− 12	− 16	+ 5	+ 10				
450mmHg								
Control	5.90	3.38	42.7	7.45				
Fasting, No H_2O	4.90	2.62	46.6	8.49				
Change	−1.00	−0.76	+ 3.9	+1.04	3,590	3,490	2,015	293.5
%	− 17	− 23	+ 9	+ 14				

TABLE VIII

Percentage Shift in Fluid: Observed and Estimated

Asmussen and Nielsen (30)

Environment	Subj.	Calc. Loss in ECW	Obs. Inc. in Plasma Pr.	Calc. Loss in BV	Calc. Inc. in RCV	Obs. Inc. in RCV
760mmHg	L	6.7	8.5	3.8	4.0	3.5
	K	4.8	10.0	2.8	3.1	5.6
450mmHg	L	6.3	11.4	3.5	3.6	7.8
	K	7.6	12.6	4.3	4.6	14.1

Subject L: 21 years, 72 Kg, 184 cm
Subject K: 23 years, 74 Kg, 181 cm
ECW is extracellular water
BV is blood volume
RCV is red cell volume

TABLE IX

Total Body Water Flux in Liters per Day:
From D_2O Biological Decay Curves

	Nevison, et al. (17)	Buskirk, et al. (11)
Sea Level	2-3	1.5-3.0
Altitude	3-4*	1.7-2.4**
Net Mean Difference	0.63	0

*Altitudes above 15,000 feet, climbing
**13,100 feet, daily running
Pugh (38) estimated 5 liters/day for men climbing Mt. Cho Oyu.

TABLE X

Body Fluids in Peruvian Sea Level Residents and those at 4,500 meters

Picón-Reátegui et al. (18)

	Sea Level	Altitude	Δ	P
n	28	28		
Age	24.2±0.4	27.6±1.6	+3.4	.05
Body Weight	62.5±1.4	54.3±1.1	-8.2	.001
% TBW (Antipyrine)	58.5±0.6	59.4±0.8	+0.9	NS
% ECW (Sucrose)	16.4±0.3	17.9±0.3	+1.5	.01
% ICW	42.0±0.6	41.4±0.8	-0.6	NS

Values in percent of total body weight
Sea Level – white medical students
Altitude - native mine workers

between subjects L and K in the magnitude of the fluid shift in response to low pressure.

Water flux. Values are available for total body water flux under field conditions, but in each study proper control was unattainable. Rates of body water turnover are presented in Table IX. Both Nevison (17) and Pugh (14) suggest that body water turnover is higher at altitude. The question becomes: water turnover is higher with respect to what reference? Clothing worn, environmental temperature, work load, state of nutrition, and water availability among other factors alter the rate of water turnover. In the study by Buskirk et al. (11), their runners were working in a warm environment prior to going to altitude, and a cool environment at altitude; hence, that water turnover at altitude was no different than on the Penn State campus was not particularly surprising. In field work, one must accept the outdoor temperatures that exist, and even though one attempts to keep other extraneous factors constant, the basic relationship between environmental temperature and the sweating mechanism is of considerable importance in the resolution of problems in fluid balance. It can be said, however, that the results shown in Table IX indicate that water turnover may be quite high at altitude, particularly if ventilation rates are high and the subjects are working hard when exposed to high radiation load.

Indigenous groups. A comparison of fluid volumes in sea level natives and comparable individuals who resided at 4,500 meters was made by Picón-Reátegui et al. (18). It was found (Table X) that only the sucrose space was significantly greater in the altitude natives. The differences between physically active and inactive residents at altitude are shown in Table XI. In the active natives percent total body water and intracellular water was higher than in the inactive natives. Similar differences associated with chronic activity have been found at lower altitudes. (See section on exercise.)

Another comparison of percent total body water between two groups of residents at sea level and altitude in Peru was made by Siri et al. (19) using tritium dilution. They found that the altitude residents (5,380 m) had about 9% more body water on a relative basis than the sea level residents. The mean values for the two groups were sea level, 55.6% of body weight, and altitude, 60.6%. Obviously there must be a reason for the discrepancy between results for total body water in these two studies, but the reason is not immediately apparent.

Athletes. Measurements of the D_2O dilution volume in six well-trained young men who continued training at altitude is provided in Table XII. It

appears that on both ar absolute (liters) and relative (ml/Kg) basis, a transient gain followed by a loss in body water occurred at altitude. On the subjects' return from altitude, their body water increased to above the level it had been prior to their going to altitude. Since all of the determinations of D_2O dilution in body fluids (blood and urine) were performed in the laboratory at Penn State and not in the field, the differences shown may be significant. Additional work is necessary to clarify this point. Measurements of urinary specific gravity made between the 8th and 44th day at altitude indicated greater dilution of urinary solutes with respect to control measurements.

Rats. While this presentation is primarily devoted to a discussion of body fluid volumes in man, it may be useful to look briefly (Figure 1) at a weight loss and a water loss curve obtained on rats acutely exposed to 4,920 meters in a low pressure chamber (18). Smooth curves for body weight and water loss are presented, but it takes at least six days for body loss to reach maximal values. The time course may be different for man, as indicated in Table XII, and man may store water even when his plasma volume is lower than normal during the first few days at altitude. Again data are too limited to draw distinct interspecies comparisons.

DR. HORVATH: Is this simply due to the fact that they just won't drink water that first few days, that there is some sort of inhibition toward water?

DR. BUSKIRK: This is what Mell claims, that there is an inhibition of the thirst mechanism at altitude, but Cohen doesn't mention this, and I don't recall that he gives the figures for water intake.

DR. WEIHE: Yes, this is certainly due to the reduced water intake of the animals.

DR. BUSKIRK: Have you done this sort of thing?

DR. WEIHE: Yes.

TABLE XI

Body Fluids in Active and Inactive Subjects at 4,500 Meters
Picón-Reátegui et al. (18)

	Active	Inactive	Δ	P
n	18	10		
Age	24.4±1.5	33.3±2.9	+8.9	.01
Body Weight	53.4±1.1	56.0±1.6	+2.6	NS
% TBW (Antipyrine)	60.9±0.8	56.5±1.2	−4.4	.01
% ECW (Sucrose)	18.2±0.4	17.5±0.4	−0.7	NS
% ICW	42.8±0.8	39.1±1.2	−3.7	0.5

Values in percent of total body weight
Active — Mine workers and sports participants
Inactive — Hospital and office workers

TABLE XII

Total Body Water (D_2O liters) in Six Track Athletes
in Relation to Movement to and from Altitude (4,000 m).
Age Range 19-22 years.

Subject	PSU Control	Peru A_8	Peru A_{44}	PSU D_{70}
JB	47.2	50.8	45.9	50.5
DG	51.8	50.8	49.6	53.0
RL	52.0	53.1	47.2	52.7
GM	45.0	45.4	45.0	48.6
AM	51.4	54.2	49.3	53.8
RR	45.0	47.9	43.6	46.6
Mean	48.8	50.4	46.8	50.9
Mean Body Weight Kg	71.47	70.30	70.37	73.39
$\bar{x}$ ml/Kg	683	717	665	694

A_8 and A_{44} refer respectively to the eighth and forty-fourth day at altitude.
D_{70} refers to the seventieth day after return from altitude.
PSU refers to Penn State University at an altitude of 360 meters.

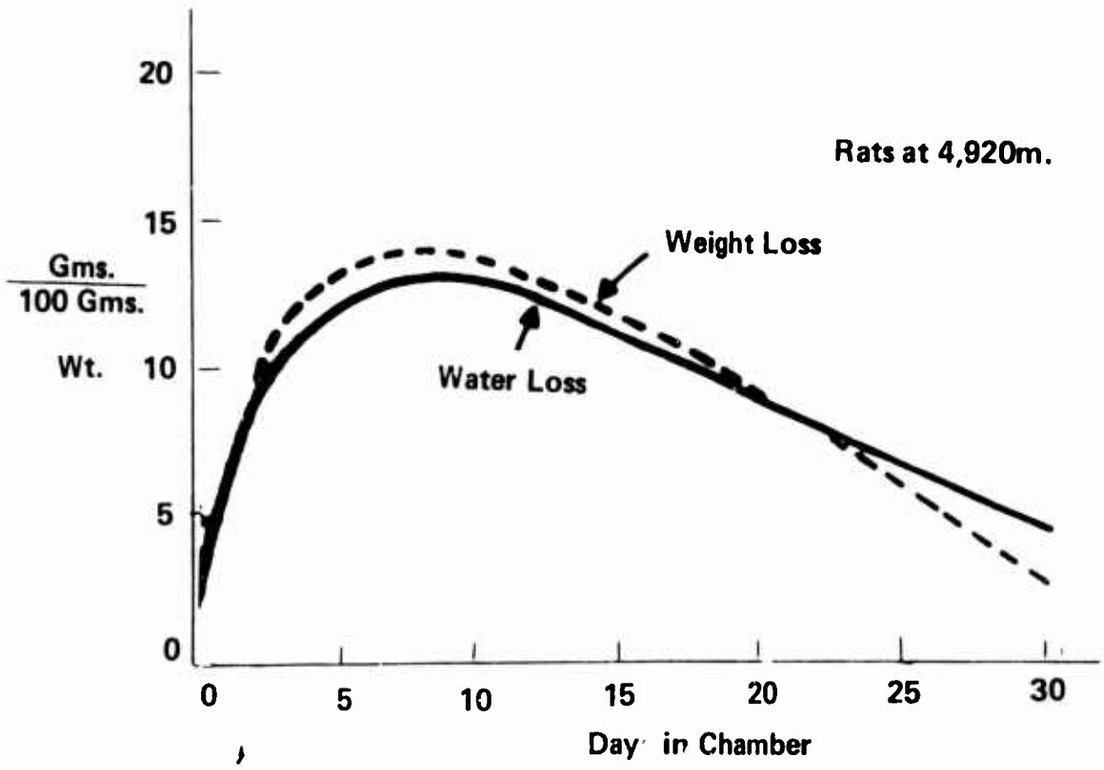


Figure 1
Body Weight and Body Water Loss in Rats Acutely Exposed to Altitude. Redrawn from Picón-Reátegui, et al (33)

DR. BUSKIRK: What do you get?

DR. WEIHE: We get the same.

DR. BUSKIRK: Do you have any idea what mechanism is involved, I don't–

DR. CHIODI: Food intake is down, too, isn't it?

DR. WEIHE: Everything is down.

DR. BUSKIRK: Well, the food intake is down in most of these animals, and we have a feeling of course that it's down in man, too, without actual measurements. They do have some measurements at the Nutrition Lab in Denver, and it's very definitely down in their series.

DR. HORVATH: Well, some of the water loss is due to the diarrhea and vomiting that some people experience, too.

DR. BUSKIRK: Because one has the diarrhea, particularly going to Peru or some of the other highland areas, one can't get there and avoid all the bugs, so . . . it's pretty difficult to do so, and so that this is complicated by an anorexia perhaps, complicated by the diarrhea, and there are other factors here too. Since water, for example, must be boiled, they may not prepare quite enough water. We think we had plenty of water, because this was the first job that was done each morning, but again one has to go to lengths to get this water.

DR. EAGAN: I think I have some data on this, Dr. Buskirk, and we took particular pains on this to make certain that food intake was adequate and also water intake. In an exercise group of subjects, they gained 300 grams on the average in the first week at altitude, and lost 900 grams during the second week, and for an unexercised group they lost 700 grams during the first week and 1,800 grams during the second week. I have the figures on the food intake and they were adequate—probably—in the first group but not in the second.

Exercise

As indicated previously by the study of Picón-Reátegui (18), intracellular water and total body water are usually larger on a per unit weight basis in active individuals. After extensive physical training body water and intracellular water are also increased, as demonstrated in a training experiment conducted by Pascale et al. (20). Mean data from Pascale's study are presented in Table XIII. A reciprocal relationship exists between percent body fat and total body water (21), because adipose tissue contains 30% or less of water while lean tissue contains 65% or more.

TABLE XIII

Fluid Volumes as Mean Percent of Body Weight in 12 Soldiers Before and After 3 Weeks of Paratrooper Training
Pascale et al. (20)

Volume	Before	After	Δ	P
TBW	62.7	65.4	+2.7	0.01
ECW	19.0	18.5	–0.5	> 0.10
ICW	43.7	46.9	+3.2	0.01

TABLE XIV

Percent Fluid Volumes and Activity Habitus
E. R. Buskirk (30)

	Habitually Sedentary	Intramural Athlete	Varsity Athletes
n	15	8	6
% ECW	23.9	25.4	25.3
% TBW	37.6	43.9	43.4
Avg. Age	22	22	21
Avg. Wt.	77.5	79.5	73.4
% Fat	16.5	9.4	3.6

ECW measured with NaScN and total body water with antipyrine

TABLE XV

Mean Plasma and Blood Volume and Activity Habitus
E. R. Buskirk (31)

	Habitually Sedentary	Intramural Participants	Varsity Athletes
n	15	4	6
PV liters	3.27	3.79	3.54
" % Wt	4.32	4.71	4.85
" % FF	5.16	5.30	5.07
BV liters	6.10	6.82	6.44
" % Wt	8.11	8.51	8.80
" % FF	9.66	9.55	9.22

Further proof that total body water forms a larger fraction of the total body weight in more active men is shown in Table XIV (12). Again a reciprocal relationship is indicated between percent fat and total body water. Essentially no difference in the relative hydration of lean tissue was found among groups who varied in activity habitus. Plasma volume and blood volume were studied in the same groups and no differences were found when plasma and blood volume were expressed per unit body weight or fat-free tissue. These data are presented in Table XV.

Comparison of blood volumes in relation to height and weight in prison inmates revealed that the inmates who exercised regularly had blood volumes no larger than their more sedentary colleagues (22).

Cold

The changes in body fluids with cold exposure and hypothermia have been adequately reviewed elsewhere (1, 23-26). Plasma volume and blood volume have frequently been found to decrease with acute exposure to cold. Typical results from an acute exposure to cold are reproduced from the work of Bass and Axelrod, as reported in the review by Bass and Henschel (6), in Table XVI.

DR. BRAUER: What was the exposure time in this experiment?

DR. BUSKIRK: I think this was five days. We repeated this later for 14 days and got essentially the same picture.

If exposure to cold continues, little difference is found between plasma and blood volumes under thermal-neutral and cold conditions, particularly if nutrition is comparable (1). Continuous cold stress appears to have a minimal impact on other fluid volumes, although Rogers et al. (27) maintain that an isotonic contraction of extracellular fluid can occur when men live and work under survival conditions in the cold. The first day or two in the cold may be accompanied by small negative water balances associated with cold diuresis but the trend is transitory (1). Hypothermia apparently produces a decrease in plasma and blood volume, although a delayed mixing problem when a dye like T-1824 is used complicates interpretation of results. There is also an apparent decrease in total body hematocrit (25).

TABLE XVI

Changes in Plasma (PV) and Blood Volume (BV) as a result of Acute Cold Exposure in Seven Male Subjects.

From Bass and Axelrod as cited in Bass and Henschel (1).

	85° F	60° F	Δ, %
PV	2.94	2.74	− 7
BV	5.28	5.12	− 3

TABLE XVII

Seasonal Variation in Body Fluids

Yoshimura (28)

Variable	Technique	Summer	Winter	Δ
PV (serum)	Congo Red	50.2	46.1	− 4.1
BV	Congo Red	85.0	81.0	− 4.0
TBW	Antipyrine	63.3	56.8	− 6.5
ECW	NaSCN	23.7	20.6	− 3.1
ICW	—	39.7	36.2	− 3.5
ADS		27	8	−19

Water intake in winter was less than in summer and fraction of intake excreted was greater. Antidiuretic "substance" (ADS) was less in serum in the winter.

The larger blood volume attributed to race or history of chronic cold exposure, found principally in the Eskimo, has been critically discussed (1). The recommendation was made that additional blood volume studies on Eskimos and other comparable groups should be performed with perhaps more careful control of potential artifact-inducing variables. Possible seasonal, nutritional, and other sources of variation complicate interpretation of results obtained to date on the Eskimo.

Seasonal variations in fluid volumes have been investigated by Yoshimura (28) and Doupe, Ferguson and Hildes (29) among others. Yoshimura's findings on a group of Japanese subjects indicate that all fluid volumes were reduced during the winter months (Table XVII). Yoshimura attributes this difference to the circulation of lesser amounts of antidiuretic substance.

DR. BRAUER: What kind of subjects were these?

DR. BUSKIRK: These were Japanese men, university students.

DR. CHIODI: One important thing I think must be shown is the difference in metabolism between Japanese and Caucasians.

DR. HORVATH: The Japanese have a very strong seasonal variation in metabolic pattern?

DR. CHIODI: Yes.

DR. BUSKIRK: This is typical of all individuals?

DR. CHIODI: Yes.

DR. BRAUER: Did the Ama studies produce any fluid volume data—because remember in the Ama studies, at least in the Korean Ama, I know

there were some summer and winter comparisons made, and I think those investigations might have some fluid data for girls.

DR. HORVATH: The Japanese Amas and the Korean Amas were different, though?

DR. BRAUER: Yes, I know, that's why I'm asking about the Korean Amas.

DR. BUSKIRK: I don't know.

DR. BRAUER: There may not be.

DR. BUSKIRK: I have seen those data but I didn't pick them up. I think that in the more active Amas it was slightly lower, was it not?

DR. GROVER: These figures would give a seasonal variation of hematocrit, wouldn't they, a higher hematocrit in the winter?

DR. BUSKIRK: Yes.

DR. GROVER: Have other people found this with other populations?

DR. HORVATH: Well, Hildes did some on Canadians back in the '50's and he showed a somewhat similar pattern. This is up at Winnipeg, but actually there has been so little work done on it that Dr. Buskirk is completely correct. All we are seeing at the moment are trends; no one has done a systematic study.

DR. EAGAN: I think Hildes got very different values when he repeated it.

DR. BUSKIRK: It's very difficult to do, there are so many factors which operate throughout the year, and it's very hard to follow someone unless you have them regulated and put them in some sort of a metabolic unit.

COL. GOLTRA: Wouldn't this be an ideal place to make these determinations because of the rather large number of incoming troops we have here during the summer months?

DR. HORVATH: It seems to me that somebody is going to have to do this and do it very systematically.

DR. DILL: You have a nutritional problem to consider also, the possibility that there's quite a different diet in the–as there is in Japan, many parts of Japan have very different diets, summer and winter, and there have been some papers from Japan concerned with hemoglobin that have shown very considerable changes in hemoglobin concentration in some areas, summer and winter. I couldn't believe this was right when I first read it, it's so different from what has been reported in this country, but it seems to be true, so I think that needs to be looked into.

DR. BUSKIRK: I don't think one can get into this sort of thing without looking at nutrition very carefully, looking at the environmental conditions very carefully, and looking at what people are doing seasonally very carefully, because certainly the osmolar load for the body will vary and this has to be taken into consideration, the actual nutrient composition of the diet with respect to major constituents, at least, has to be taken into consideration. There is this training effect that we have pointed out, so that this isn't an easy type of study to become involved in and it may be easy to say that there are differences between summer and winter, but then it behooves one to try to explain them.

Doupe et al. found that plasma volume (T-1824) increased during the summer and decreased during the winter. Some subject variability was clear, and the seasonal cycles were larger in some years than others. The red cell mass, circulating hemoglobin, and plasma protein all varied in essentially the same

way. Measurements made on a few occasions of total body water (antipyrine) and extracellular fluid (inulin) indicate that the seasonal effect is most pronounced on the vascular system.

Discussion

Extensive information exists to relate fluid volumes to body weight and age. Appropriate regression equations are presented in Table XVIII.

For proper interpretation of the results presented, it should be remembered that only an estimate of a fluid volume can be made by the dilution of a chemical in that volume. Because of the nature of the methods used and the stresses under discussion, the various fluid volumes are probably never identical from day to day, nor are the chemicals handled and diluted in exactly the same way. Extracellular water measurements, for example, is on theoretical grounds extremely difficult to describe, and on a diluent basis is even more difficult to measure. Despite the inability to determine actual fluid compartments, the concept of their being has brought reason and rationale to data normally difficult to interpret. Therapy in particular has benefitted measureably from this approach (21).

Any presentation of fluid volume changes is beset by the question: how specific are the volume changes in relation to the variable under consideration? Unfortunately, a single independent variable can seldom be dealt with exclusively. Osmolar, vascular, renal, cellular, and respiratory variables are all involved in the interpretation of any change in a fluid volume. Body position at the time of measurement, previous activity, and past history of habitual activity—each of these also contribute to both intra- and interindividual variability. Anti-diuretic hormone, vasopressin, and aldosterone release, their circulation inhibition and rate of destruction, all operate important control features of fluid volume regulation. Sensitivity of central centers to pO_2, pCO_2, pH, and specific osmolar changes are also of considerable consequence. The topic of mechanistic interactions, in relation to control of body fluids, will surely provide an important subject for discussion.

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TABLE XVIII

Regression Equations for Estimating Fluid Compartments in Males

Moore, et al. (21)

1) $\frac{TBW}{B.\ Wt} \times 100 = 79.45 - 0.2389(B.Wt) - 0.1477$ (age in years)

Henschel et al. (32)

1) PV (ml/Kg) = 49.6 (B.Wt.) – 0.0348	r = –0.19
PV (ml/Kg) = 45.02e – 0.0014 (age in years)	r = –0.15
2) TBW (ml/Kg) = 826.0 (B.Wt.) – 0.11128	r = –0.52
TBW (ml/Kg) = 601.1e – 0.00329 (age in years)	r = –0.41
3) ECW (ml/Kg) = 502.2 (B.Wt.) – 0.17684	r = –0.75
ECW (ml/kg) = 323.3e – 0.01177 (age in years)	r = –0.72

DISCUSSION

DR. BLATTEIS: Dr. Buskirk, could you tell me whether in the studies, particularly those that were done in the natives, the environmental temperature in which they normally live was taken into consideration, in other words, whether that was cold and altitude or altitude alone?

DR. BUSKIRK: The dates are given. I don't believe they report the actual environmental conditions, but since the dates are given and the weather reports are available for Morococha, this would be available. I assume that it was colder in Morococha than it was at Lima, but I don't recall the exact season of the year when the measurements were made.

DR. HORVATH: How cold was it when you were doing your studies?

DR. BUSKIRK: Well, this is an interesting thing. It's about eight degrees south of the equator, and the ambient temperature early in the morning was about 24 degrees Fahrenheit, then it would come up to perhaps 55 or 60 at mid-day and then decrease. It was always windy, and if one could be protected from the wind, for example, during mid-day one could be comfortable without a shirt, standing outdoors, but not if one was exposed. Of course the solar load is high and these subjects were working under these conditions. During running their skin was usually dry but they were sweating and sweating appreciably.

DR. HANNON: One thing that may influence body fluid losses which has been mentioned is caloric intake. In the two recent studies at Pike's Peak, one confirming the other, one was by Frank Consolazio, and the other more recently by Morton Surks, they found besides a reduced caloric intake, a negative nitrogen balance, and this in itself may increase water loss at altitude.

DR. BRAUER: Is that at all affected by exercise?

DR. HANNON: In one case it involved people who were exercising and in the other case it didn't, and it seemed to apply in both cases.

COL. GOLTRA: Was it greater in those exercising?

DR. HANNON: I don't recall whether it was or not.

DR. BUSKIRK: Of course, in consideration of this sort of thing, one has respiratory, vascular and renal changes, one is working with changes in pO_2, and pCO_2, arterial and venous. There's some evidence that venous pressure is slightly changed at altitude and what is going on specifically, let's say in a given vascular bed, is pretty hard to determine. There may be a slight increase in pressure, within certain capillary beds for example, which would mean an increase in hydrostatic pressure and a shift from vascular fluid volume to an extra-vascular volume, and in addition to that one has the renal factors to consider, antidiuretic hormone, etc., and until your work, Dr. Hannon, in which you started measuring

some sodium potassium shifts, no one really has taken a good look at this either, so in terms of mechanisms we're pretty much in the dark.

DR. HORVATH: The osmotor receptors certainly appear to be be implicated by Yoshimura's data; after all, the marked change in ADH is quite striking and we would suggest that a real look at this mechanism would be not only appropriate but would be absolutely essential before any discussion of what is apparently an obvious fact goes any further. I think we're sort of stuck right now, we're just observing things and not looking at mechanisms sufficiently.

DR. BLATTEIS: Are these data available on the reverse situation, altitude back to sea level?

DR. BUSKIRK: Yes, I didn't show that slide, if you're interested in that I have a table here that you're welcome to look at that shows this information. (Table II. ed.).

DR. BRAUER: What does it show, could you summarize this?

DR. BUSKIRK: We have studies extending from one to ten days and there's a study by your cousin, Dr. Reynafarje, going out to 245 days. In general, plasma volume goes up. There is one here by Lawrence et al., covering a period of ten days, in which there's no change. The other changes were all from 16 to 35%. Blood volume either goes up a little bit or doesn't change appreciably; it stays pretty much the same.

DR. DILL: I wonder if you could generalize about the changes that occur in young men at altitude, something along this line. There is a change during the first days at altitude in young men, based chiefly on a decrease in plasma volume and no change in red cell volume, and that eventually, and whether this is one week or one month—it may vary with the individual—you begin to get an increase in red cell volume without much further change in plasma volume at the moment, and that eventually, as judged by your work in Peru on the residents,

the plasma volume comes back to about its original level and the red cell volume steadily climbs for maybe a year until you reach a new equilibrium between the rate of formation and destruction of red cells. Isn't this about what happens?

DR. BUSKIRK: I think this is about what happens, but the change in plasma volume too apparently is very slow; it comes down initially.

DR. DILL: Yes, I think the first change is very rapid, because all the evidence from hemoglobin concentration indicates there's a rapid changeover for one to three days, then it's slower.

DR. BUSKIRK: This is also indicated by the rat data. One sees a maximum depression in rats by three to five days, and then one has to go out beyond two months apparently before plasma volume starts coming back toward normal.

DR. DILL: This is something that Steve mentioned Monday, but I think may be worthy of emphasis, partly indicating what a shrewd observer Haldane was, and also illustrating the importance of recording your individual data in some way or other, even in the documentation center. There were four of them on Pikes Peak for about 40 days, something like that, and with very few exceptions Haldane did a hemoglobin concentration with his hemoglobinometer every day. There were a few days missing, chiefly on Snyder who went back home down to Colorado Springs two or three times. The rest stayed right on the mountain, and although these results were published, they weren't plotted, but Haldane's conclusion on this was that all showed a rapid increase in hemoglobin concentration at the beginning except in Haldane in whom it wasn't so rapid. I plotted those values, smoothing them out some, running averages. I think Haldane was 51 at that time. This curve represents Douglas who was 29, I think, and the other two, Yandell Henderson and Snyder, happened to be the same age (35), and they were in between. Now it wasn't as nice as this, there were two or three times when this jumped up there, perhaps, and came down, but that was the trend, and of course Haldane wouldn't have been at all justified in saying my curve was lower because I was older. However, this data certainly fits in with the idea that the response in plasma volume differs with age and eventually will

reach a point where it goes up instead of down. There were six of us who were at White Mountain in 1962, ranging from age 58 to 71, on whom we did hemoglobin concentration. Keyes was one of the youngest; he showed no change in hemoglobin concentration during the first days, while all of the others of us showed at least one or two hemoglobin concentrations that were below the sea level values. I was the oldest and I showed the greatest decrease which was about ten percent, reached at the end of ten days. It was three weeks before I got back up to my sea level values.

DR. HORVATH: I want to bring up something that came up from yesterday's discussion, namely the problem of regional distribution of blood volumes. Dr. Saltin pointed out in one of his slides the importance of looking at the pulmonary blood volumes as a fractional component, and certainly this must be relatively important in other areas of the body at the same time. I was wondering if you had any thoughts on that, Dr. Buskirk, because if there's going to be a marked re-distribution of blood volume to the various tissues of the body, this in a sense may indicate one reason why there may be an adequate or inadequate performance. Have you given that any consideration at all?

DR. BUSKIRK: Well, I suppose there is good reason to believe that we should take a careful look at the central blood volume in relation to the total blood volume, and there would probably be good reason to look at kidney functions fairly carefully to see what are the actual renal blood flows. At altitude this is usually complicated by exposure to cold with peripheral vasoconstriction, and a centralization, let's say, of the blood volume, which means the receptors now are responsive to a larger volume which may be associated with the diuresis which one sees during the first few days.

DR. HORVATH: You also want to remember you see a marked diuresis in many people, not all, in cold per se, so there is a double diuresis. You might have a terrific diuresis at a combination of cold and altitude which will again even further modify your blood volume and distributions.

DR. EVONUK: We're going to do some of this next week, at Mt. Wrangell, on blood flow distrubtions on dogs resting and exercising.

DR. HORVATH: This is blood flow distribution, right?

DR. SALTIN: In Vogel's data there is an increase in stroke volume, the first week at altitude, and I have some doubt about that increase, but it fits in with the bigger cell volume, and if that increases then it's possible with a bigger stroke volume.

DR. GROVER: Concerning kidney changes, Richard Noya, of Burlington, Vermont, who is a pathologist and goes in for morphometrics, has examined the size of the glomeruli of children native to sea level and native to 3100 meters. He found that the average diameter of the glomerulus was 25% greater in the altitude residents. This perhaps could reflect a chronic increase in renal blood flow if you say that with a higher hematocrit to maintain a normal plasma flow you must have a greater total blood flow, just to make up for the greater red cell concentration.

DR. BRAUER: Do you know whether the increase in size reflects larger cells or more cells or what? Or didn't he look at this?

DR. GROVER: He may have looked at it, but I don't recall.

DR. BRAUER: Because there are some data on differences in cell numbers in hypoxic mice, hypoxic-reared mice.

DR. GROVER: I do know that in the same paper he looked at the pulmonary blood vessels and concluded there were more muscle cells in the arterials through hyperplasia.

DR. HORVATH: Have there been similar studies on the various pathological studies obtained from residents at altitude?

DR. REYNAFARJE: About blood volume content?

DR. HORVATH: No, in terms of these other areas, kidney, liver and so forth.

DR. REYNAFARJE: I don't know, but I have found that the blood content of the tissue is much larger in the high altitude natives than sea level ones.

DR. BRAUER: At rest?

DR. REYNAFARJE: At rest.

DR. BUSKIRK: This is taking a piece of muscle and drying it – –

DR. REYNAFARJE: Yes, we take a piece of muscle and put it into clamps in order to have the amount of blood circulating at that moment, and we measure the hemoglobin content of a gram of tissue. We have found that it is much larger, but it could be evaluated for the increase in hemoglobin.

DR. HORVATH: You separated out the hemoglobin from the myoglobin?

DR. REYNAFARJE: Right, and it seems that they have much blood volume there . . .

DR. DILL: What is the estimate of the volume of blood in the capillaries at rest and at work, muscle capillaries, at rest and work?

DR. BUSKIRK: You mean per unit of muscle?

DR. DILL: No, total volume of blood which is in the tissue capillaries at any one time, isn't this the order of one or 200 ml's? The actual quantity present in a particular capillary at any one time, and it seems to me that the figure that I have in mind is probably not right, but I believe it is extraordinarily small.

DR. SALTIN: Oh, yes, it is very small.

DR. BUSKIRK: Of course this can change, I imagine, depending on how long the person has been working because you do get considerable swelling of the lower extremity, too.

DR. DILL: You have more open capillaries.

DR. GROVER: Valdivia looked at the skeletal muscles of guinea pigs at high altitude and at sea level and found that the density of capillaries is much greater in the altitude animal, which would be in keeping with what Dr. Balthasar said in the human, and so for a given weight of tissues you would have a greater volume of blood in the capillaries.

DR. BRAUER: There was some German work in which they tried to compensate for the hematocrit effect, upon this old debate about are we dilating capillaries or are we getting more of them, and as I recall the same pattern came around that after you culled the hematocrit correction out you would still have, as I recall, a factor of 2.5 increase in capillary number and capillaries found in the altitude.

DR. DILL: This means that a guinea pig that's born with X-number of capillaries can have three-X capillaries if it's brought up at altitude.

DR. BRAUER: This is their contention in the regions they looked at.

DR. DILL: I though the large consenus was that this can't happen, you're born with a given number of cells and that's it.

DR. BRAUER: Oh, no, you can get blood vessel proliferation quite easily. You do every time you cut yourself on the finger.

DR. GROVER: We looked at this for heart muscle and found that you could produce two hyperplasias in the young animals.

DR. DILL: It's not larger cells or not smaller cells that have been to maturity, grown up, so to speak?

DR. GROVER: No, it's a true increase in number.

DR. BUSKIRK: Is this a slow phenomenon or a rapid phenomenon?

DR. GROVER: We didn't really look at it to see how rapidly it occurred, we looked at it in terms of whether it could occur in the adult as well as in the newborn, and we found that it could only occur in the newborn, that you could get hypertrophy in the adult but not hyperplasia.

DR. HORVATH: It's normal to get hypertrophy in the newborn, isn't it, because the ratio of capillaries in the foetus to the number of muscle fibers is about one to six, whereas in the adult it is up to one to one.

DR. GROVER: Perhaps I didn't make myself clear, I'm talking about hyperplasia of muscle cells, and not hyperplasia of capillaries. I probably didn't make it clear.

DR. BRAUER: Do you know that there are not more nucleii being formed?

DR. GROVER: We did use triciated thymadin and autoradiography. We did DNA, RNA ratios, at rest.

DR. REYNAFARJE: In high altitude native guinea pigs, certain muscles have really two portions, one red portion and one white portion, and the proportion of red portion in high altitude natives is much larger than the proportion of red blood portion at sea level, and taking guinea pigs from sea level to high altitude, the red portion increased and I don't know if this is because capillaries are open or new capillaries are forming.

DR. BRAUER: This goes along with the myoglobin increase, doesn't it, pretty much?

DR. REYNAFARJE: No, it does not, I determined myoglobin by separation and increase in cytochrome C, . . .

DR. BUSKIRK: Halo has presented some work indicating that this happens with training or chronic exercise, there is a slight shift here and the interesting thing is that not only is there a shift, apparently, but there is a metabolic shift, too.

DR. REYNAFARJE: Yes, of course, because the white portion of the muscel is more aglycolitic than the red portion, the red portion is more oxidative.

DR. BUSKIRK: There is a high proportion of free fatty acids in the metabolic mixture, too.

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ENDOCRINE CHANGES IN WORK AT ALTITUDE AND IN THE COLD

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> "They appeared in the form of a copious review of a work on Chinese Metaphysics, Sir," said Pott.
>
> "An abstruse subject, I should conceive," said Mr. Pickwick.
>
> "Very, Sir," responded Pott, looking intensely sage.
>
> "He crammed for it, to use a technical but impressive term; he read up on the subject—in the Encyclopaedia Britannica"—
>
> "He read, Sir" rejoined Pott—with a smile of intellectual superiority – "He read for Metaphysics under the letter M, and for China under the letter C, and combined his information, Sir!''
>
> Ch. Dickens, The Pickwick Papers, Ch. 51.

In the literary tradition of this Conference, the above quotation epitomizes the character of the subject matter I am supposed to cover. The difference is that I should have to look in three, not in two, places, and that, as many of the presentations at this meeting have illustrated so well, it is unlikely that the Encyclopaedia Britannica could have very much to say on any of the three key words of my title. All I can hope to achieve here, therefore, is to provide some framework for discussion and perhaps some clarification of the problems that might call for early study. Since, furthermore, I can lay no claim to having worked actively in this particular field, you should feel quite free to criticize and comment without any fear of hurting my professional pride!

At the outset I want to express my very pessimistic impression of the status of present knowledge regarding the relationship between endocrine changes and adaptation even to cold or altitude alone, and much more so with respect to any interplay between work performance and extended altitude or

cold and altitude exposures. To illustrate the nature of my misgivings, I should like to recall the work of Dr. Heroux on cold-acclimated rats. His original work (1) confirmed previous observations of thyroid hypertrophy in rats exposed to cold in constant low-temperature rooms, with minimal changes in the adrenal cortex in these animals. Extending his studies from laboratory-raised cold-box acclimated animals to wild rats caught either during the summer or during the winter near Ottawa, he was struck with the almost complete reversal of this situation: there were minimal thyroid changes but rather marked adrenal hypertrophy in the winter rats (2).

His next step was to produce cold acclimation in laboratory rats by exposure in outdoor cages to the chilly Ottawa winters. Such animals, when tested by the conventional methods for assessing the degree of cold acclimation (shivering thresholds, survival times under rather severe temperatures, presence of non-shivering thermogenesis, and enhanced susceptibility to the metabolic effects of norepinephrine), were found to be fully as effectively cold acclimated as those kept in cold boxes in the laboratory (3). These outdoor cold-acclimated rats, like the wild winter rats, showed minimal changes in thyroid size, but marked increases in adrenal size. Tests of thyroid function confirmed that the outdoor acclimatized rats did not show enhanced thyroid activity; furthermore, it soon became evident that the enhanced thyroid activity of cold-box acclimatized rats also was not associated with significant increase in blood thyroxin levels, but rather appeared to reflect to a large extent a marked increase in fecal excretion of thyroxin and thyroxin derivatives (4). Thus, in the fully cold-acclimatized rat, increased thyroid activity was not essential to cold acclimation, and such enhancement of thyroid activity as was seen in the cold-box acclimated animal could not be taken as proof of special hormonal effects in the tissues of the cold-acclimated rat, but rather seemed to be an incidental complement to a change in dietary or excretory habits. The whole situation illustrates well the extreme difficulty of establishing causal relations between endocrine changes and adaptation to the conditions we are studying.

I shall not review here the extensive body of data on the stress reaction, and the role of the pituitary adrenal axis, nor the debate as to whether cold exposure as such constitutes "stress" in the sense of that type of analysis. I would like, however, to call attention briefly to the fact that such reactions typically are associated with the transition from one environment to the other, and as such are apt to be quite transitory. Thus, for instance, the several groups who have studied saturation dives of men in several oceans from this point of view (Cousteau's Precontinent II and III, the U.S. Navy's Sealab I and Sealab II, as well as Ocean Systems chamber dive to 650 ft.), all found significant changes in ketosteroid excretion or in urinary sodium to potassium ratios during the

early phase of the dives. In all cases, the reaction seems to have subsided by the end of the third day of the experiment, and the various parameters examined returned to substantially normal values (5). It may be a serious mistake to infer from the subsidence of these so-called stress indicators that these people had ceased to be subjected to a severe load on their adaptive processes. Indeed, the physical and mental condition of the subjects emerging from the prolonged dives may well provide an illustration of the problem posed in our Chairman's opening remarks relative to the deterioration of subjects during prolonged exposure to the combined stresses, such as cold, altitude, and work. Published data on this kind of phenomenon are scarce.

The classical descriptions of high altitude deterioration—chronic mountain sickness—by Monge and by Hurtado and his co-workers, as well as the more recent revision of some of these concepts by Dr. Chiodi on the basis of his own rather heroic experiments (6), all involve time intervals which may place the phenomena outside the scope of the present discussion. On the other hand, the rather acute deterioration of mountaineers during somewhat extended sojourns at altitudes beyond 17,000 ft is a good case in point. They are well-illustrated by the reports from the British Scientific and Mountaineering Expedition to Mt. Everest regarding the deterioration of the group, which had resided for several months at 19,000 ft preparing for an assault on the peak (7). The data clearly indicated the deterioration of the physical performance of these men when compared, even at this altitude, with men freshly arriving after having wintered below 16,000 feet. In addition, this group, as well as others under similar conditions, showed evidence suggestive of CNS impairment, such as increased irritability and some impairment of motor coordination. There was also an early transition to negative nitrogen balance. More complete data on these subjects are lacking; the material gathered by the American Mt. Everest Expedition likewise has not yet been analyzed to the point where one could attempt to evaluate the possible role in these effects of changes in the levels of several steroid hormones involved in nitrogen metabolism.

Another phenomenon that might bear a relation to the negative nitrogen balance which seems to be common in men subjected to multiple stress associated with heavy muscular work is diffuse muscle injury at a microscopic or submicroscopic level. In men, as well as in horses and in rats, one can demonstrate increases in the levels of certain enzymes in the blood indicative of muscle destruction (8, 9, 10). In the case of horses, this syndrome can be associated with quite high levels of myoglobin elimination in the urine. In the case of exercising rats, more severe, microscopically visible foci of muscle necrosis have been described (10). Whether such changes are purely local in

origin, whether they are generally associated with significant levels of nitrogen loss, and the extent to which they might be complicated by altitude or cold exposure are all points which have not been documented to date.

Another aspect of the same subject has been raised by Dr. Reynafarje's observation that changes in muscle enzyme composition which he found associated with altitude acclimation in guinea pigs paralleled an increased proportion of red muscle elements in normally white muscles (11). So far as I know, this observation has never been followed up by the anatomists. In birds, as well as in mammals, rather marked morphological differences exist between the two types of muscle fibers under normal, as well as in some pathological, conditions. This refers in particular to the numbers of nuclei and to their distribution with respect to the fiber axis (12). It seems to me such morphological study would help us understand the extent and nature of the transition observed by Dr. Reynafarje; humoral factors might be studied as a first step toward clarifying whether the change is a purely local response, or whether it is founded upon more general humoral changes.

DR. WEIHE: Heroux has made some morphological studies.

DR. BRAUER: Yes, I am aware of these. I still feel, however, that I am correct in saying that no anatomist with an interest in muscle anatomy has looked at the particular anatomical relations between red and white fibers from the point of view I am suggesting here. I rather think that Dr. Heroux himself would concur with this because his interests at the time were a bit different and certainly did not involve the sophisticated type of quantitative microanatomy required.

Very little work has actually been done so far from the point of view of analyzing the nature of interaction between different stresses. Perhaps this reflects good judgment on the part of the investigators who might well feel that even single stresses such as cold, altitude, or work are so poorly understood that one should profitably concentrate for some time to come upon developing meaningful descriptions of these relatively simple events before entering into the exploration of interaction. Yet, as a matter of practical importance as well as of basic fact in the design of experiments, it might well prove that this presumed simplicity is illusory, and that any kind of exposure to any one of these conditions of necessity puts a burden on the individual which is entirely

comparable to that which would be placed on him by deliberately designed multicomponent stresses. Illustrative of this might be the fact that severe cold exposure without shivering, or severe work exposure without perceptible degrees of tissue anoxia, are not likely to be observed.

Patterns of Change

It might be profitable, however, to consider a different approach, the Dickensian approach, if you will, by looking at the different patterns of change said to be associated with work, with altitude, or with cold stress separately (or as separately as one can get them), and then to combine these to see to what extent they overlap or conflict. From this position, one might then be able to make some projections regarding the nature of endocrine changes that one might expect to accompany superposition of these several changes.

Regional ischemias. Any kind of exercise performance, as well as, surely, altitude exposure, can confidently be expected to place a load on the oxygen transport system. Teleologically one might argue that in exercise performance, maximum transport of tissue metabolites is quite as important as transport of oxygen. Hence, a degree of polycythemia which, in connection with altitude acclimation, might be helpful in improving tissue oxygenation, might prove less desirable in exercise conditioning per se as a factor that could impair blood flow through small vessels. Such reasoning, however, is purely theoretical at present. While effective blood viscosity in isolated systems has been studied as a function of hematocrit, work performance in experimental animals or in human subjects with either induced or spontaneous polycythemia has not been explored. Yet such information would shed interesting light on the interaction of at least two components of our stress system. In connection with altitude acclimation, a fairly extensive body of data indicates that iron incorporation into erythrocytes or erythrocyte precursors as well as circulating reticulocytes and myelograms occurs very quickly. I am not aware of any comparable data on exercise conditioning. Van Dyke and his colleagues have over the last several years developed methods for demonstrating, with some assurance, changes in erythropoietin excretion which, likewise, would seem to indicate that under certain circumstances of altitude exposure this goes up quite promptly (13). I believe he was just recently in Argentina studying this effect in yet another group there.

DR. CHIODI: No, he is not. I believe he is studying the mechanism of anemia in Ancylostoma subjects.

DR. BRAUER: I thought he was going to look at the altitude subjects but I may be mistaken. In any case, the enhancement of the erythropoietin production on altitude exposure, I believe, is well established.

DR. BUSKIRK: Excuse me for a moment, but you probably have also talked to Siri. He published a paper recently in Journal of Applied Physiology on chamber work. However, in all of the samples they brought back from Mt. Everest, I believe they failed to find any changes, is that correct?

DR. BRAUER: Yes, that is correct. I don't believe they understand the difference. On the other hand, in the chamber exposures, I think the situation is clear, and similarly, I believe that in animals the changes can be demonstrated. The discrepancies that have developed in this work are reasons why some of it is being repeated in Peru. The work on Mt. Everest, of course, does not reflect merely altitude exposure but represents superposition of fairly severe exercise on the altitude exposure, and it is precisely for this reason that I brought the point up. It would seem reasonable on hemodynamic grounds to expect that exercise might in some way interfere with the development of a polycythemia. Experiments on this specific point are needed.

DR. CHIODI: Dr. Skarlo, who was working with me at high altitude, measured the hemopoetic erythropoietin changes that occurred in individuals during the first eight days at high altitude, and found a big increase in erythropoeitin in the first 24 hours, after which it goes down but is always significantly a little higher than in natives living at 4000 m.

DR. BRAUER: There is some data indicating a sustained increase in iron turnover in the high-altitude people if pool sizes are taken into account. This seems to apply to some extent even to the fully-acclimatized high-altitude natives.

DR. REYNAFARJE: In the natives it is the same, but in the newcomers it is somewhat elevated.

DR. BRAUER: Yes; a more marked response in the newcomers is a typical "transient" situation and perhaps is not altogether unexpected. What makes this whole situation a bit bewildering is that presumably erythropoietin production involves a renal response to limited anoxia. You will recall that Dr. Saltin's data, like other data on visceral blood flow during moderately severe or severe exercise, show that under those conditions visceral blood flow, and specifically renal blood flow, is considerably reduced. One might expect, then, that exercise even at sea level, and assuredly at altitude, ought to enhance erythropoietin production. Yet the Everest data make it appear as though this were not the case. Control studies on this are obviously required since in the Everest situation these were probably not the only two factors involved.

DR. CHIODI: Dr. W. Siri has also been in Bolivia and told me that with the natives they didn't see any difference even at sea level, in contrast to Dr. Skarlo's results.

DR. BRAUER: This would seem to match the Andean group where the differences at least are not very large. I do think it is worth noting the difference here between the relatively clear and coherent picture with reference to the transition from sea level to altitude alone, in contrast to the negative picture with regard to what I take to be a combined stress situation in the mountaineers.

DR. GROVER: Have you seen Dr. Donald Van Dyke's statement about Choclataya? He studied erythropoietin in the urine of people residing at 5,200 meters and found that their levels were twice what he would find at sea level, and I believe he thinks that this is a first demonstration of a true increase in natives residing permanently at altitudes.

DR. DILL: He probably hasn't seen Hugo's work. His was what, four or five years ago?

DR. CHIODI: Yes, they know that, because Dr. Van Dyke has mentioned that paper in their publication on high altitude. However, it is interesting because he first told me that there was no difference in the natives, but now it occurs in Choclataya. Perhaps it is at a higher elevation.

DR. GROVER: He sent me the manuscript two months ago and it's probably not published yet.

DR. DILL: Ralph, I think you'll find that after the native is fully adapted and has an equilibrium between destruction and formation of red cells, the rate of destruction is unchanged.

DR. BRAUER: There is, of course, increased cellularity of the bone marrow, and one would expect an increased erythropoietin production. Dr Van Dyke's data—which I am glad to learn are as yet unpublished so that I don't have to feel guilty about them—would seem to fit this whole concept quite nicely.

DR. REYNAFARJE: In connection with this, I would like to call your attention to the fact that my cousin found that in high-altitude natives who come down to sea level, an erythropoietin depressing factor starts forming from the first day that the natives come back to sea level. By eight days he found a considerable amount of this factor. He has been able to demonstrate it clearly in rats where iron absorption may be reduced by at least as much as 50%. This may of course be related to endocrine factors or . . .

DR. WEIHE: This lasts about three weeks, according to the observations of your cousin.

DR. BRAUER: It seems to me this is an extraordinarily interesting point, but one which perhaps we should avoid in the present discussion. I think the whole matter of reversibility of effects, and reversibility of adaptation, is well worth reviewing and possibly might form part of another symposium later. Such matters as the capillary proliferation, the enzyme changes, and the extent and mechanism of reversal of the enhanced hematopoietic activity all make exciting biology (14).

To return to this matter of regional ischemias and their effects, it seems to me reasonable to surmise that interaction of cold, high altitude, and muscular work may entail localized ischemia of viscera, and of peripheral tissues, including possibly even muscle, and that this occurs rather more frequently than is

commonly admitted. Under such circumstances the matters of ischemia, of tolerance of ischemia, and of the biochemical and possibly humoral factors which influence this, may be quite pertinent to our discussion. A good many years ago Rein, and later on his collaborators Meesmann and Schmier (15), conducted a series of experiments which led them to think that venous blood from the splanchnic area, and more particularly splenic vein blood reaching a liver simultaneously subjected to some degree of hypoxia, resulted in the elaboration of a factor which they called Hypoxylienin. This factor appeared to have a rather remarkable positive intropic effect on the hypoxic heart, and there was some suspicion at the time that this effect might not be limited to cardiac muscle but might be exerted upon other striated muscles as well. Since the dissolution of Rein's group at the Max Planck Institute in Heidelberg, there has been no sequel to this preliminary work; yet it seems to me it might be worth recalling it in our present context. Whether it is proper to refer to a substance that is only elaborated under emergency conditions as an endocrine factor, I prefer to leave to those whose interests are primarily semantic.

Diving reflex. A second group of related data, and one quite appropriate to a seminar held in Alaska, a state surrounded by diving mammals, involves the consequences of the so-called diving reflex in these animals. This reflex in ducks and other diving birds was described a good many years ago by Richet (16), and since then has been investigated extensively in a number of laboratories, including Irving's and Scholander's in this country, and Anderson's in Norway (17). It consists of a reflex slowing of the heart rate, and in many of the diving mammals, particularly in the pinnipeds, this is very marked (e.g., in the harbor seal from 140 to 3 hearbeats per second). This bradycardia is associated with what appears to be an equally marked peripheral vasoconstriction resulting in almost complete ischemia of the abdominal viscera and—in resting animals at least—of the skeletal muscle (18, 19). The cardiac output apparently is distributed to heart and brain and little else. There is a suggestion in such data as are available that this reflex is active even in animals swimming freely underwater (though blood flow data are not yet available here) and that, furthermore, the bradycardia is associated with a reduction of total computed oxygen consumption (or oxygen debt) in resting animals, well below what one would have expected had the rate of energy production established prior to apnea been sustained through the dive (20). Considering the fact that some of these animals are capable of sustaining dives of the order of 45 minutes, swimming actively and diving to depths now documented in excess of 1,300 ft, it seems evident to me that special biochemical adaptations must have taken

place in these animals. Ischemic work and the accumulation of muscle lactic acid levels of the magnitude commonly demonstrated in pinnipeds could not be tolerated for more than a few minutes. Here again, we lack data to determine to what degree these adaptations are purely local in character and to what degree they entail more generalized sensory or humoral and neurohumoral adaptations.

The diving reflex itself has been studied sufficiently to establish that it is mediated via the para-sympathetic outflow, specifically through the inhibitor branches to the heart, and can be blocked by atropine (17, 21). The whole set of data, beyond posing the specific question of adaptation which concerns us here, also raises the question of the degree to which our classical picture is correct, that a basic level of energy metabolism must be sustained if the tissues are to be kept intact. It seems quite possible that we are here facing one instance of a more generalized phenomenon of metabolic regulation in hypoxic or hypoxic and ischemic tissue which conflicts with these older concepts. These data are no longer unique, but rather constitute only one of a number of examples which seem to suggest that this whole picture is likely to require revision in the near future, and that, indeed, oxygen tension in the tissue can have a regulatory effect upon metabolic rates at levels well above those in which the cytochrome oxidase system as such should be saturated (22, 23).

Hypatic dysfunction. There is yet one other aspect to the problem of visceral ischemia in exercise. The region thus affected involves a number of tissues prominently involved in the metabolism both of steroids and polypeptide hormones. This is particularly true of the liver, where such processes are well documented. One might expect, therefore, that protracted moderately severe exercise could influence hormonal balance to an important extent. Such work as that of Dr. Chiodi, on his infant rats (24) has shown that altitude exposure alone under circumstances where the functional load upon the liver is heavy may suffice to tip the scales toward hepatic dysfunction. Data with respect to cold exposure are more limited. The results obtained in this laboratory at Fairbanks seem to account for the hepatomegaly so frequently observed among some Eskimo groups in terms of dietary factors (25). This makes one wonder about the large livers reported for cold-acclimated rodents. It seems to me that this subject may warrant pursuing, especially inasmuch as the negative nitrogen balance observed in some of the stress situations we have discussed may find a partial explanation in such work. With these considerations in mind, I cannot but be delighted at the fact that Dr. Hannon has just told us that he has begun to work with superposition of exercise and altitude stress in girls, where clearly any such factors ought to follow a rather different course.

Temperature regulation. If we now turn our attention to the general regulatory processes which we know will be called into play when we superpose exercise and cold exposure, the basic problem becomes one of temperature regulation, of the balance between heat production and insulation of tissues against heat loss. Exercise would seem highly compatible with cold stress from the point of view of heat production, since muscular work certainly is a most effective way of inducing calorigenesis. Indeed, if the insulative properties of the body envelope are not sufficiently variable, exercise in a cold environment rapidly becomes limited by inability to dissipate the excess heat accumulated. Arctic experience has certainly shown that subjects adequately dressed for sitting and sleeping outside, when expected to exercise, rather rapidly find themselves converted from runners into swimmers because of excessive sweating. If, on the other hand, we consider subjects genuinely subjected to cold stress, the situation is different and far more complicated: while exercise results in increased heat production it also entails increased perfusion of peripheral tissues, which in turn can cut down on the insulative properties of these portions. Experiences with inadequately clothed subjects exposed to cold water suggest that heat loss to the critical point occurs somewhat more rapidly in subjects who are swimming actively than in subjects resting as quietly in the water as may be and who depend upon shivering for extra heat production (20). So far as I know, actual data on thermal gradients across the tissues of such subjects have not yet been published.

DR. HORVATH: Captain Beckman from the Navy is going to publish this. While I hate to put it out before he does, allow me to mention that he has just finished a fairly extensive study involving men either swimming or lying quietly in water as cold as 10° C. His conclusions, if I may possibly misstate them a bit, are quite in opposition to those of Keatings', and so here again we are somewhere back to where we started.

DR. BRAUER: These data certainly would be most helpful. In any case, I think it is proper to call your attention to the fact that swimmers immersed in the medium provide an excellent situation for studying heat transfer, as well as energy metabolism, under conditions where both the environmental temperature and the work output can be controlled and varied over fairly wide limits. For purposes of studying the rather subtle changes which I suspect we are dealing with when attempting to talk about endocrine responses to combined stress of this type, it seems to me this may be a nearly ideal situation.

Metabolic requirements. With respect to endocrine response to cold, I think I have indicated at the opening of the present discussion my impressions of this subject and the difficulties under which it labors. From the point of view of superposition of exercise upon cold, the key elements here seem to be the question of respiratory fuels and their mobilization, and of metabolic pathways. There is a large body of data relating the catecholamines to the mobilization of both fatty acids and glucose as the fuels for muscular exercise; similarly, we are all aware of the excellent work which has established in several species the relation of cold acclimation to increased susceptibility to the metabolism-stimulating effects of norepinephrine. Yet, when one attempts to link this type of information to the metabolic requirements of man performing muscular work in the cold, the literature is less than clear. The exciting data Dr. Saltin presented here earlier, suggesting that there may be qualitative differences between the metabolic fuels used in severe and in relatively moderate exercise, pinpoint the nature of the uncertainty under which we are laboring. This point is further underscored by the observations of Dr. Reynafarje suggesting that in addition to a shift in fuel, tissues, in his case of altitude-acclimatized animals, give preference to metabolic pathways different from those employed under similar conditions by nonacclimatized animals. Data on catecholamine elimination (and, incidentally, I believe Dr. Blatteis has made a far more complete and ambitious survey than I have been able to prepare on this subject) seem to indicate that here, too, there is a difference between moderate and severe exercise; in the former, epinephrine is the substance preferentially excreted by man, while in the latter, norepinephrine spillage appears to predominate (27). Once more, we are left to speculate on the possible effects of superposition of cold, or for that matter, of altitude, stress upon the muscular work.

It seems to me that in this context it would be worth making use of the observations of the several groups who have studied body temperature during sleep in different ethnic groups, and who have been able to identify at least two quite different patterns of response. Studies of catecholamine output in those groups showing their cold adaptation by metabolic regulation and tolerance to shivering, compared to those who normally tolerate more or less severe degrees of nocturnal hypothermia with minimal metabolic response, may well be profitable in clarifying the role of neurohumoral factors in adaptation of man to the joint stress of cold and exercise.

Nutrition studies. A few words may be in order regarding yet another general approach to our subject, the point of view of nutrition studies. Athletes

attempting to function at altitudes tend to express a strong preference for low fat, high carbohydrate foods. Pugh, in reporting on this subject, makes the point that his mountaineers were relatively intolerant of the fats in their diet, and also did not express a strong liking for high protein foods (7). These dietary preferences may be either cause for or expression of the factors underlying the negative nitrogen balance characteristic of subjects sojourning for some time at altitudes beyond those to which they can acclimate adequately. I gather that experience in the arctic and antarctic, in subjects exposed to cold and exercise, and only to a minor degree to altitude, has been quite the opposite: relatively high fat foods are well tolerated, as are diets quite high in protein, while carbohydrate diets are said to be unsatisfactory. It seems to me that such qualitative evidence, though highly suggestive, invites more analytical followup. Yet, data on glucose tolerance, on insulin effects, or on cases of endocrinologically-based obesity under these conditions, to name but a few examples, seem to be lacking. Some of the military laboratories concerned with food supply under such conditions may have data on food intake, on food preference and, perchance, on food utilization. If so, it would be valuable to have a review summarizing this material and its possible bearing on the tolerance of man to protracted exposure to work at altitude or in a cold environment.

Animal experimentation provides some additional data suggesting that this is an interesting approach. Many years ago, McCay and his colleagues showed that by restricting the food supply of young rats so as to virtually inhibit growth, one produces animals with markedly enhanced life expectancy (28). While the original McCay rats were sterile, a less drastic restriction compatible with normal sexual maturity extended life expectancy (29). The question was posed in recent years whether the inhibition of growth or the reduction of food intake was the factor primarily responsible for the prolongation of life in these rats. To test this, rats were placed in a cold room at a relatively tender age, and supplied food ad libitum (30). Under such conditions, these rats, like McCay's rats, failed to achieve their full size. However, they did so in spite of a food intake vastly in excess of that of normally reared rats. In contrast to the hypocalorically reared animals, these cold-retarded rats were found to have a markedly reduced life span, not much more than 50% of normal, and showed a 50% incidence of arteriosclerosis when one year old, a phenomenon not heard of even in the normal rat, and surely not in the McCay type of animal. A still further preparation of interest to us here was briefly described at this spring's Federation Meetings (31). This is a mouse reared in a hypoxic environment. These animals, too, are stunted in their growth. No information on their life span is available so far. However, a most interesting special finding here sheds

light on some of the processes involved in the growth limitation: in hypo-calorically reared rats, and mice, the stunted tissues contain normal number of cells, but there is said to be a decrease in average cell size. In the hypoxia stunted mice, the stunting entails cells of almost normal size, but markedly reduced in numbers.

While none of these three types of growth restrictions have been studied to the point where the data would be directly applicable to our deliberations, it seems to me that they hold forth an extraordinarily tempting invitation to apply this type of technique to the study of the effects of protracted exposure to single or combined environmental stresses in which exercise is made a factor. Descriptively, as well as in terms of clarification of mechanisms of interaction, a series of relatively straightforward experimental designs along these lines should yield a valuable harvest of information.

Urinary secretion. I had originally planned to include in this discussion diuresis and its relation to exercise and other factors. Since Dr. Buskirk has covered this so well, I shall merely call your attention to the fact that the most marked effects in this, as in so many other cases, are not associated with the steady state but rather with the transition from one environment to another. I would also like to raise the question to what extent such changes in antidiuretic hormone secretion as do occur are directly associated with adaptation or accommodation to a changed environment, and to what extent they may be merely incidental indicators of generalized changes in activity of the pituitary/adrenal system. One further point that may be worth mentioning in this context is the great importance of diurnal or circadian rhythms for urinary secretory activity (32). There is some evidence that diurnal cycles can be partly dissociated rather rapidly by transferring people to environments to which they are not at the moment adapted. One might expect this to be particularly prominent when the environment in question is recreated in an environmental chamber. In the case of subjects transferred to Little America during the Antarctic winter, the loss of diurnal rhythmicity was quite pronounced, and undoubtedly affected the pattern of urinary secretion (33). However, so far as I am aware, it is not known how such alteration affects overall secretion rates averaged over a 24-hour period or over multiple 24-hour periods. In the case of Alaskan Indians, studies have been reported to indicate that the normal diurnal cyclic changes of urine volume and potassium secretion are wholly absent (34).

Future studies. Enough has been said to indicate the frustrating state of this field and possibly to point to some areas which seem to hold some

reasonable promise of success for future approaches. While I am well aware how limited my literature coverage has been, I have a suspicion that, if I had had two or three times as much time at my disposal and could have performed a really complete literature survey, the end result would still have constituted substantially a series of tantalizing questions which one can just perceive through a haze of incomplete experiments from highly complex experimental situations. I feel sure that this is not an accident, but rather reflects the fact that the time course of endocrine changes is generally a good deal slower than that of the processes which are more readily accessible in the kind of environmental situations where multiple stresses are at present imposed upon the individual. Where these stresses are imposed for a prolonged time in an operational setting, the phenomenology of the changes which occur is apt to be so extraordinarily complicated by the interplay of emotional, physical, nutritional, and environmental factors, that analysis is indeed difficult. If our experiments start with people coming from a "normal" and comfortable environment, then transposed to the relatively stressful one which we wish to study, we are clearly confronted with a situation in which a large part of our data is apt to reflect transient changes rather than the properties of a new steady state, and in which this very fact, by the preponderance of readily measurable stress-like responses during the transition phases, is apt to obscure the more subtle reactions specific to the particular situation we really wish to study. I suspect that we ought to be quite insistent that future experiments intended to contribute to our understanding of neurohumoral regulatory processes must follow an A-B-A design; that is, a design in which a good control period is followed by an adequate period of stress to reach a new steady state, and this again followed by a period after return to normal conditions, with observation series in all three periods to eliminate secular factors as far as possible. Regarding studies involving longer exposures, all who have listened to Dr. Dill's presentations will have come away impressed that for the recognition of subtle differences extended longitudinal series with careful collection of data on relatively few individuals are essential.

Physiological Studies on Natives

I would, finally, like to say a few words about the problems of extracting physiologically meaningful observations from studies on "natives." Such studies occupy a prominent place in any discussions of environmental physiology, have done so for several years, and are likely rightfully to continue to do so. Yet, it seems to me, all too rarely have the physiologists involved taken time out to

consider under what conditions meaningful comparisons can be made between the several groups which they commit themselves to comparing. Intercomparison is obviously essential if one is going to talk about the influence of one or another environmental factor in human biology. The problem is easy only when one merely wishes to point out differences in patterns existing between different ethnic groups, without any attempt to determine underlying mechanisms or the significance of these mechanisms from a biological or an adaptive point of view. When rather subtle mechanisms are to be the prime subject of study, any observations that do not include meaningful control groups are doomed to futility from the outset. Allow me to demonstrate briefly the nature of my misgivings by turning to a population about whom I know something, specifically, the Quechua-speaking Indians of the Peruvian, Bolivian, and Ecuadorian Andes.

I became interested in these populations some years ago while attempting to formulate an experimental approach to study the interplay between aging and environment. At that time I argued: "One must locate a population of fairly uniform genetic background, i.e., representing a fairly uniform variance of key traits in all pertinent geographic subpopulations, living in communities sufficiently large for sampling while yet of manageable size, distributed over a geographic range of such dimensions and such character that a reasonable range of physical environments will be included in the overall habitat. The material culture, as well as the social structure, of such a population should not only be fairly uniform throughout the area of occupation and should not vary too much between several types of community, but these elements must also be of such character as not to result in such severe stratification within the communities or in such heteorgeneity within the population than analyses become impossibly complex. Finally, their way of life should be such that the individuals will experience considerable exposure to the environment in which they are presumed to live."

Among populations which might possibly fulfill these requirements, the Quechua-speaking Indians living in and along the Andean antiplanos and the adjacent valleys in Peru, in southern Ecuador, and in parts of Bolivia, appeared particularly promising. Accordingly, in the fall of 1964, Dr. Berendsohn and I visited some 20 communities in this area, distributed as shown in the accompanying map (Figure 1). Populations visited were selected on the basis of linguistic information (35), since it was desired to restrict our work predominantly to Quechua-speaking populations in the hope that this would assure some degree of cultural uniformity among the groups.

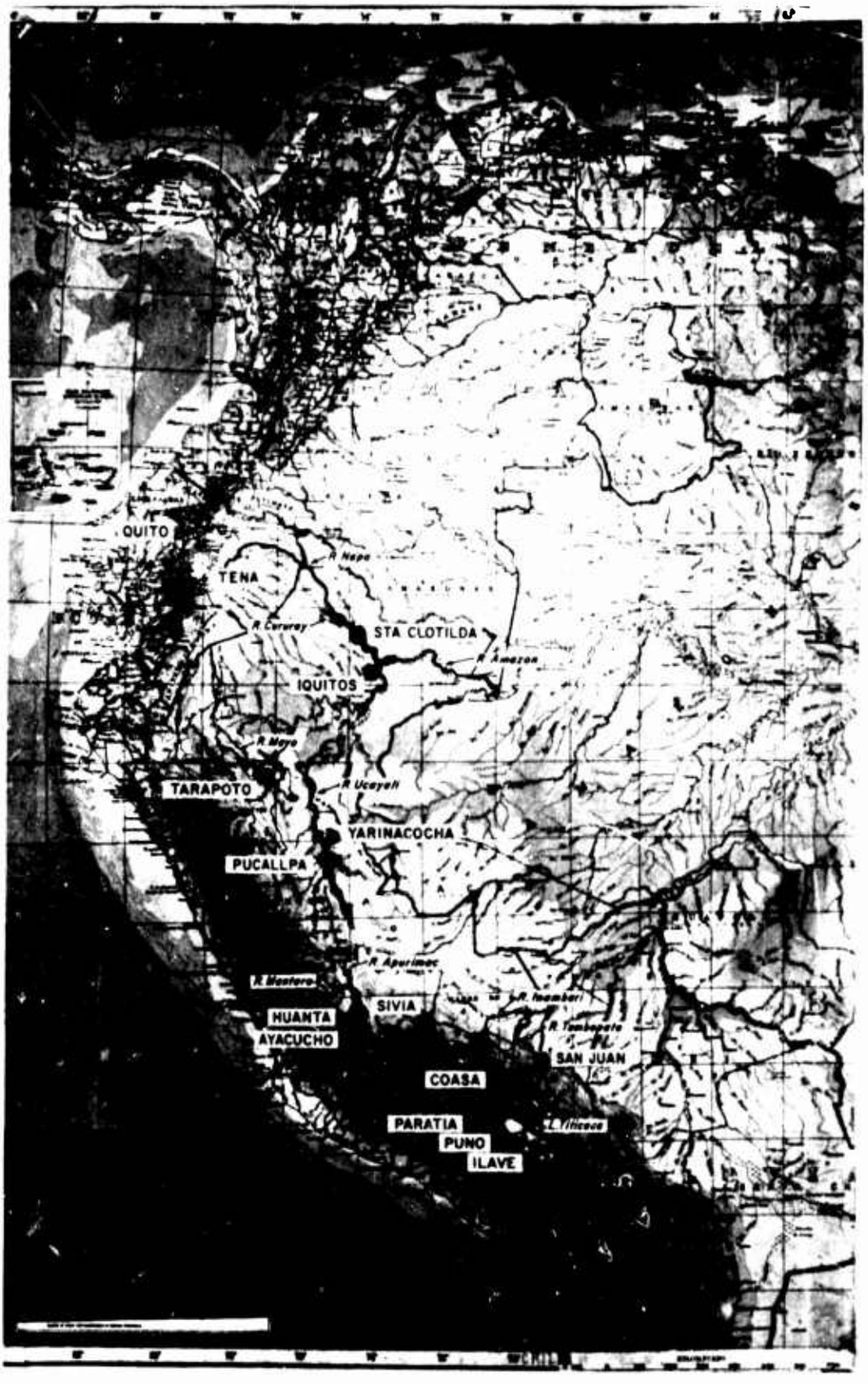


Figure 1
Map of Northwestern South American communities described in the tables and illustrating the geographical relation between the several pairs of communities.

While one could not hope to find a territory of such magnitude occupied by any single group that could be considered even approximately homogeneous, our visits convinced us that we could subdivide the population into a series of useful subpopulations along geographic lines by dividing the total area into a series of strips running in a generally west-easterly direction across the Andes and extending into the upper (and in some cases into the lower) river valleys of the Peruvian and Ecuadorian Amazonia. These populations arise from what appears to be a common pattern of population movement, according to which populations in the upper regions of the rivers in the Andean high plains and valleys move in search of better social and economic conditions toward the eastern slopes of the Andes. These movements are of relatively recent origin, having occurred mostly within the last 100 years and including some which continue to the present day. It has thus been possible to locate Quechua-speaking populations in the Montaña and in the river valleys of the lower Amazon basin who can document their origin from specific communities in the upper regions of the rivers, in the Andean valleys, or in the Puna as the case may be. These subpopulations may be designated by the names of local tribal groups with which they seem to be associated, such as the Yumbo, Lamista, Chanca, and each in turn can be subdivided into at least two elements: one which continues to inhabit the more western environment at relatively high altitudes, and one which occupies the eastern, warmer and less elevated environment, and arises from the former by group migration.

The following tables briefly describe these populations. In each case, communities occupying the lower and the higher zones of the habitat of a particular subgroup are compared, and constitute essentially a natural experiment concerning the effect of change of environment upon a population which has been split some time ago along lines which I have reason to think are only mildly selective. In each of these tables I have included, as far as we could become aware of them in the rather short periods of time we could stay with each group, a description not only of physical but also of social, nutritional and occupational environmental factors. Perusal of any one of these tables will very quickly show that it is a far cry from even these natural experiments, taking place under nearly optimal conditions, and the type of situation one re-creates in the laboratory to study effects of environment on animal subjects. In each case, the change in physical environment is inextricably linked with profound changes in social structure, in principal food sources, in occupation, in the things one gets drunk on, and even in such details as the manner in which the children and parents distribute themselves during the night in their sleeping accommodations. It seems to me certain that any study of physical differences between these

populations is likely to yield misleading information if it is not informed by an understanding of the multiple factors which make up the overall ecologic changes associated with the migration. At the same time, the fact that a number of such translocations have occurred in subpopulations originally not too dissimilar may permit the formulation of factorial designs which offer some chance of analyzing the effects of complex ecologic changes. Table V shows the types of environmental differences that separate the eastern and western elements in several of these subpopulations, and indicates the type of factor analysis that might be achieved with the limited samples we explored.

TABLE I

QUECHUA/AYMARA SUBGROUP

Name of site	S. Juan/Oro	Coasa	Paratia	Acora
Location	(R. Tambopata)	(Above R. Irambari)	(Lampa Plateau	(Lake Titicaca)
Elevation ⟶	1500 ft	9,500 ft	15,400 ft	14,800 ft
Population	~ 4000 stable ~ 15,000 total	~ 4000	~ 800	4500
Sojourn in area	Recent to 30 years	50 + years	50 + years	50 + years in area
Language Group ⟶	Aymara – 40% Quechua – 50%	Quechua	Quechua	Aymara
Mobility	Stable and seasonal houses	Formerly parcialidades	Stable core village	Stable
Community setting	Village and separate houses	Village and parcialidades	Hollow core village	Villages
Marriage pattern	?	Village endogamy	?	?
Socio-economic status ⟶	Landholders + peones	Landholders	Landholders	Landholders
Economic basis ⟶	Coffee + chacra	Potato, sheep	Sheep, auquenids	Potato, sheep, fish
Staple foods ⟶	Yucca, papa japon.	Potato	Maize, olluca, barley	quinua, olluca
Meat, animals	Cattle (1/wk/15000) Lamb (chalona)	Lamb, local cheese	Lamb, local cheese	Chicken, rabbit, guinea pig
Wild meat	?	?	Wild birds	Fish, totora root
Drinks	?	?	Aguardiente	Aguardiente
Coca use	Yes	Yes	Yes	Yes

⟶ – Indicate important points of difference.

TABLE II

YUMBO SUBGROUP

Name of Site	Puca Barranca, Sta. Clotilda, R. Curaray	Tena, Archidona, Cotunda
Location	(Lower Rio Napo)	(Upper Rio Napo)
Elevation →	300 ft	1500 ft
Population	~ 3000	~ 10,000
Sojourn in area	30-50 years	50 + years
Mobility status	Move along river, mobile peones	Relatively stable, formerly peones now mostly landholders
Community settling →	Isolated houses or small clusters ?	Clusters of houses – family groups "clan" exogamy
Economic base →	Palo de Rosa lumbering + (chacras)	Coffee, cattle + chacras
Staple foods	Yucca, Platano, pan de arbol	Yucca, banana, (beans, rice)
Meat animals →	Pigs, chickens, guinea pigs, (cows)	Cattle (sold, some meat bought) chickens (eggs sold)
Wild meat →	Fishing (paiche), game (tapir, pig, monkey) turtles + turtle eggs	Little fishing and hunting
Drinks	Masato, aguardiente	chicha de yucca (aguardiente) Huayusa
Coca use	None	None

→ – Indicate important points of difference.

TABLE III

CHANCA SUBGROUP

Name of site	Sivia, Rosario	Huanta, Tambo
Location	(Lower R. Apurimac)	(High valleys near Ayacucho)
Elevation ⟶	1500 ft	900 and 13,000 ft
Population	~ 800	~ 2000
Sojourn in area	30-50 years	50 + years
Mobility ⟶	Limited seasonal nomadism	Mostly stable
Community setting	House clusters and roadside village	Village + house clusters
Marital pattern	Family exogamy	?
Socio-economic ⟶	Landholders	Colonos or landholders
Economic base ⟶	Coca, coffee, cacao	Potato, wheat, sheep, goats
Staple foods ⟶	Yucca, papa japon.	Maize, barley, potato
Meat animals ⟶	Pigs (1/yr/family) chickens (1/month/family) (cattle – milk and eggs little used)	Goats, sheep, guinea pig
Drinks	Chicha de Yucca aguardiente	Chicha de Mais, chicha de jora, aguardiente
Coca use	Considerable	Considerable

⟶ – Indicate important points of difference.

TABLE IV

LAMISTA SUBGROUP

Name of site	Maceda, Pucacaca, Sta. Ana Flores	Lamas
Location	(Middle R. Mayo)	(Plateau of Lamas)
Elevation ——→	1000 ft	3000 ft
Population	~1350	~3000
Sojourn in area	50 + years	50 + years
Mobility	Stable	Stable, limited trade nomadism
Community setting ——→	Villages, separate houses near fields	City barrio
Marital pattern	Exogamy relative to village	"clan" exogamy
Economic base ——→	Cotton, coffee, (cattle) + chacras	Trade (?) + chacras
Staple foods	Yucca, Maize, (banana)	Yucca, Maize
Meat, animals	Pigs, (cattle = milk?)	Same ?
Wild meat	Game, little fishing	Same ?
Drinks	Chicha de Mais, chicha de jora aguardiente	Same ?
Coca use	Little	More ?

——→ – Indicate important points of difference.

TABLE V

SUMMARY

Subgroup	Environmental differences
Yumbo	Occupation, climate, social setting
Lamista	Occupation, climate, social setting
Chanca	Elevation, occupation, diet, social setting
Aymara/Quechua	Elevation, occupation, tribe, diet

Conclusion

To return to our original subject, differences in endocrine patterns which might be associated with the different patterns of superposition of work and environmental stress are surely among the more subtle distinctions that one could wish to explore, quite comparable to the aging patterns we were thinking of when viewing these Indian groups in search of a suitable population base. The above considerations lead to the conclusion that profitable exploration of this type of phenomenology and involving "native" groups, must be accepted as part of a broader ecological study of the population groups in question. Such a study is likely to require a span of time of the order of five years at least, to allow the investigators to become accepted by the societies they are studying, and to provide a background of understanding of the multiple factors involved in meaningful comparisons of any human ecological situation. Despite these difficulties, the use of migration patterns to provide natural population experiments concerning acclimatization effects in man seems to me worthwhile and a promising approach. If, at the outset, it leaves the beholder a bit overwhelmed with the difficulty of defining meaningful questions concerning the endocrine effects of such environmental shifts, such an impression is very much in line with the one I wish to convey, and, indeed, brings me back to the comments I made at the start.

Perhaps, however, you will allow me to close by pointing out that what we are viewing here is merely one aspect of the problem of the interplay of environmental history and population quality. At a time when technological advances bring us ever closer to the day when sizeable groups of people will be able to select at will the sequences of environments under which they live their lives, this problem is of the most critical importance, and any considerations that help us to bring it into focus should be welcomed by us as students of the environmental physiology of man.

DISCUSSION

DR. HORVATH: Thank you, Dr. Brauer. I thought I might start the discussion off by asking Dr. Morrison if he wouldn't mind making a few comments in relation to some of the things that he is doing with mice.

DR. MORRISON: I think this very nice presentation of Dr. Brauer's reflects in some ways some of your introductory remarks on where we need to go to find out some of these things. I will take this invitation to comment to promote a particular interest of my own. I think there is a parallel here even as laboratory rats and mice are used as model animals for critical experiments on man, and so too I think our natural populations of rodents offer in some ways even more advantages in simulating the conditions that we have in natural groups of humans because we can avoid many of these built-in difficulties to which Dr. Brauer has already alluded. These are very restricting difficulties, the fact that in terms of humans we're dealing with a very limited population, utterly inadequate in terms of statistical matters, just handsful of people, we have all the problems of dealing with humans, of course, sometimes even complicated because of the fact that they are native peoples, the histories, the diets, all these complicating factors are often unknown and do not go in the direction we want them to. But with natural rodent populations we have literally continua of local groups that can exist across a wide expanse, in terms of simple distance but also across environmental transitions, both north and south and up and down, and these animals are available in large numbers, they're always there, we know that they've been there, not only as a—and this is another thing you don't get perhaps with human populations, but you have the availability in the same conditions or closely the same conditions of quite different types of animals, the different species and sub-species that have evolved independently and therefore are living successfully with the environment but with differing sets of attributes. This gives us a degree of freedom that you don't have with humans, because they generally pretty well absorb or exterminate sympatric groups.

Well, in terms of these model systems, again I think that we have to—and I think this has been brought out in these comments—we can't say that the completely controlled situation is the only way to do it, give us the answers, or we can't say that the completely natural sampling situations are the one way, I think we must always work with both of these and I think that this is something that hasn't been done much in the past. It's best too if we work with the same group of investigators, because only in this way do we have the same techniques and the same realization of the phenomena and the gains to be gotten from both groups, and I think eventually one has got to build a bridge across there, that is, a bridge from the completely uncontrolled natural situation to the completely controlled laboratory situation that is in terms, one, of starting to control the environment where the animals are, step by step, to a degree and two, by introducing, one by one, degrees of freedom, environmental freedom, into the controlled situation. When one can construct a bridge across here, then we can

get the answers to these situations as described in the Ottawa experiments where the responses of the animals in the cold room were diametrically opposed to those outside, completely different. We have to come to a common ground this way.

Well, I think that this is just a point of view and I think this is a very broad one, because it involves probably all environmental variables, and actually there is the view too that these variables are not separate but there's a common ground with many of them, and the synergetic effects are separate from those of individual ones. I read a very capable article by Rene Du Bois a couple of years ago in Bioscience on this, that this view of adaptation in environmental phenomena cannot be solved by what has become to be the traditional methods of biology, that is to say the complete control of all variables except one and in fact this has come to be such a firm view that there are many people who will state that it is not science unless you have done it in this manner, but environmental phenomena are too complex for that and we must accept them as they are. This simply means that we must accept these uncontrolled multi-factoral situations, but we must define them. This is an entirely new view, in a way, of going about these things, but we aren't going to find the answers unless we do, and this means a very complicated situation and if they are complicated, so they will be expensive, in terms of the number of measurements that have to be made, the number of people that have to be involved simultaneously in an effective analysis of the situation, and the kind of facilities that have to be available. But of course expensive things aren't good because they're expensive, and to spend more money isn't good and yet you know very often we have this problem raised: here are the physicists who are making great advances and they're doing it because they've got money available for expensive facilities and techniques, but the biologists aren't moving forward, there is nothing that they need that costs money, it's just to go on as they have. Yet I think in terms of this environmental analysis—and frankly I feel sincerely there is nothing more important in terms of a scientific venture for us at this stage than to understand what our environment is, what it's about and what is the inter-relation to man and animals in it—that simply because of the number of variables involved, the number of individuals that are going to have to be handled in any effective assay situation, that this will have to become a rather expensive matter before it's solved effectively.

DR. HORVATH: Do you know of any endocrine relationships that have been related in terms of animals of the same sub-species which reside at different

altitudes, and consequently are subjected to different stresses of thermal environment in an almost natural situation?

DR. MORRISON: No, I think the only place where this has been looked at is White Mountain. There has been some work done down there, some endocrine viewing, but it's –

DR. BRAUER: Ray Hoek while at White Mountain has worked a bit on this. The data, however, haven't been analyzed as yet.

DR. MORRISON: It is not related to endocrine factors, though.

DR. BRAUER: The National Academy of Science is looking right now into the question of the feasibility of setting up, at a national level, a multi-environment animal breeding facility which could give us groups of animals reared under different environments. I think this is a most important device, basic to the kind of work that we have been discussing. At the moment, though, this is only in the talking stage.

DR. HANNON: Ralph, you have some comments about nutrition and environment, and there has been a fair amount of work done on this sort of thing. I would like to mention some of it. Now in the cold as well as at altitudes, animals have been fed diets high in fat, high in carbohydrates, high in protein. I'm talking about laboratory rats, now. A high fat diet seemed to promote the best growth. This was a surprise. Protein diets seemed to be the least well tolerated, particularly at altitude, and growth was severely reduced in these animals. As I mentioned earlier, protein metabolism–

DR. BRAUER: How high was the protein content?

DR. HANNON: On the order of 80 percent.

DR. DILL: What species?

DR. HANNON: This is in rats. This reduced tolerance for protein is coupled with—as I said earlier—a negative nitrogen balance. It's been shown that in rats the incorporation of amino acids in protein is reduced by altitude. In respect to cold, growth in these animals depends on their initial age at exposure to cold. Young animals can tolerate the cold much better than older animals. In fact very young animals, on the order of 80 or 90 grams in weight, when put in the cold or in moderate cold will show very little suppression of growth. About all you see is a stasis of growth for a day or two, and then they continue to grow about like the controls that are warm, although the curves are displaced in time. Older animals will actually lose weight.

DR. BRAUER: How severe is the cold in these experiments?

DR. HANNON: About 5° C.

DR. BRAUER: How old is old?

DR. HANNON: I'm speaking of weight now. I don't remember exactly what the ages were, but they're normal animals. But you compare, say, a 100 gram rat with a 400 gram rat. The 100 gram rat will probably not lose any weight.

DR. BRAUER: Yes, but won't he gain any?

DR. HANNON: He will gain after about two days, he will accelerate and by the end of a week he will be growing just as fast as the controls. It will take a 400 gram rat upwards of three weeks to balance his caloric intake so that he will again resume his growing like the control animal, so I think the point here is that it depends on what age of animal you're looking at. And the problem of effects on the life span, this I think is a very controversial thing. As we mentioned, Canadian workers have found a reduced longevity, but Lawrence Houseman has found no effects on longevity. I don't recall offhand what the quoted change was . . .

DR. BRAUER: Houseman reported that it doesn't change. Certainly the Canadian data looks consistent and clear, and I suspect it did not involve pulmonary disease, such as one would normally think about.

DR. HANNON: Well, the point is, there is some question about it yet.

DR. BRAUER: There are conditions we don't understand.

DR. HANNON: Right. With respect to something that is pertinent here and also to Dr. Buskirk's talk, namely body composition, we did a fairly detailed analysis of body composition in animals exposed to altitude at Climax, Colorado, which is about 3,500 meters, with respect to different diets and stunted growth. We found the usual things, namely protein diets were poorly tolerated, as I mentioned earlier, and all diets caused a reduction in body fat content, and the altitude caused a reduction in body fat content in all animals. There was normal body water, there was a slight reduction in lean body mass, particularly in the protein-fed animals, and there was an increase—and this was estimated from potassium analysis of the carcass—an increase in intracellular space. I think that's all I have to say on this.

DR. HORVATH: What about that work that's being done on the thyroid hormones and their extractions at your place?

DR. HANNON: There's a repression of thyroid function during acute exposure to altitude. Dr. Martin Surks has worked through this and has fairly well pinpointed where the defect is in the intermediary metabolism thyroid hormone. I can't recall offhand exactly where this is—it's been published in summary—but he does have data on this subject.

DR. BRAUER: His emphasis in the published reports has been again on the first three days of the tests.

DR. HANNON: He has actually done a total of six studies on this, which

are in varying degrees of publication, on both humans and animals. He's spent up to four weeks on the studies of humans; the animal studies don't extend quite that long.

DR. WEIHE: I think when we talk about endocrine changes at high altitude we shouldn't be so pessimistic as you are, because there are two different processes. There is the acquired acclimatization and there is the natural acclimatization. In natural acclimatization, I fully agree with you, there is probably very little change. We have to do lots of studies in order to find out. But in acquired acclimatization we find striking changes, and they apply to the adrenals, they apply to the medulla and the cortex both, they apply to the thyroid. These are transient changes but they definitely occur.

DR. BRAUER: Yes, I'm sure the transient changes occur. The main question about which I feel negative now is: once that first transient period is over, when you have established some measure of acclimatization, I have yet to see—barring possibly some of the data you mention—but I have yet to see convincing data that documents detectable endocrine changes. I suppose you could argue quite comfortably that in fact a new equilibrium has been established, where endocrine differences now become matters of slight quantitative shifts which are not readily detected by the methodology with which we are concerned.

DR. WEIHE: Because you have the same changes in cardiac output and so on as soon as adaptation has taken place. But there are many papers published recently on catecholamine excretion, and we should discuss them, because the findings disagree. Some people find an increase of noradrenaline and others find only an increase of adrenaline in the urine. There is a majority of findings that the noradrenaline content increases during the first two to three weeks at altitudes above 4,000 meters.

DR. BRAUER: Under what conditions?

DR. WEIHE: This is just life—nobody describes clearly under what

conditions, unfortunately. They just say they go up to high altitude. A French paper, for example, stated that there is an increase of adrenaline. Now the question is, is this an effect of ambient temperature? We don't know, and this is certainly very difficult to sort out as long as nobody describes under what conditions he has investigated this presence

DR. CHIODI: With respect to sexual organs—if you consider that spermatazoa secretion or production is part of the endocrine system—San Martín has been working with animal fertility, and he has described, when you take the animals to high altitude, not much—you couldn't consider it really transient because it will last many months—

DR. BRAUER: In the ram?

DR. CHIODI: In the ram, yes, and also I think there has been work done on spermatazoa counting in men. They found some change for a few months, and then the count returns to normal. Even so it shows that there are some changes that could be taken into consideration, and so I agree with Dr. Weihe that we should not be so pessimistic, even if I also agree that a really big change has still to be described. I remember also hearing someone at the Kyoto conference talk about the thyroid change in sheep in the cold; he described fairly accurate studies on the sheep, showing that changes were real although transient.

DR. BRAUER: Here again is the question of causal nexus. I'm fully aware of the sperm data, but I think the data do not necessitate any endocrine changes, because we can simulate this quite well by tampering with the oxygen supply to the testes. If you tie off some of the arterial supply you get identically the same changes. So I think that you cannot take this as evidence, although I think you can quite legitimately take it as a question which somebody should answer. In the same vein, the thyroid changes in the sheep, which I'm quite sure are real, suggest a question to me, because the Heroux data make me wonder whether these changes are incidental or whether they're pertinent to the reaction we're discussing here. And remember I was supposed to be concerned not with endocrine changes in the cold, nor with endocrine changes at altitude, but with

endocrine changes with work in cold at altitude. The lack of information, I think, can't be painted black enough.

DR. CHIODI: Yes, well, coming back to man, also I remember the work they have done on adrenals and ACTH in men at high altitude, including natives, and they have shown that there is some change. The natives are perhaps less sensitive to ACTH, and the investigators suggested that they needed more ACTH for maintaining the same level of cortisone. They didn't see any change in the cortisone levels, but when they injected ACTH, they found that the native at high altitude in some way needed more ACTH than they needed at sea level. That is a very interesting problem. Also they showed the eosinophilic level–

DR. BRAUER: Who is "they," for reference purposes? I think this is a reference we should have.

DR. REYNAFARJE: Marcelo. They published most of it in Lima.

DR. CHIODI: And also they showed that the eosinophilic reaction was much less. I saw the same in rats. And it looks as if even in long-term experiments, it shows in the same way. I think another very interesting problem is why in certain animals the adrenals will increase in size, will increase function for a transient reaction, then apparently the level of secretion of hydrocortisoids will remain normal, but still the adrenals are bigger than normal. I always saw that.

DR. REYNAFARJE: It has been shown that the ACTH isn't reduced.

DR. WEIHE: May I add a comment concerning diurnal rhythms? We did some studies . . . I know the chairman told us not to talk about animal experiments, but . . .

DR. HORVATH: This is all right afterwards.

DR. WEIHE: Then with your permission, I'll talk about rats. The circadian rhythm, according to my investigation, does not change. I have investigated food and water uptake, and the oestrus cycle in rats.

DR. BRAUER: Now this is in your laboratory at altitude?

DR. WEIHE: At altitude, at constant room temperature, with changing humidity, with changing temperature, at altitudes from 20,000 down to 5,000, with animals which we have fully investigated.

DR. BRAUER: But a natural life cycle?

DR. WEIHE: Yes, that was constant. But anyway, when you investigate an animal's feeding period, you find that an animal with about a twelve hour light cycle eats from 8 o'clock in the evening to 6 o'clock in the morning, if it is at a room temperature of 22° C. When you change the temperature to 16° C, this period will enlarge, will be wider. The animal starts feeding earlier and stops feeding later. And this is a very good parameter to investigate further.

DR. BRAUER: You don't mean that the diurnal cycle gets shifted to 25 hours, say. The 24-hour cycle persists.

DR. WEIHE: It persists. We have two periods, a resting period and a feeding period. The feeding period enlarges.

DR. BRAUER: Right, at the expense of the resting period.

DR. WEIHE: With this decrease in temperature. If you now move this animal up to high altitude, the cycle at a temperature of 22° C will be smaller, the feeding period will be smaller, and that's because the animal reduces its food intake. When you decrease the room temperature, you find no change: there is

also a smaller feeding period because the cold stress adds only to the hypoxic stress. And the same applies to the water uptake. The oestrus cycle does not change in our animals. But there's an important thing that should be looked at when you do animal experiments: do they have free access to a running wheel or are they limited to their cage? Because the more limited they are, the more extreme their responses are.

DR. BRAUER: You had a running wheel?

DR. WEIHE: We did both.

DR. BRAUER: I think this is a very important suggestion that very rarely do we follow.

DR. VAUGHAN: These were hypoxic animals also?

DR. WEIHE: Yes.

DR. VAUGHAN: I ask because we can train animals to eat all their feed in two hours, at five to seven degrees, but they are not hypoxic. They are normal, and they'll grow quite well.

DR. BRAUER: but you could still get this cycle by getting the exercise period, which I suspect would stay well up . . .

DR. VAUGHAN: Yes, of course.

DR. CROVER: There is some work regarding hormonal effects due to hypoxia on the circulation which has not been mentioned. This is the work of Jennings, at Queens University in Kingston, Ontario. He works with dogs in a

cross-circulation setup, and he finds that when the dog is made hypoxic, his heart-rate increases and his cardiac output goes up. Now if he takes the blood from this hypoxic dog, passes it through an oxygenator, and infuses it into a second dog, that dog's heart rate will go up and his cardiac output will increase. Now one's first reaction to this is, well, you've stressed the animal, he's produced more norepinephrine and epinephrine, and that's what's doing it. But if you actually measure levels of the adrenal steroids, you would find that it would take levels 20 times those which actually exist to produce the response on the heart which Jennings finds with this cross-circulation. Now to my knowledge, he doesn't know what this—

DR. BRAUER: He does have control experiments? He knows that the mere handling of the blood is no problem?

DR. GROVER: Yes. I mean if he has the cross-circulation going, and doesn't make the donor hypoxic, then nothing happens. I don't think he knows what this substance is, but he believes that it is independent of the adrenals.

DR. BRAUER: And is this similar to Hypoxylienin? Because this experiment sounds very much like the old Rein experiment on coronary circulation.

DR. GROVER: It sounds like what?

DR. BRAUER: There was a series of experiments done which sound a good deal like what you've described, with somewhat similar results, in the 1940's. They were started in Rein's laboratory, and they were completed after Rein's death by Schmier. With this substance they called Hypoxylienin it was I think evident that this required blood going from the spleen to the liver—hence the name—in order to elicit these rather marked cardiac changes in hypoxic animals.

DR. GROVER: To my knowledge, this was a cross-circulation between the artery of the donor and the systemic vein of the recipient—

DR. BRAUER: Yes.

DR. GROVER: —without going through the splanchnic vein.

DR. BRAUER: I realize that, but the substance would be circulating.

DR. GROVER: Yes.

DR. BRAUER: I think the question of humoral factors involved in the hypoxic animal is a terribly important one, and one which we're just beginning to explore. I'm delighted to hear about this.

DR. BUSKIRK: Didn't Lim do some work with Luft on this, with about the same results?

DR. CHIODI: Yes, and they found also the same in anemia. They work with both anemia and hypoxia.

DR. HANNON: I'd like to ask Dr. Evonuk to comment on this. He's done a lot of cross-circulation studies on dogs exposed to cold for a long period of time.

DR. EVONUK: The studies consisted of producing cold stress on the donor dog, then cross-circulating with a homothermic dog. We've produced the same type of response—very marked cardiovascular effects on the homothermic dog. We find this in the warm-acclimatized but not in the cold-acclimatized. With two cold-acclimatized dogs there's no response whatever. On two warm-acclimatized dogs we get a very marked cardiovascular response. The donor dog is being cooled, cross-circulated into a homothermic dog, with this basic response in the recipient. We're getting a marked reduction in cardiac output and then bloodflow.

DR. BRAUER: Reduction in cardiac output?

DR. EVONUK: Oh yes. But on the cold-acclimatized dog no response to speak of. We associate this with probably histamine-type substances.

DR. BRAUER: This is of course why I was asking about blood handling, because with dog blood in particular this is an artifact one can produce easily. It can be pretty well avoided, though.

DR. BUSKIRK: Did you get any changes in urinary output? Did you do any renal blood flows?

DR. EVONUK: We didn't investigate those.

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BLOOD TISSUE CHANGES DURING HIGH ALTITUDE AND COLD ACCLIMATIZATION

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In warm blooded animals, changes in the environmental conditions, such as high altitude hypoxia or low temperatures, call into play compensatory mechanisms which tend to maintain tissue oxygen pressure or body temperature within normal limits. But both environmental variations and compensatory mechanisms induce changes in blood and tissues which are more noticeable under chronic exposure.

The present paper will deal with such changes, making first an appraisal of the separate effects of each environmental condition and afterward an appraisal of the effects of the two acting together.

High Altitude Acclimatization

In man, chronic hypoxia activates a series of compensatory mechanisms which eventually will produce physiological, chemical, and sometimes anatomical changes integrating the process known as acclimatization.

The degree of acclimatization will vary with different levels of hypoxia, and there is also a level of hypoxia beyond which the subject can no longer compensate for it and cannot attain acclimatization. It is considered that 4,800-5,200 m above sea level is the upper limit to which man can become fully and permanently adjusted.

An acclimatized man living at high altitude has a somewhat greater pulmonary volume and a higher minute ventilation than that of a sea level man (1, 2). Corresponding to the ventilatory increase and to the greater size of the alveoli, there is also permanent dilation of the capillary bed. The alveolar pCO_2 will decrease proportionally to the increase of the pulmonary ventilation, while the alveolar pO_2 will decrease proportionally to altitude. For example, at 4,500 m the pulmonary ventilation is about 29% higher, the alveolar pCO_2 about 6 mm Hg lower, and the alveolar pO_2 53 mm Hg lower than at sea level (2). Newcomers at 4,500 m will have a higher ventilation, a lower alveolar pCO_2, and a higher alveolar pO_2 than the acclimatized subjects (2). How long it takes the newcomers to reach the levels of acclimatized subjects, and why they do so, are

still matters of conjecture. Pregnancy is associated with a hyperventilatory effect over and above the hyperventilation already existent on the basis of residence at altitude (3).

Pulmonary hyperventilation will diminish the tracheal-alveolar gradient (1). In spite of a sustained hyperventilation, chemoreceptor sensitivity to changes in oxygen pressures is less in the acclimatized man than in the newcomers at high altitude, as shown by inhalation of pure O_2 or low oxygen mixtures. Results on the magnitude of the alveolar-arterial oxygen gradient in the acclimatized native are contradictory, and further studies are needed before a conclusion can be reached on the existence of a decreased gradient at high altitudes which would act as a compensatory mechanism for the lower pO_2 in the inspired air (4,5).

Subjects at high altitude develop a polycythemia manifested by an increase in the number of red cells, the amount of hemoglobin, and the hematocrit values with normal or slightly reduced plasma volume (6,7). There is evidence that the high altitude polycythemia is the consequence of a hyperactivity in the formation of red cells and hemoglobin in the bone marrow. The number of reticulocytes increases in the peripheral blood and there is hyperplasia of the erythroid element of the bone marrow of adults and infants living at high altitudes (8,9). Whether the red cell life span of high altitude natives is similar to that of a lowlander is still to be ascertained (10,11).

Recent studies indicate—confusingly—that the presence of significant amounts of erythropoietine in the urine decreases but remains significantly higher than at sea level (11) or disappears completely (12). Plasma from highlanders injected in man or animals produces an increase of the hemopoietic activity (13).

In man there is an increase of iron intestinal absorption during the early period of exposure to an altitude of 4,540 m. The red cell iron turnover increases, beginning two hours after a man's arrival at high altitude and reaching its maximum after 7 to 14 days of exposure. The highlanders have a red cell turnover rate approximately 30% higher than healthy subjects at sea level (14).

In natives residing at high altitudes there is an increased total bilirubinemia due to an elevated unconjugated bilirubin. Fecal urobilinogen is also increased. The high unconjugated bilirubinemia is perhaps the result of a saturation of the conjugating mechanisms of the liver by an elevated red cell turnover rather than by a decrease of liver function (15).

The increase of the hemoglobin in high altitude residents, which is within certain limits proportional to the degree of hypoxia, results in a greater arterial oxygen content in spite of a lower oxygen saturation of the hemoglobin. This

higher oxygen content helps to maintain a higher pO_2 in the tissues and so must be regarded as a compensatory mechanism. The greater viscosity of the blood produced by its high hemoglobin content will tend to increase the work load of the heart and, at very high levels of hemoglobin, would imply an impending menace of thrombosis.

Barcroft et al. (16) described in a few Andean natives a slight shift to the left of the oxyhemoglobin dissociation curve, which they interpreted as a compensatory mechanism facilitating a higher saturation of the hemoglobin with oxygen in the presence of a lowered alveolar pO_2.

Reynafarje (17) found in a large group of high altitude natives a shift to the right of the oxyhemoglobin dissociation curve of about 2 mm Hg of pO_2 at $Hb=HbO_2$ and pH 7.40. This displacement to the right, which corresponds to a decreased affinity of the hemoglobin for oxygen, would favor the passage of this gas from blood to tissues.

No significant structural changes of the hemoglobin molecule has been depicted so far in natives living for many generations at high altitudes (18, 19).

The permanent hyperventilation of the high altitude residents, lowering the alveolar pCO_2, brings about modifications in the blood acid-base equilibrium. In the newcomer there is an increase of the pH which thus becomes somewhat alkaline. To restore blood pH to normal, a proportional reduction in blood bicarbonates occurs. Although the CO_2 transport is facilitated by the increased amount of hemoglobin, a lessened capacity to neutralize strong acids exists.

When compared to sea level controls, native residents at high altitude have the same renal maximal reabsorption of bicarbonates (20), a significant decrease in filtration rate, an effective renal plasma flow, and an effective renal flow with an increase in filtration fraction (21).

Hurtado et al. (22) measured plasma electrolytes in Andean natives living at high altitude; the only difference they found with sea level controls was a moderate increase of chloride anions and an almost parallel decrease of the bicarbonate anions, confirming previous findings of Dill et al. (23).

The pH of the CSF of Peruvian Andean natives is not different from that found in normal sea level residents (24).

After a few weeks at high altitude, the initial increases in heart rate, cardiac output, and blood pressure return to normal sea level values or even to the lower normal limits in long term residents at high altitude.

A mild degree of pulmonary hypertension is present in child (25) and adult natives or long term residents at high altitudes (26), a probable cause of the known right heart ventricular hypertrophy (27-30).

The greater muscularization of the pulmonary arteries and arterioles found in adult Peruvian Andean natives (31, 32) has been interpreted as the result of a delayed and incomplete involution of the fetal characteristics of the pulmonary arterial tree brought about by hypoxia acting from birth. This anatomical finding has its counterpart in the physiological observation of an increased pulmonary precapillar resistance.

Cerebral blood flow was increased 24% after 6 to 12 hours and 13% after 3 to 5 days at 3,810 m, showing a significant dilation of the brain vessels under hypoxic stimulation. No data is available on the CBF of natives living at high altitude (33). However, electroencephalographic studies of subjects living permanently above 3,600 m showed a greater stability of the EEG and an absence of slow waves during voluntary hyperventilation when compared to sea level controls (34, 35).

In man, changes in the sympathetic system due to high altitude stress have been followed through changes in plasma and urinary epinephrine (EP) and norepinephrine (NE) levels. A highly significant steady urinary increase of the NE excretion was found in men from the second to the 14th day of sojourn at 3,800 m (36). Similar increases of plasma and urine NE levels were obtained in healthy subjects while they were staying at 4,560 m for 12 days (37). No significant changes were seen in the EP levels. On the other hand, no changes in the plasma level of catecholamines were found either in high altitude natives living at 4,330 m or in sea level natives studied 36 hours after their arrival at high altitude.

Results of the adrenal cortex response of newcomers at high altitude are somewhat contradictory. No change in urinary output of 17-hydrocorticoids was found in subjects during a 14 to 21 day sojourn above 6,400 m or in the climbers of the 1963 American Mt. Everest expedition (11). On the other hand, an increase of the urinary excretion of 17-hydrocorticosteroids and a decrease of circulating eosinophils was found in the first days at 4,330 m, but by the fifth day both parameters were returning to sea level values, confirming previous results from others (39, 40). Another report, although incomplete, describes a reduction of urinary excretion of 17-ketosteroids and 17-ketogenic steroids at 5,790 m. With continued exposure to hypoxic stimulus, function of the adrenal cortex seems to return to normal.

No differences were found in cortisol secretion rate, in the stimulation of the adrenal cortex with 20 units of ACTH and in response to Metopirone administration between high altitude native residents and sea level residents. However, administration of 1 to 5 units of ACTH produced less urinary excretion of adrenal corticosteroids in natives at high altitude than in men living

at sea level. On the basis of these results a need for greater ACTH production to maintain a cortisol secretion rate similar to that of the sea level resident was postulated.

A recent study (41) has shown a decreased urinary excretion of I 131, thyroidal uptake of I 131 being similar at 2, 4, and 6 hours but greater at 24 hours in high altitude native residents than in lowlanders.

Urinary testosterone excretion in young male native residents at 4,330 m was similar to that of sea level residents (42).

In sea level subjects exposed 14 days at an altitude of 4,330 m, there was lessened number and motility (with morphological abnormalities) of spermatozoa, when compared to those obtained in the same subject before ascent (43).

To specialists in the field of high altitude acclimatization, perhaps one of the most attractive and cherished hypotheses is the existence of tissue adaptation processes to hypoxia. Direct studies in man are obviously difficult, and in most cases we can only appreciate changes in tissue activity through measurements of total oxygen consumption of the whole body. No changes in the BMR of high altitude residents were found using Boothby or Harris and Benedict sea level standards (1, 44), but when related either to fat-free body mass, cell mass, or cell solids, a moderate increase of the BMR value was seen (45).

A study of the myoglobin content and enzymatic activity in muscles of high altitude residents (46) showed a higher myoglobin concentration and an increased activity of DPNH-oxidase, TPNH-cytochrome c reductase, and transhydrogenase than that found in similar muscles of sea level controls. The respiratory capacity of the muscle is apparently higher in the altitude native resident, and the enhanced enzymatic activity is probably related to its higher myoglobin content.

In the last decade progress has been achieved in the knowledge of the pathology of the adaptation and acclimatization processes. A well-defined clinical form of acute mountain sickness, high altitude acute pulmonary edema, has been reported by several authors (47). A recent paper (48) reports 332 cases in men 18 to 56 years old staying above 3,700 m. Two hundred sixty-one cases of the 332 were still suffering from acute mountain sickness symptoms when the pulmonary edema occurred. Seventy-nine percent of the cases occurred within the first 3 days of arrival at high altitude, with a few as late as 240 days. The mechanism remains obscure.

On the other hand, chronic mountain sickness still remains an ill-defined entity in which an exaggerated polycythemia is the key sign for the diagnosis of

the illness (49). However, in the author's experience (50), not all high altitude dwellers with an exaggerated polycythemia should be considered chronic mountain sickness cases, and vice versa: chronic mountain sickness can occur without enhanced polycythemia.

In a high altitude acclimatized man, a normal pH of the arterial blood and of the cerebral spinal fluid with low arterial pCO_2, low blood bicarbonate levels, increased hemoglobin and red cell count, increased circulating reticulocytes, slight changes in serum chlorides, etc., indicate that a new homeostatic equilibrium has been reached which allows the acclimatized man to lead a normal life at high altitude, judged by sea level standards. Is there no difference, then, between an altitude-acclimatized man and his sea level peer? Although not enough data is yet available at present, we think one of the essential differences is the lesser stability of the new homeostatic equilibrium in the altitude man which makes him more prone to present pathological changes not currently seen in lowlanders of similar physical condition. High altitude pulmonary edema in acclimatized subjects returning from a [illegible] o low levels, excessive polycythemia, hemorrhages in the central nervous system, etc., illustrate the unsteadiness of the high altitude homeostatic equilibrium. This unsteadiness, which is perhaps due to a somewhat depleted reserve of compensatory mechanisms, should be ta[illegible] into account when evaluating the reacting capacity of the high altitude acclimatized subject when he is confronted with another stress.

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Cold Acclimatization

Physiological cold adaptation in homeotherms involves mainly insulative and metabolic changes. The most effective, economical, and specific adaptation is to increase the insulation (piloerection, vasoconstriction, thicker fat depot, etc.), avoiding an excessive loss of heat. When decreasing heat loss is not able to maintain body temperature, increased heat production will occur. Initially, increased metabolic activity is produced by shivering, which in a later stage of cold exposure can be totally or partially replaced by the so-called chemical heat production or non-shivering thermogenesis.

It is now a well accepted fact that cold acclimatization, at least in small mammals such as the laboratory rat (1), is a metabolic process which has four distinguishing features: (a) the animal has a higher than normal metabolic rate at all ambient temperature; (b) it has an enhanced capacity to produce heat without shivering (non-shivering thermogenesis); (c) it has an ability to raise the metabolic rate to a much higher level than can the non-acclimatized control; and (d) it has an improved ability to resist cold injury and hypothermic death.

It is still doubtful to what extent man is able to acclimatize to cold following a pattern of changes similar to that found in the rat. Apparently there exist racial differences in the response of man to prolonged cold exposure. Lapps, Arctic Indians, Northern Norwegian fishermen (2), and Alacaluf Indians (3) have higher basal metabolic rates than those found in subjects living in more

temperate climates. Whether the increased metabolism is due to acclimatization resulted from a high fat and protein diet is still in doubt.

No changes in the BMR of Caucasian men living in the Arctic or Antarctic have been observed (4, 5), but a lesser increase of the metabolic rate when exposed to 5° C was found in a group of them after three or more months in Antarctica (6). Evidence is claimed for a sensory adaptation to cold discomfort, which has the effect of reducing the metabolic response of skin stimulation to cold.

Tikhomirov (7) mentions Russian studies showing that in large Arctic settlements where social and communal conditions are favorable, there is an increase in the basal metabolism of the inhabitants, especially during the cold period of the year.

BMR of adult Japanese is lower in summer than in winter. In a recent study, Yoshimura et al. (8) measured monthly the BMR of Canadian monks who were living in Japanese style houses, using as controls Japanese subjects of similar ages. The measurements revealed the Canadians did not present any consistent seasonal variation, while the BMR of the Japanese mostly decreased in summer and increased in winter. Again in this case a different diet cannot be discarded as a causal factor of the difference in the seasonal metabolic response.

David and Johnson (9) claim a highly significant decrease in shivering and a less significant decrease in heat production during winter in subjects exposed to a standard cold condition. According to the authors, man seasonally acclimatizes to cold, and this acquired acclimatization is lost during the summer months. The proportionally lesser decrease of the metabolic rate than that of shivering could be explained by the existence of a non-shivering thermogenesis.

Wyndham et al. (10) state that "David et al.'s evidence, although the best so far of this process of cold adaptation in man, cannot be accepted as a final proof. An exact quantitative relationship between the degree and extent of shivering and the rate of metabolism was not demonstrated by them," which seems the most realistic conclusion to be reached on the basis of our present knowledge of the subject.

On quadriplegic subjects with a complete transsection of the cervical spinal cord, we did not observe any increase of the metabolic rate before the onset of shivering, whether the sentient part of the skin was kept cool or not, and the central temperature had fallen around 0.6° C. Actually, a slight decrease of the oxygen consumption was found from the beginning of the cooling period up to the onset of shivering (11). How different from normal the reactions to cold of the quadriplegic patients were remains an unanswered question. It is worth mentioning that patients with a complete transection of the cervical spinal cord

have low noradrenaline and adrenaline plasma levels and a high count of circulating eosinophils (12).

Girling (13), in his group of unacclimatized normal subjects, found no increase in oxygen consumption for the initial 15 minutes of exposure to cold. After 15 minutes the oxygen consumption increased by about 45% and appeared to be coincident with shivering. The group of acclimatized subjects showed an immediate increase in oxygen consumption on exposure to about 45% above control values, and shivering was delayed or absent.

Arnett and Watts (14) found that one hour urine samples from subjects exposed to cold stress contained increased amounts of catecholamines, particularly adrenaline. They concluded that the secretion of these amines is involved in the chemical control of heat production during exposure to cold. A significant seasonal increase of the norepinephrine-epinephrine ratio was observed by Feller and Hale (15) in 230 healthy men living in a subtropical climate. Cold exposure did not increase the catecholamine excretion in the urine of Gaspe fishermen or the control group of subjects. Both groups excreted more hydroxycortisone in the cold, but the excretion was higher in the control subjects (16). Cold acclimatization increased the calorigenic effect of norepinephrine in cold exposed men (17).

In a group of men who stayed for one year in the Antarctic, serum cholesterol levels rose above the normal upper limit while clotting time, which was significantly correlated with serum cholesterol, rose to a very high level and later fell. Serum cholesterol increase was not due to a high fat diet (18).

Hanson and Johnson (19) observed a significant increase in plasma FFA during cold exposure of four healthy subjects as compared with similar control periods. Although hyperketonuria did not develop in the same subjects, the levels of plasma ketones were elevated in the cold exposure period in the first week. During the second and third weeks there was no difference between the cold and control plasma ketone concentration. Nicotinic acid (20) strongly suppresses plasma FFA concentration during acute cold exposure, in contrast to the usual increase in plasma FFA which is observed with cold exposure. Excretion of vanilmandelic acid increases during the recovery period following acute cold exposure. The data suggest that FFA is mobilized as a metabolic substrate during cold exposure and perhaps this mobilization could be produced by the action of l-norepinephrine. The sympathetic innervation of adipose tissue is probably of fundamental importance in mediating the release of FFA from peripheral storage.

Cold stress that produced almost constant shivering in men and a metabolic rate about twice the BMR induced a negative nitrogen balance with

four different types of diets. In the post-exposure period the negative nitrogen balance persisted for 4 to 6 days despite an 18-fold increase of the protein intake. Issekutz et al. (21) suggested that an increased activity of the thyroid or the adrenal cortex or both may be responsible for this after-effect of cold exposure. A study of the thyroid function of Ama (22) only showed a more rapid loss of I 131 from the thyroid glands compared to that of the controls. There was no seasonal difference in the rate of loss of thyroid I 131, although in winter the BMR rose 20 per cent above DuBois standards. Therefore, although the thyroid function of Ama is clearly different from non-diving women, their increased BMR in winter cannot be attributed to a seasonal increase of thyroid activity as measured by the tests used by the authors.

Monthly blood examinations of 10 healthy subjects in Antarctica revealed in 5 of them an increase of 5 to 11% of the red cell count, the hemoglobin, and the hematocrit by mid-winter. In eight of the ten men, the white cell count rose 20 to 70% above their baseline levels. The increase involved mainly the lymphocytes which rose 10 to 48% above their temperate zone averages. All ten men showed an eosinophilia of 50 to 100% above their baseline levels (23).

In contrast to what happens in the high altitude field, more information on cold acclimatization comes from animal experiments than from studies in man.

As stated, one of the distinguishing features of the acclimatized rats was an enhanced capacity to produce heat without shivering (non-shivering thermogenesis). Shivering, judged by the electrical activity of muscle, decreased during long exposure to cold but metabolic rate remained elevated. Further evidence of non-shivering thermogenesis in cold acclimatization was obtained, showing that curare did not inhibit the increase in oxygen consumption when a cold-acclimated rat is transferred from a 28° C ambient to one of 5° C. The mechanisms of non-shivering thermogenesis are still not clear.

In a recent review, Masoro (24) suggests that thermogenesis must involve one or both of the following mechanisms: (a) an increased electron transport related to a decreased phosphorylative efficiency, and (b) an increased ATP utilization without a rise in network yield. In relation to mechanism (a), two specific biochemical mechanisms have been suggested. One possibility is that partial uncoupling of oxidative phosphorylation is induced in rats on prolonged cold exposure, but its importance is still equivocal. The other possibility is that during prolonged cold exposure electron transport pathways of low phosphorylative efficiency (calorigenic shunts) are activated, but this is far from proved. In regard to mechanism (b) there is no apparent reason to suspect such an increase in ATP turnover in the absence of shivering. However, many

metabolic activities can occur that might bring it about, and among them, the one involving lipid metabolism is seriously considered nowadays.

The review of Masoro (24) on the ways in which lipids would participate in the non-shivering metabolic response to cold obviates the involvement of a plain physiologist, as I am, in the intricacy of the lipid metabolism. For this reason I will quote his conclusions: "There is no doubt that the adipose tissue reserves of triglycerides are mobilized to meet the increased energy requirements of the cold-induced shivering thermogenesis that occurs on initial exposure to low environmental temperatures. Also, in cold-induced non-shivering thermogenesis, which is so well developed on cold acclimatization, there is evidence that neither fat nor any other foodstuff is the preferred fuel; rather the data point to the increased utilization of each of these materials as fuel. Although there exist many data consistent with the possibility that elevated levels of plasma FFA may play a key role in promoting cold-induced thermogenesis, it is difficult to establish a cause and effect relationship between plasma FFA levels and cold-induced thermogenesis. Moreover there are recent data showing that cold-induced thermogenesis can occur in the absence of elevated FFA levels."

The nervous controlling mechanism of the non-shivering thermogenesis appears to be the sympathetic system directed by the central nervous system, norepinephrine acting as the humoral agent linking the nerve endings to the thermogenic tissue sites.

On the basis of his results with eviscerated cold-acclimatized rats, Depocas (25) concluded that the abdominal viscera are not essential and suggested that the large muscle mass is an important site of non-shivering thermogenesis. However, on the basis of temperature measurements of various organs, it was concluded that liver and intestine but not muscle are the important heat production sites.

Although both the thyroid and adrenal cortex have been implicated as playing a part in survival in cold, it seems unlikely that they are mediators of non-shivering thermogenesis. Both thyroid and adrenocortical hormones have been shown to potentiate certain actions of catecholamines.

According to Leduc (26) exposure of rats to cold elicited an immediate large increase in the noradrenaline excretion which persisted as long as the rats were kept in the cold, although it slowly declined with time. The noradrenaline secretion bore a close relationship to the time of exposure to cold, which was interpreted as a sign of increased sensitivity of cold-acclimatized rats to this hormone. The adrenaline excretion gradually rose to a maximum, reached in about one week in the cold, and decreased rapidly thereafter. This was

associated with a high rate of resynthesis in the adrenal glands. Blockade of the release of the physiological effects of catecholamines renders warm- and cold-acclimatized rats unable to withstand cold exposure. Noradrenaline would be the main mediator in the chemical regulation of heat production, and adrenaline would act as a second line of defense which would supplement the readily limited synthesis and/or secretion of noradrenaline.

Rats injected chronically with noradrenaline acquired an increased sensitivity to its metabolic action, but, although they developed increased resistance to low temperatures, they were less resistant than cold-acclimatized animals. It appears that increased sensitivity to noradrenaline is not the only cause for the better resistance of cold-adapted rats to low temperatures.

One interesting throphic change occurring in cold-acclimatized rats is the hypertrophy of the brown fat tissue which is found predominantly in the interscapular region of the newborns. This brown fat is abundantly vascularized and has a high metabolic activity with a subsequent greater heat production than in the non-acclimatized animal. The recent review of Smith (27) should be consulted for details.

Perhaps a word of caution should be said about any hurried extrapolation to man of conclusions drawn from experimental studies on laboratory animals, particularly the rat. Chaffee et al. (28) showed that cellular chemical thermo-regulatory response patterns of the squirrel monkey are very different from the rat, although changes in the weight of the organs are similar in both.

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Influence of altitude acclimatization on cold acclimatization and vice versa

On exposure to cold, new born and adult animals, including man, increase their oxygen consumption. This increase is reduced or suppressed by acute hypoxia. Bilateral section of the carotid sinus and/or vagus nerve did not impair the inhibiting effect of hypoxia on the increase of oxygen consumption produced by cold. The metabolic action of intravenous infusions of noradrenaline and isoprenaline was reduced, but not suppressed, by low oxygen at both 35° and 25° C (1).

In foals, calves, and piglets born and reared under natural conditions in the field, the rate of oxygen consumption at rest is greater in a cold climate at high altitude than in a warmer climate at sea level (2).

Infants with chronic hypoxemia due to heart or vascular congenital malformations were able to respond with an increase of oxygen consumption when they were exposed to environmental temperatures below the neutral temperature (3).

Limited studies on the effect of hypoxia upon temperature regulation in adult man have yielded conflicting results. Hypoxic shivering inhibition and body temperature depression by moderate hypoxia in a cold environment has been described in man (4, 5), but results from others have reported little effect (6, 7) or an increase of the shivering activity under hypoxic stress (8).

There are not many studies on men or animals previously acclimatized to either cold or high altitude who have been exposed afterward to the other stress or to both together. In most cases acclimatization to both altitude and cold has taken place simultaneously, making difficult a clear picture of the influence of one on the other.

Pugh (9) studied the perhaps unique case of a 35-year-old Nepalese pilgrim, a native of a village located at 1800 m, who could be considered

acclimatized to cold on account of the cold climate, poor housing facilities, and light clothing he had in his native village. He survived without ill effects 4 days of continuous outdoors exposure at 4500-5300 m in midwinter, wearing only light clothes and no shoes or gloves. He slept soundly in spite of the snow and bitter cold and so did not become exhausted. In a 3 to 4 hours' experiment at 4650 m and 0° C, his rectal temperature and skin temperature over the trunk showed only minor changes, and his hand and foot temperatures did not fall below 10° to 13° C. His maintenance of body temperature was accounted for by the elevation of metabolism.

The absence of visible shivering while his metabolism was 35 per cent above the expected level (sitting) raises the question of whether this subject had a high level of non-shivering thermogenesis. Another important difference from unacclimatized subjects was the progressive increase in metabolism to 2.7 times the calculated basal level associated with moderated sustained shivering without any discomfort. This is in contrast with the vigorous paroxismal shivering and fluctuating oxygen consumption seen in unacclimatized subjects.

In the Nepalese pilgrim, hypoxia did not interfere with the metabolic increase produced by cold nor did cold seem to interfere with the capacity to adapt himself to a rather severe hypoxia. Whether the unusual resistance to cold and hypoxia shown by the pilgrim is only due to a rather exceptional individual condition or if the previous cold acclimatization enhanced his adaptation capacity to hypoxia remains an unanswered question.

Tikhomirov (10) reported a group of subjects who spent one year at the South Pole at about 4,000 m above sea level (average barometric pressure being 468 mm Hg). Apparently the subjects underwent the usual changes described during acclimatization to high altitudes in less cold environments but showed a greater hyperventilation and a lower arterial oxygen saturation than those found at similar altitudes in subtropical areas.

Fregly (11) studied the reciprocal effects of cold and high altitude chronic hypoxia in rats and concluded that there is a negative cross-acclimatization both between cold and altitude and between altitude and cold.

Although the data at hand are too scanty to draw any valid conclusions about the influence of cold acclimatization upon altitude acclimatization and vice versa, it is perhaps useful to make a comparison of the fundamental changes taking place in both processes of acclimatization and to speculate a little about the possible reciprocal influence of such changes.

The increased heat production of cold acclimatized animals will be an unfavorable condition when they are exposed to hypoxia, since a greater heat

production implies a greater need for oxygen and therefore a lower tissue pO_2 than when hypoxia would act alone.

Animals acclimatized to chronic hypoxia seem to respond to cold exposure as if exposed to this alone, but further studies are required to clarify this point completely.

In both cold and hypoxia, the adrenal glands seem to be stimulated at the beginning of exposure but return to normal after acclimatization, although in both conditions the gland size will remain significantly greater through the length of exposure.

Plasma and urine catecholamines, although increased in the beginning of the acclimatization to high altitude, return and remain at normal levels in the acclimatized subject. During man's acclimatization to cold, catecholamine changes seem to follow a pattern similar to that seen at high altitude, but the point is far from being proved.

In rats, cold acclimatization elicits an increase of noradrnealine excretion which persists as long as the rats are kept in the cold.

If the increase of catecholamines, particularly noradrenaline, in plasma and urine is taken as an index of increased sympathetic activity, it seems that it is only transient at high altitude while it seems to be, at least in the rat, one of the basic changes in the acclimatization process to cold.

DISCUSSION

DR. DILL: One point that Dr. Chiodi brought up near the end is that the increase in metabolic rate with cold might be a disadvantage, but on the other hand all the organism needs to do is to increase cardiac output a little as you would in exercise, and we have said that exercise may increase the rate of acclimatization so maybe the increased metabolic rate in cold increases the rate of adaptation.

DR. BUSKIRK: What did you find here on the Wrangell experiment in metabolic response to cold and altitude?

DR. EVONUK: We didn't do any metabolism studies at altitude. Comparing subjects before and after their altitude experience, there seemed to be a reduction in the response to cold, a reduced metabolic response to cold. It was rather surprising, and this was true whether it referred to moderate cold exposure or to what we called our maximum shivering test.

DR. BUSKIRK: We had a series at Minoa, comparing the Cacho Indians living there to our white athletes, and this data hasn't been examined very thoroughly, but they look identical. The natives look identical to the athletes.

DR. BRAUER: They are acclimatized to cold or rather to altitude.

DR. BUSKIRK: Well, at the time we got to these experiments it was near the end of our stay there, so it was about 40 days after arriving in Minoa, and of course the Indians lived in this area, and the metabolic response to the two-hour exposure to 50 degrees that we used in our tests is apparently the same in athletes and in the male Indians. The one difference that may come out of this is that they keep their extremity temperatures just a little higher, and this has been shown before in other groups of this kind. They do have this tremendous sole on their foot, you know, and this is really something They've got a shoe on their foot without putting one on, and it remains a question why even over this very large piece of dried-up tissue the temperature could still be high.

DR. BLATTEIS: Did your athletes have the same metabolic rate at altitude that they had in Pennsylvania?

DR. BUSKIRK: Essentially the same.

DR. BLATTEIS: Very much the same? Where are their differences?

DR. BUSKIRK: Well, this business of putting people in the cold and getting an identical response—I defy anybody to do this. There is no such thing, and if we're in the cold on two occasions, our response will never be identical. It's a variable sort of thing and so that within the margin that one has to work with I would say, no, there has been no change; perhaps someone who examines this data very carefully might find one.

DR. BLATTEIS: Well, we too haven't fully analyzed our data, but the

impression was that the metabolic response to the same cold load was lower at altitude than it was at sea level.

DR. HORVATH: You mean less?

DR. BLATTEIS: Yes.

DR. CHIODI: In the newcomers?

DR. BLATTEIS: Ir the newcomers and even in the natives. We took natives from three different altitudes and we took sea level people and exposed them to three different altitudes, and there appeared to be a decrease in the oxygen consumption at altitude as compared to sea level. The level of oxygen consumption response in the newcomers at altitude and after six weeks acclimation was identical with that of the natives exposed to the same environment. When all those people were brought back to sea level, including the natives, then they had a more elevated oxygen consumption on exposure to cold than they did up there. We also saw what you referred to as the warmer skin temperature; in our case we had a three-hour exposure. The group that was acclimatized to cold and altitude showed a rate of skin temperature fall that was progressively less the longer they remained in that environment. If there was no change—there were no apparent changes in oxygen consumption.

DR. EVONUK: Was this a greater reduction in simple body temperature at altitude?

DR. BLATTEIS: There was in some degree, yes.

DR. TODA: In Japan several years ago we did experiments on the cold tolerance of Japanese civilians and Japanese soldiers. For the index of cold tolerance we used exposures to cold environment at 15° Centigrade, 10° Centigrade, 5° Centigrade, for up to three hours. I measured skin temperature,

rectal temperature, and metabolism. The variation is large, but I want to say the insulation of shell is a most important factor of cold tolerance. For some people who take very poor food, the danger of vasomotor degradation is very large.

DR. CHIODI: The increase of cardiac output will not be seen in the acclimatized man, there will not be an increase of cardiac output.

DR. DILL: Not after acclimatization, no.

DR. CHIODI: No, I was speaking about the acclimatized man, and also I don't know how well, perhaps it would be favorable to the organs, central organs, because there is a vasodilation, but that would be worse for the skin. I think at high altitude there is a disadvantage to vasodilation in the peripheral tissues, and that would be against the central organs because some of the blood that should be in the central organs would be in the peripheral skin and that would increase the hypoxia in the organs which are more important. Of course that's just a speculation, I don't think there's much data about it.

DR. BUSKIRK: One thing we found with these natives, they're very apprehensive. We had to throw all of our first records away, virtually, and do additional exposures because they were quite worried about the first exposures. We worked with plastic hoods so we could measure the metabolic rate continually and they had to go through this once to make sure that they would survive, so based just on our first experiments, we got a tremendous increase in metabolic rate.

DR. HORVATH: It's been a typical mistake, I think, in experiments with natives—this failure to appreciate the strangeness of our technical approaches to them. Sometimes we infringe upon their taboos and so forth, which causes them to respond quite differently than they would if they were followed with two, three, or four studies in a row. Of course, we see that sometimes with our own subjects, the first time we do them is nowhere as good as what we see if we've done them three or four times.

DR. EVONUK: One of our experiments up here, the suggestions are almost the reverse of it, we're working with Eskimos at Anaktuvik and soldiers, and the Eskimos have been through this so many times it's old hat to them--the soldiers didn't quite know how to take it.

DR. EAGAN: I think besides that the Eskimos hadn't learned to be apprehensive of us yet so they were more placid for this reason, while soldiers are always a little more suspicious.

DR. BUSKIRK: What's the latest on circulating norepinephrine with acute or chronic cold exposure? You referred to this as being elevated in one study and not in others. We've never been able to find it. What is the experience here?

DR. HANNON: I think the measurements of circulating norepinephrine and epinephrine are very difficult to do accurately. The excretion rates though are definitely elevated. I don't think there's anybody that has data that –

DR. CHIODI: Well, didn't they find in Peru . . . didn't they find any even in subjects taken at high altitude –

DR. HANNON: Are you talking about animals or people?

DR. CHIODI: Natives, native people.

DR. HANNON: I was talking about animals.

DR. HORVATH: I think the whole viewpoint on norepinephrine is going to have to change. We've got a complete new concept as to what is going on in terms of the sites of the norepinephrine storage and liberation, the effects of certain substances on the liberation of this material, or liberation to the storage

sites for its utilization, and I think most of us are still thinking in the good old-fashioned terms of this material being something which produces an effect. We don't consider the fact that in some conditions we actually may be storing epinephrine, in other words when you will get blood levels which are practically normal or constant there can be a storage of norepinephrine as well as a secretion of norepinephrine. If we utilize some of the newer approaches of epinephrine/norepinephrine metabolism we might be able to evaluate some of the findings that look somewhat nebulous to us at the moment.

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GENERAL ADJUSTMENTS OF ACCLIMATIZED AND UNACCLIMATIZED MAN TO COLD, WORK, AND ALTITUDE

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An analysis of the processes of adjustment of man to cold, work, and altitude begins with a close look at the important factors in the ecosystem of man at a given altitude environment. The important factors consist of those from the physical, biological, chemical, and socio-cultural environment (1). Only those of the physical environment will be considered for this symposium. The important factors of the physical environment in a high altitude area are: low partial pressure of oxygen, low vapor pressure, low temperature, radiation (ultraviolet and heat), and air movement (wind).

During the exposure period man has to acclimatize to the given climatic conditions with the short-term periodic and aperiodic weather changes in addition to the given partial pressure of oxygen at that altitude. Hence, strictly speaking, adaptation is two-fold, first to hypoxia, second to climate. The adjustments to the limiting factors, i.e., shortage of oxygen at rest and at work, increased cooling from cold and wind, and increased heat from radiation, all involve definite systems within the body, those for oxygen transport, oxygen utilization, and temperature regulation. General adjustment patterns and limits of tolerance of the body to cold, work, and altitude, therefore, have to be looked for within these systems.

Those individuals who go to high altitudes are usually at that period of their life of highest adaptability and greatest working capacity. This has been seen many times in human history: the Spanish conquest of South America (2), the Chinese occupation of Tibet, the building up of the Indian defense system in the Himalayas, the working of mines in Peru, and the climbing of the highest mountains in the world. Mere living at high altitude requires some working capacity far below the limits of tolerance, while these limits are often reached in working at high altitude, as in the case of road building, mining and mountaineering. Since these strenuous activities are carried out with great efficiency at high altitudes, it is obvious that a high working performance is possible. The best information available so far on the acclimatization processes in the field is obtainable from mountaineers interested in physiology who were able to consider the factors involved and evaluate them according to importance.

From such reports it is known that with increasing altitude, adaptation to cold becomes more and more necessary.

The exact study of the adaptation processes could be more easily carried out under standardized environmental conditions with variation of only the three factors, work, altitude, and cold, of the multitude of those in the ecosystem. In recent times, ambient temperature has been little considered in such standardized studies on the effect of altitude in low pressure climatic chambers, climatized mountain laboratories or in the open air on mountains in the equatorial zones. Though it is well known that cold occurs with altitude, it has been a common thing in the past and still is an unfortunate custom today that environmental temperature is not routinely stated in high altitude studies. Much more information would be available today had editors of scientific periodicals advised their authors to state more precisely under what environmental conditions and on what dates their studies were performed.

The lack of precise information on the physical activity of the individuals, animals, and men, their state of training and maximum working performance constitutes a second important omission in available reports. In systematic studies, such as those at Jungfraujoch (3), some mean data were computed from the combined results of individuals who had undergone extensive physical activity and exposure to cold and solar radiation and of individuals at rest in laboratories. It is no wonder that with such great variation of experimental conditions different results were obtained which often could not be reproduced. A change in research took place when experiments with laboratory animals were introduced into environmental physiology because they can be carried out more easily under better standardized conditions. The results of such experiments have greatly helped to interpret the sporadic observations on man, and provided concepts for the best arrangement of human studies.

In former times, interest was limited to the effects of high altitude on the body at any given time. At present, the time course of the various adaptive responses has gained in importance. As a result of such time studies, the great significance of physical training and exercise for the acceleration of acclimatization has been recognized. It is now realized that in studies on the adaptability of man to altitude parallel investigations should be carried out on untrained and trained, non-exercising and exercising subjects (4).

Studies on the effect of altitude, cold, and exercise on man are three-factor investigations. If such a study were planned with animals at least nine experimental groups would be necessary. Since this is almost impossible in man, experiments are performed consecutively. It might be of historical interest that one of the first two-factor investigations in altitude physiology was the

expedition of Kronecker, Professor of Physiology in Berne, Switzerland, to the Theodulpass in 1894 to study human response to altitude at rest (5). The expedition consisted of trained mountain guides and the professors who were carried up in baskets on the backs of the guides. In this way, exercising and non-exercising men were exposed to the altitude of over 3,000 m simultaneously. The party stated that not only with exercise, which was already known, but also with passive transport this altitude had no harmful effects on them. This led to the decision to build the railway up to Jungfraujoch (3,450 m).

When nowadays general adjustments of man to particular climatic conditions are studied, two methods of approach are recommended: first, the study of natural acclimatization in natives, and second, the study of acquired acclimatization in newcomers under laboratory and field conditions. Only a comparison of the results in both groups will give a true picture of the acclimatization characteristics.

Climatic Conditions

In the study of natural acclimatization, an orientation on the distribution of man throughout the world is of value. In Figure 1 populations of over 2.5 million people in the various parts of the continents are shown as dots. It can be seen that the majority of people live between the latitudes of 20° and 60° north and south. The density of human populations thins out towards the poles due to the decreasing mean annual air temperatures. This map does not consider altitude, and temperature decreases with altitude. However, standard data of temperature at various altitudes (6) lead to confusion since the mean annual temperature at altitude depends on the latitude and land mass of the continents. This is demonstrated in Figure 2, which gives the 0°, 10°, and 20° C isotherms for the minimum annual temperature at various altitudes. The figure clearly points out how important it is to mention temperatures with altitudes when studies are done in the various altitude stations.

In Figure 3, the four significant groups of man, characterized by their preferred climatic zone for living, are shown in a climatograph taken from the data of Figure 1 and 2. The temperate zone, which extends into the dimensions of latitude and altitude, contains the greatest part of the world population. North of the temperate zone at low altitude levels is the populated arctic zone. The corresponding zone in the south is small, since the southern continents do not reach as far south as the northern ones extend north of the equator. The altitude populations are also distributed to higher latitudes in the northern

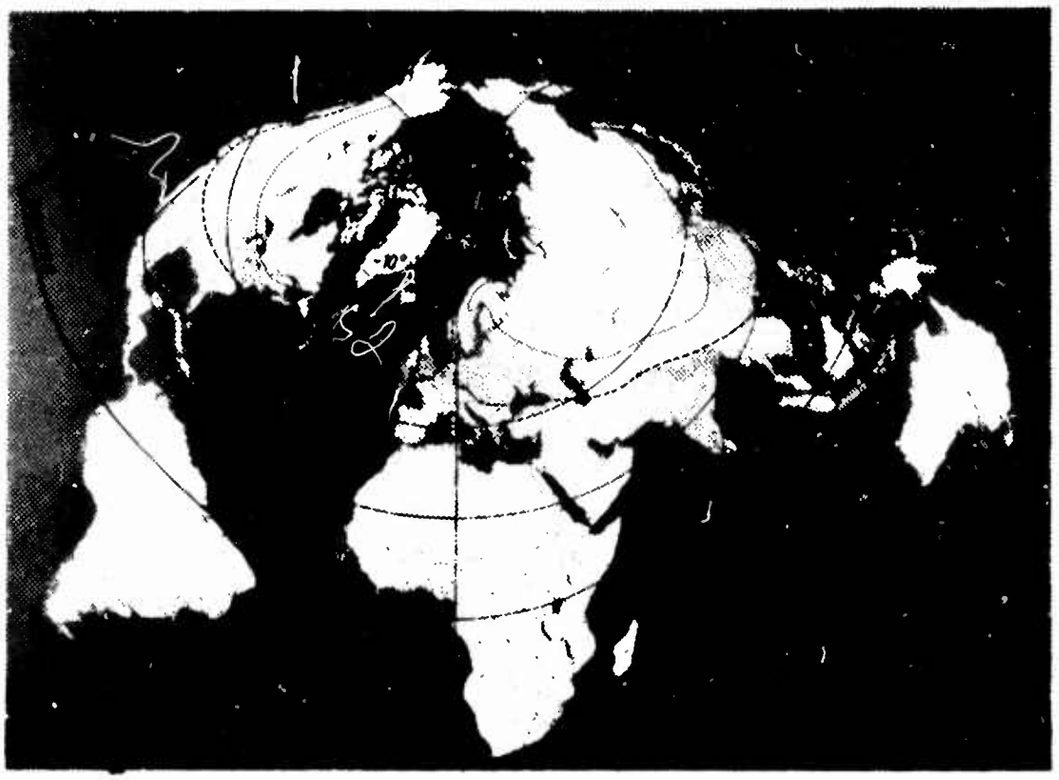


Figure 1
Distribution of the world population. Each dot represents 2.5 million people. (Modified after H. Boesch, 1965).

hemisphere because of the higher mean temperatures in Asia than in South America at similar altitudes. The significance of mean temperatures of various altitudes is also seen from a temperature-humidity climatograph in Figure 4, showing Berne, Jungfraujoch and Lhasa. The change from Berne to Jungfraujoch corresponds to that from a temperate to an arctic climate because of the 3,000 m difference in altitude. In Lhasa (3,710 m), which is at the same altitude as Jungfraujoch Station (3,700 m) and only 15° latitude further south, but at quite a different longitude on a large continent, the climate is almost temperate. Therefore permanent life is possible in Lhasa but not at Jungfraujoch, where mean monthly temperatures above 0° C are never reached.

Migration north or south of the equator confronts man with cold; migration to altitude confronts man with reduced partial pressure of oxygen and cold. Man does not avoid altitudes in general, but does avoid cold altitudes. (Animals are found at altitudes of above 5,000 m in the Andes [8]). Limiting for life at these temperate high altitudes near the equator is not cold but the decrease of reproductive and working capacity.

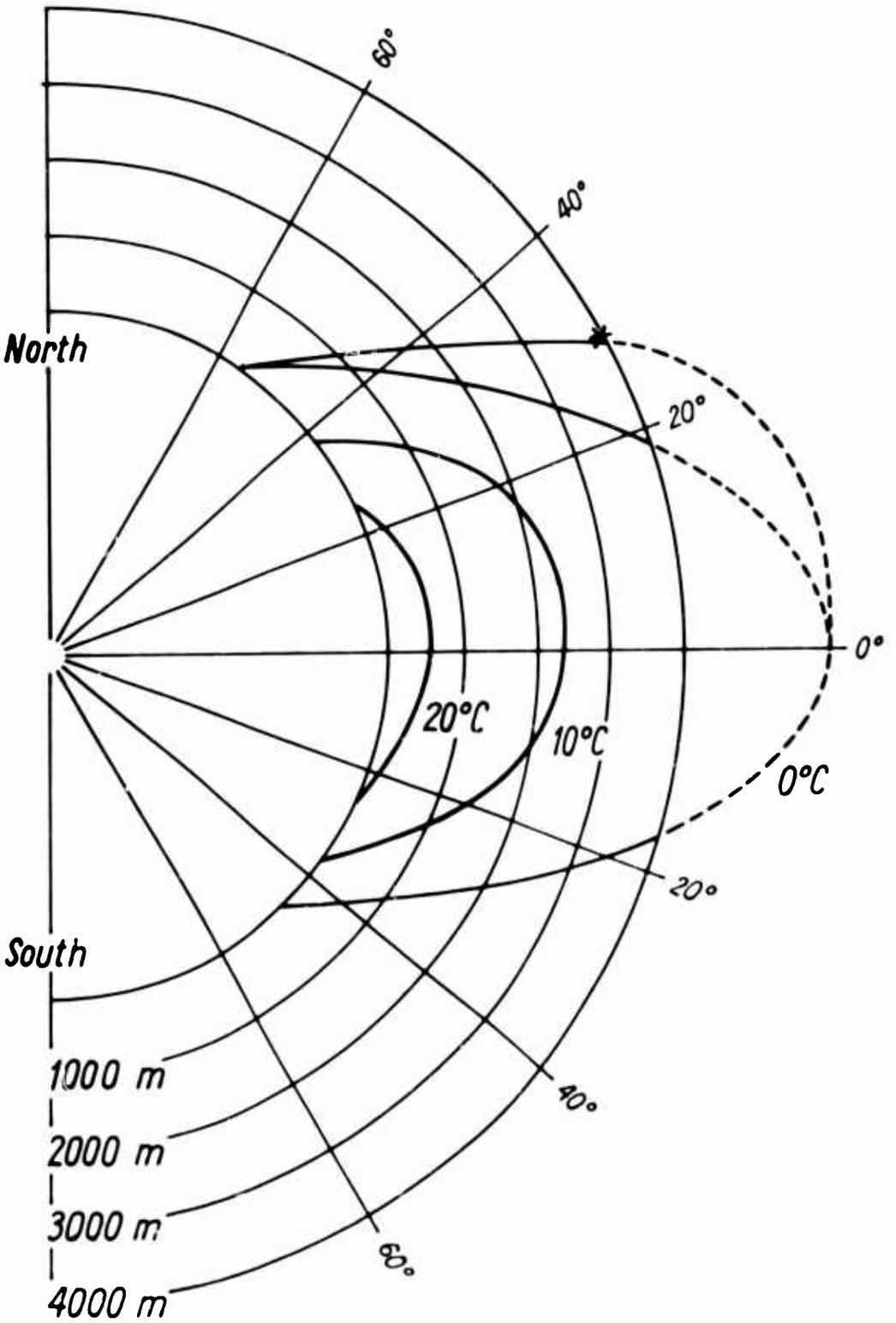


Figure 2

Distribution of the O, 10 and 20 minimum daily annual temperature isotherms on the globe at various altitudes. Data of 110 meteorological stations for the construction of the curves have been taken from the Meteorological Office, Air Ministry, London, M.O. 617 a, 1958. Note that the O C isotherm at 4,000 m reaches further north on the northern hemisphere. The slopes of the curves above 4,000 m are based on estimates.

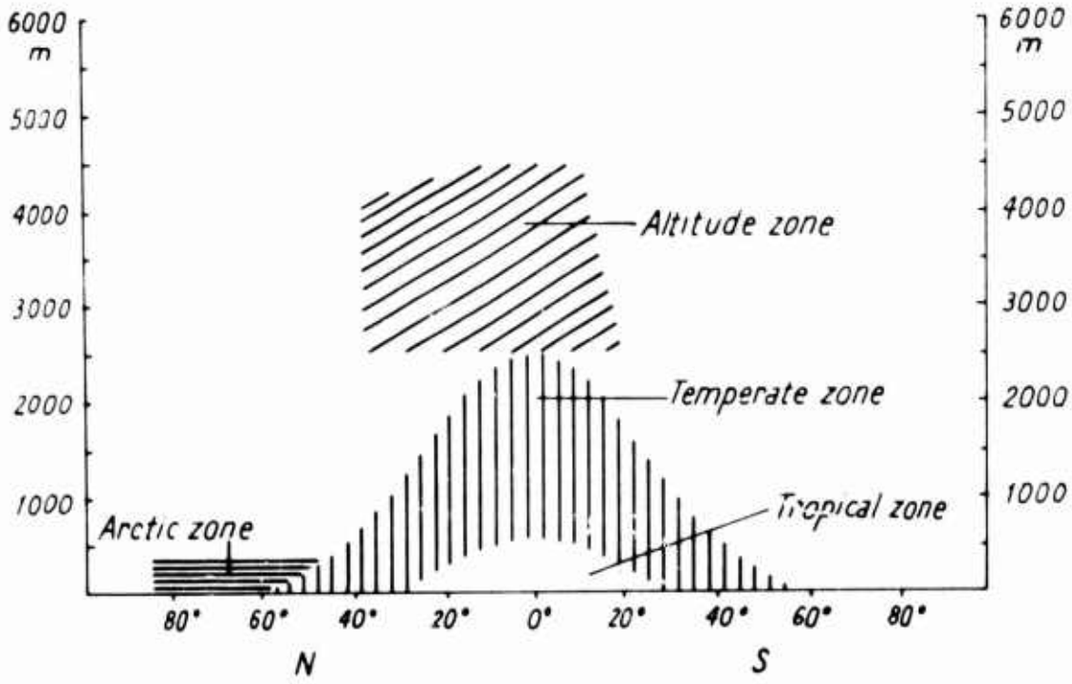


Figure 3
The four main climatic zones for the distribution of man.

From these considerations of the distribution of man on the continents (9), it can be concluded that extreme cold and high altitude when combined make living impossible for man. With decrease of air pressure and temperature, air vapor pressure decreases more rapidly, resulting in extreme dryness of the air at high altitudes and latitudes. This dryness of the air of less than 1 g H_2O/m^3 is an additional limiting factor for life in these climatic zones and deserves consideration from the physiological point of view. A further factor is solar radiation with extreme heat effects. Unfortunately, very little is known about heat radiation at high altitude (10) where the extremely wide diurnal temperature variation may exceed 50° C between day and night (11).

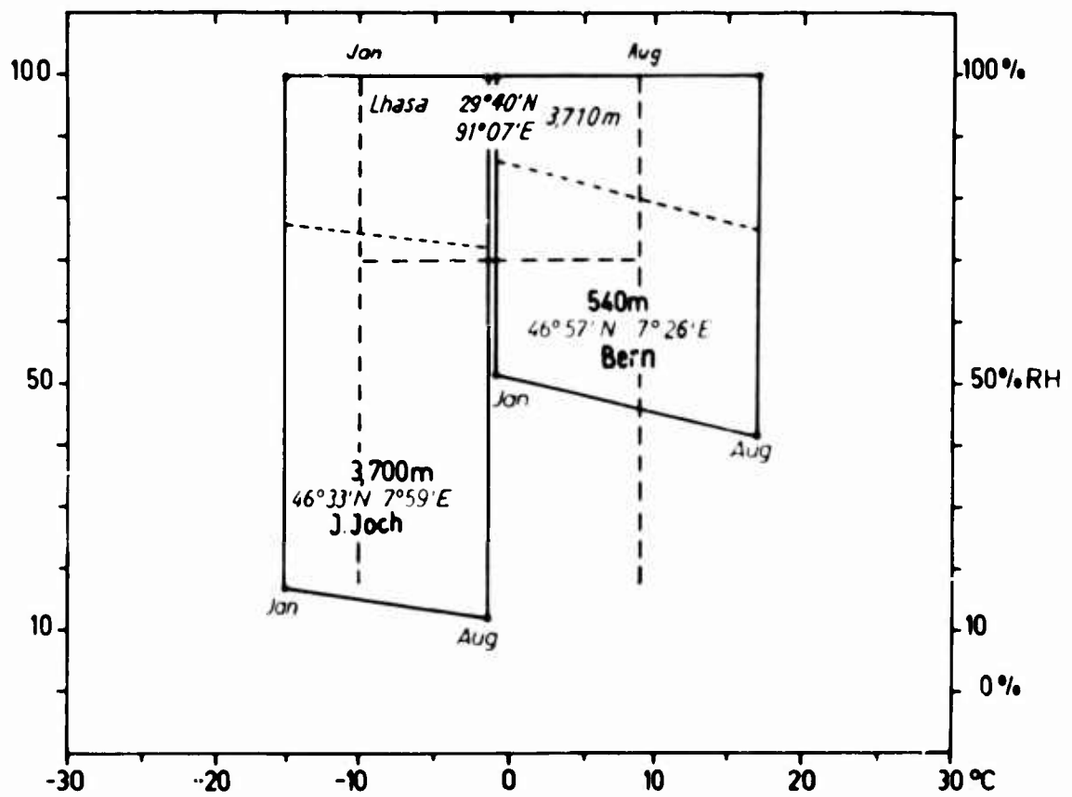


Figure 4
Temperature-humidity climatogram for the three different altitudes; mean monthly temperature and minimum and maximum humidity at Bern, Jungfraujoch and Lhasa for the coldest (January) and the warmest month (August).

Physiological Adjustment

The metabolic rate in naked men of various races increases below the critical temperature of 27 to 28° C. There seems to be no difference between natives of arctic zones and Negroes from the tropical zone, with few exceptions as far as we know: the localized insulative cooling mechanisms such as that reported by Elsner et al. (12) for the hands and feet of Yukon Territory Indians, and the true insulative cooling mechaanisms found in Australian aborigines who can sleep naked at freezing temperatures (13). Remarkable adjustment to cold with increased resting metabolism was found in Alacaluf Indians at the tip of South America (14), and in spiritually motivated individuals such as the Indian pilgrim in the high Himalayas described by Pugh (15).

Exposure to cold will require a higher oxygen consumption by the individual if means to prevent heat loss are not provided. The insulative value of clothing must therefore improve the further north the population lives, and reaches its highest value among the Eskimos whose caribou fur clothing is 3.5 to 7.5 cm thick, i.e. 7 to 12 clo. At a temperature of -40° C an Eskimo would require 11 to 12 clo while sleeping and less than 4 clo during work (16). Such extreme low temperatures are common beyond the annual daily minimum 0° C isotherm both in high latitudes and high altitudes. In these altitudinal zones no native populations can be found; invading men are forced to live in stations which must be provided with food from other areas, since there is no possibility of self-provision with food as there is by fishing, for example, for the Eskimo at sea level.

The Eskimo has developed high local cold tolerance for those parts that are frequently exposed to the cold, i.e., face and hands. This is not found in negroes (17). According to the observations by Johnson and Kark (18), it was expected that with permanent life in the cold the metabolic rate of man would be increased and there would be a higher energy requirement than in warm regions. It has now been proved by several investigators that the energy requirements of the Eskimo are not higher than those of man from temperate zones (19, 20, 21) provided that the insulative protection is sufficient. The basal metabolic rate (BMR) of Eskimos is not above that of Caucasians under these conditions, which leads to the conclusion that the Eskimo is not sufficiently exposed to cold to necessitate an increase of metabolic rate. The BMR is only increased by cold stress or as a direct result of a high protein diet (14, 22). No information is available on the effect of season on the BMR of man living at high latitudes.

Similar observations seem to apply to mid-altitude populations but not to

natives of the high Andes and Himalayas (23, 24). Here an increased BMR was found as high as 24% above normal in Sherpas who were acclimatized to outdoor living without the insulative protection needed by Caucasians (23). There are also various reports on increased BMR among newcomers and acclimatized lowlanders, mainly among members of mountain expeditions, even after several months of adjustments to high altitudes up to 5,000 m. In none of these reports can the possibility be excluded that the increased BMR was due to cold exposure without sufficient insulative clothing, as was the case with the natives. Recently Beckwitt, Surks, and Chidsey (25) reported a transitory increase of BMR in man at 3,800 m lasting one week. Grover (26) suggested that in his investigations at 4,200 m altitude the increase of BMR was due to enforced activity of the respiratory musculature.

General Adaptation Patterns

Increased BMR as a response to cold means uneconomical utilization of some of the available oxygen for heat production instead of work (27).

A significant difference exists in the mechanism for maintaining a normal BMR in severe cold and at high altitudes. In the cold as at high altitude, the increase of BMR is prevented by the insulation from clothing and possibly increased subcutaneous fat layers, which eliminates the cold load. While the BMR could easily increase in the cold at sea level, it cannot do so at high altitude when the insulative protection is removed. The explanation for this is the difference in the availability of oxygen, as has been shown by various animal experiments (28, 29, 30, 31). For a given insulative protection, unexercised rats respond to cold immediately with linearly increasing heat production and caloric intake (32). On exposure to cold at high altitude, these responses are greatly delayed and not so significant, and the deep body temperature drops. Similar observations were made on other animals (31, 33). Contradictory results in man were found by Lim and Luft (34) who exposed persons for 120 min to 4° C and hypoxia (P_IO_2 = 65 mm Hg) in the supine position. Oxygen consumption in the cold with and without hypoxia was the same throughout the 2-hour period. The explanation could be that the persons were under conditions of complete rest, which facilitated adjustment in this acute exposure study.

It appears that the temperature regulation involves the autonomous nervous, the endocrine, the cardiovascular and the muscular systems, and the inner organs. The cold stimulus leads to shivering and non-shivering thermogenesis (35, 36). The adjustments serve to decrease total body heat loss and to increase heat production. The multiplicity of functions involved is not

entirely known. Hypoxia can affect many links along the chain of adjusting functions, particularly those involved in oxygen transport and aerobic metabolism. The explanation for the impairment of the response of the body to cold under hypoxic conditions could be that the temperature regulation center is directly affected by hypoxia, and the insufficient oxygen supply to the tissues impairs shivering and non-shivering thermogenesis.

Cold

Before the two hypotheses can be discussed the patterns of adjustment to cold without hypoxia should be considered. The mechanisms of adjustment are very complex and definite conclusions, particularly for man, cannot yet be drawn (22, 35, 37, 38). Several changes should be listed, many of which have been found in studies with various animal species.

Oxygen transporting systems

Decrease of vital capacity and ventilation volume in the cold.

Possible rise of cardiac output and indication of left cardiac hypertrophy.

Increased blood pressure and higher peripheral resistance.

Decrease of blood volume including plasma volume and number of erythrocytes.

Shift of the oxygen dissociation curve to the left (22).

Increased diuresis.

With chronic exposure, skin temperatures increase on cold-exposed parts of the body such as hands, feet, and face (39) by means of an up to 15-fold increase in local blood flow (35).

Regional vascularization of the muscles around the body core (40).

Oxygen metabolizing systems

Increased aerobic metabolism under resting conditions. On acute exposure to cold, shivering can produce a more than five-fold increase in metabolic rate. With adjustment there is a reduced metabolic response to the cold stress, not only in natives but also in newcomers. Skin and deep body temperatures fall in individuals native to cold areas more than in newcomers.

Increased heat production in internal organs such as liver and intestines. "Shift in thermal distribution pattern towards one of greater heat production by the central core relative to that of the body shell" (41, 42, 43).

Increased fat catabolism (43).

Increased weight of the liver and decrease of muscle mass in relation to body mass (44), increase of absolute and relative weight of heart and other centrally located organs (45).
Lower P/O ratio in the muscle; no increased storage of myoglobin (46).
Increased release of catecholamines: non-shivering thermogenesis (35).

From these changes it appears that under moderate physical activities, as long as a high working capacity is not required, there is a shift in heat production at the expense of the muscle. Adjustments to increased muscular metabolism do not take place. As the only noteworthy response is some local peripheral circulatory adjustment, cold obviously does not constitute a strong stress on the cardiovascular system. The respiratory system, however, is affected in such a way that maximum ventilation is impaired with decreasing air temperature and humidity. The cold stress affects the depth of ventilation and even leads to cooling of the inner parts of the body, as was seen by Grayson and Kinnear (41) who measured the temperature of the portal blood.

Work

Work and physical training lead to adjustments in the organ systems involved in thermoregulation which are partly opposite to those significant for cold adaptation. Work increases muscle metabolism up to more than 20 times the resting level, far beyond the five-fold increase in response to cold stress. With endurance training, therefore, adjustments take place in the body which concern the uptake and transport of oxygen by the blood and its utilization in muscle tissues. During strenuous exercise the requirement of oxygen by muscle is about 50 times that under resting conditions (47, 48). The significant changes which occur with long periods of endurance exercise that seem important for this discussion are:

Oxygen transporting systems

Increased ventilation volume with maximal exercise.
Increased cardiac output through increased heart rate and stroke volume with high ceiling rates.
Increased heart volume.
Increased peripheral circulation during exercise. The postexercise blood flow is less in trained than in untrained persons (49).
Increased vascularization of the heart and skeletal muscle (50).
Increased number of erythrocytes, hemoglobin, blood and plasma volume (51, 52).

Oxygen utilizing systems

Increased heat production in the working muscle: shift of the thermal distribution pattern towards greater heat production by the body shell in relation to that of the central core (58). Increased skin temperatures over those muscle areas involved in the work, mainly arms and legs.
Increased muscle strength and muscle mass (51. 54).
Increased myoglobin.
Increased P/O ratio in the muscle and increased glycogen storage (55, 56).
Increased capacity for oxygen debt.
No increase in BMR but in maximal oxygen uptake (47, 51).
Decreased maximal exercise blood lactic acid levels.

A comparison of these adjustments to endurance exercise with those to cold shows that there are striking differences in some functions. The main difference is that with training the oxygen metabolizing systems in the muscle are activated while they are uninfluenced or depressed in the cold. In this way, the peripheral muscles under cold conditions show a reversal of all those changes which are significant for physical training.

Very recent investigations by Andersen and Wilson (38) seem to provide strong evidence for this inverse relationship. Andersen and Wilson trained two groups of young men for 4 weeks outdoors, for at least 7 hours a day, by various activities such as runs, long distance hiking, field games and road work. One of the groups was allowed to sleep in heated living quarters while the other group had to sleep with insufficient bedding in non-heated rooms to induce some cold stress. A standard cold stress was performed before and after the training period. It was found that in both the warm and the cold-sleeping group the BMR had increased to +15% after the 4-week training period and that the response to cold was +20% in both groups. Hildes (57), one of the investigators of the same team, states that "the data do not indicate that physical training plus cold exposure leads to a shift from shivering to non-shivering thermogenesis." This could not be expected on the basis of the adjustment pattern and theoretical considerations. On the contrary, the increased BMR seems to indicate that cold adaptation was necessary in both groups. If it is true that with physical training the typical changes of cold adaptation, i.e., increase of non-shivering thermogenesis, are impaired, in these investigations the BMR had to be increased in order to maintain body temperature. How could this increase of BMR be brought about? The answer might lie in the cold climatic conditions during the daily physical training. It was stated the "occasionally general cold was experienced during the daytime by all subjects." According to the air

temperature chart the ambient temperature conditions were cool if not cold during the day. Unfortunately, the authors gave no measurements on the cooling power of the air, i.e., temperature, humidity and wind.

The maximum oxygen uptake of the two groups increased about 6%. Considering that the BMR rose more than the maximum oxygen uptake, it appears that the increase in excess oxygen uptake was much smaller than could be anticipated for this amount of exercise. Under normal training conditions the difference between basal oxygen uptake and maximal oxygen uptake should increase. In conclusion, the results of the investigation strongly support the concept that through training in the cold, if the cold stress can affect the body, the two adjustments to cold and work will interfere with each other and the net result will depend on the strength of the stresses.

Altitude

Oxygen uptake increases linearly with work load. There is no difference to this correlation at altitude (4, 58, 59). However, with increasing altitude work performance decreases (58-63). According to the data of Ceretellili (64) and Margaria and Ceretelli (65) the decline is different for acutely exposed and acclimatized persons, being more pronounced for the latter. On the whole their data are in close agreement with the measurements made by Pugh during several expeditions (58). According to Pugh's data (Figure 5) on acclimatized individuals, the decline of VO_2 max increases slowly up to the altitude of about 2,500 m; above that altitude the lines for VO_2 max and PIO_2 run almost parallel up to the altitude of 5,500 m, and from then on the VO_2 max decreases faster than the PIO_2. On the right ordinate of Figure 6 the values for PIO_2 and decrease of VO_2 max in percent are given. Such a decline of adjustment with altitude is not found even beyond the critical altitude level of 5,500 m with moderate exercise, as was shown by Pugh in the same Figure 5. Similar results were found by Elsner, Bolstad and Forno (49) in native Peruvians up to the altitude of 6,400 m.

The curve of the decline of maximum oxygen uptake is the expression of the adjustment of the body at various altitudes. These adjustments are similar if not identical to those in endurance training. Some of these changes, considering conditions of rest and maximal work separately, are summarized in a diagram after Barbashova (Figure 6). The following adjustments at altitude seem of importance in this context:

Oxygen transporting systems

Increased ventilation volume. The maximum ventilatory capacity reaches

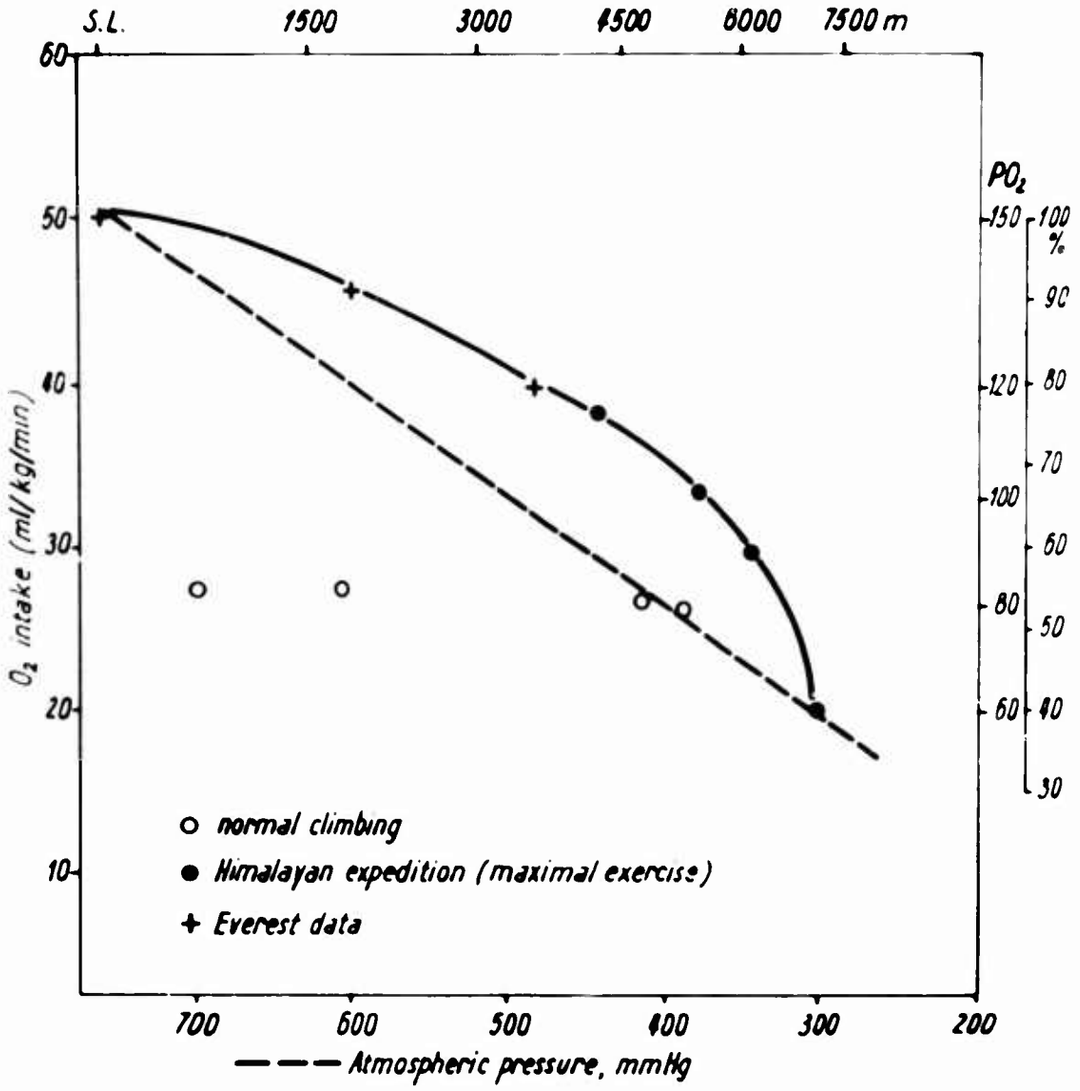


Figure 5
Pugh's data on oxygen intake of mountaineers after long periods of acclimatization at different altitudes in relation to partial pressure of oxygen (58).

ceiling rates up to 20 times resting ventilation and up to 50% higher than at sea level.

Increased diffusion capacity not in newcomers but possibly in natives (67).

Increased cardiac output through increased heart rate at rest and on exercise and increased stroke volume. These increases are found up to the limiting altitude of 2,500 m when compensation for the reduced PO_2 is still possible. Above that altitude, particularly above 4,000 m, the heart

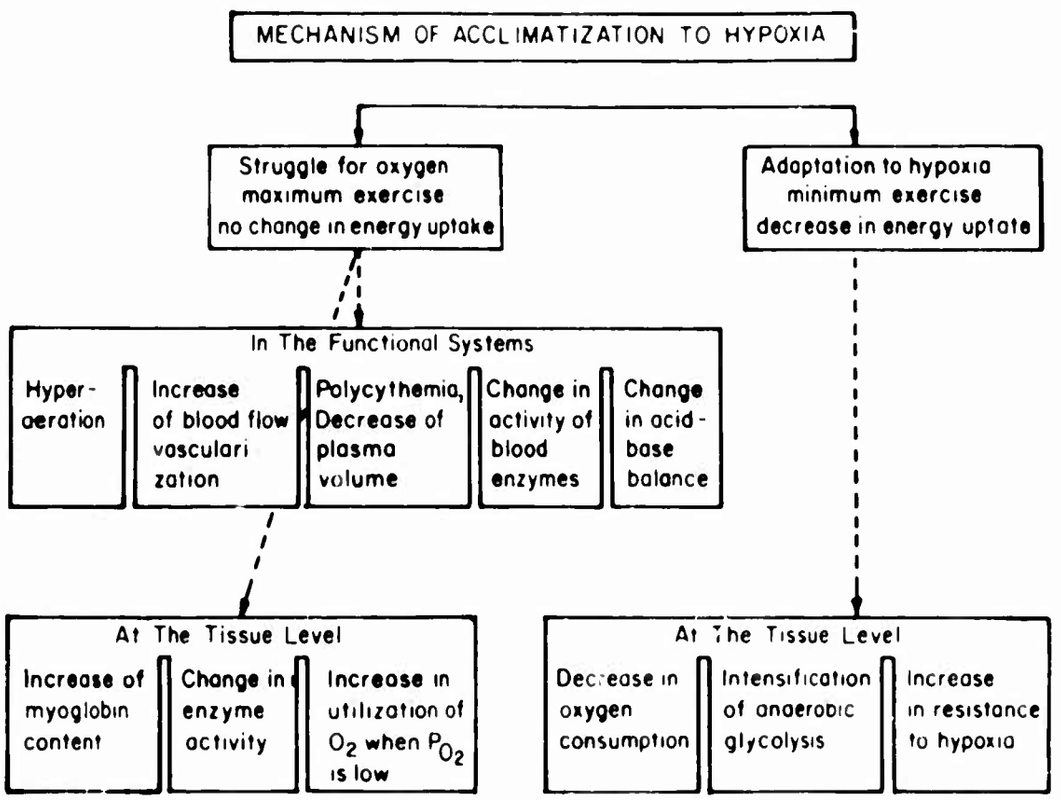


Figure 6
Mechanism of acclimatization to hypoxia at standard temperature (66).

ceiling rate decreases to below sea level values and so does cardiac output (61, 68).

Increase of heart volume. Above the critical altitude right heart hypertrophy develops.

Increased peripheral circulation with exercise which seems not impaired even at altitudes of 6,000 m (49).

Increased vascularization of the heart and working muscle (69).

Increase of number of erythrocytes and hemoglobin. This increase of Hb is positively correlated with altitude (70). The increased blood oxygen capacity compensates for the decline of blood oxygen saturation with altitude.
Increased blood volume but not plasma volume.
Flattening of the slope of the oxygen gradient (58, 71).
A small shift of the oxygen dissociation curve to the right (71).

Oxygen utilizing systems

Increase of muscle strength and muscle mass up to the critical altitude of 2,500 m or slightly above; above that altitude, decrease.
Increased myoglobin (55).
Increased P/O quotient up to the critical altitude or above (55, 72, 73).
No increase in glycogen storage above the critical altitude as seen from animal experiments and as can be inferred from studies on energy intake. Energy intake decreases above a critical altitude of 4,000 m (58, 74). The decrease of energy intake at rest which was seen in animals (28) and in man is negatively correlated with altitude.
Increase of BMR possibly only under conditions of cold stress in well-acclimatized individuals (23, 67, 72).
First an increase in oxygen debt capacity up to the critical altitude of 2,500 m, and above this altitude a decrease (72).
Decrease of lactic acid levels in the blood with extreme exercise (72).
Changes in enzymatic activity of the tissues facilitating electron transport within the respiratory chain (73).
Transient adrenal medullary and cortical activity (75, 76).

Some of the adjustments in the oxygen metabolizing systems with work, altitude, and cold are summarized in the diagram of Figure 7, which is adapted from a diagram by Hensel and Hildebrandt (55). Those changes common to physical exercise and altitude exposure are encircled by a dotted line. The similarity of the changes within the oxygen metabolizing systems is quite obvious. They are opposite to those from cold stress.

Even though there is a close similarity between the adjustments to exercise and to altitude, there is one important interfering factor which impairs adjustment above a critical altitude of 4,000 m. This factor is the decreasing energy intake due to lack of appetite. Weight loss at high altitude is well known and has been demonstrated again recently in a well-designed experiment by Eagan (77). From his data it seems that the weight change is less in physically

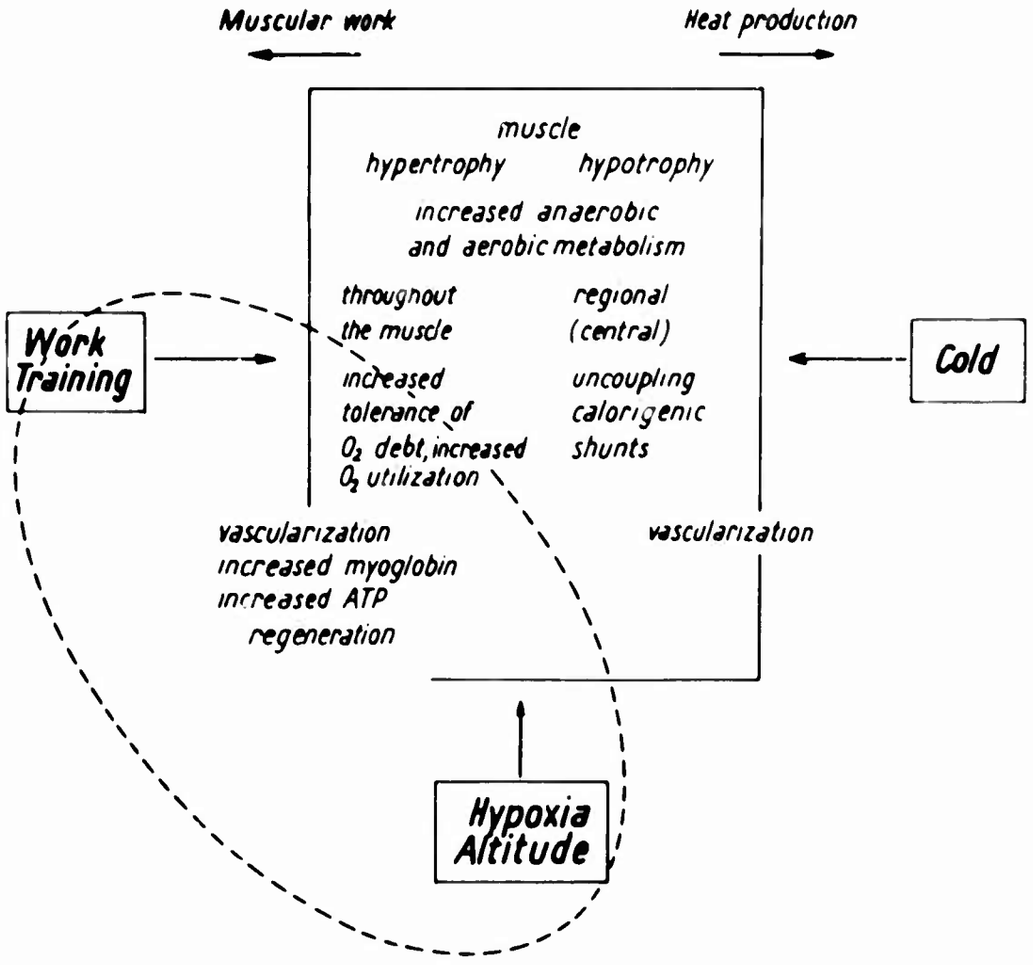


Figure 7
The relationship between the effect of work, cold and altitude on the muscular system.

trained than in untrained men at 4,200 m altitude and very low ambient temperature. Pugh states that his studies at great altitudes in the Himalayas were possible only after provision had been made to maintain an appropriate caloric intake. In previous studies he had noticed that the energy intake decreased at great heights to values of 1,500 kcal per day, just high enough to maintain a normal BMR. This increasing weight loss must necessarily lead to a decrease in muscle mass and competes with adjustments to training. Hence, decrease of fitness at high altitudes above 4,000 m, measured by maximum oxygen uptake, is not only due to limitations in the capacity of pulmonary ventilation, decrease

of cardiac output because of insufficient oxygen supply to the working heart muscle (48, 70, 78), oxygen diffusion capacity (58) and oxygen saturation of the blood, but is also due to a decrease of energy storage in the form of glycogen in the tissues because of deprivation of energy intake.

The close correlation of the adjustments to exercise and altitude has given rise to the statement that the time course of adaptation at a given altitude decreases in length as the state of training at sea level improves (4). On exposure to a certain altitude the trained body is provided with the adjustments needed for life at altitude since exercise causes a state of temporary hypoxia, e.g., there is a change from intermittent to chronic hypoxia at altitude. The untrained man is not adjusted to temporary hypoxia. Therefore, in the untrained man there is not only a lower maximum oxygen uptake or maximum working capacity (fitness) than in the trained person, but he also needs a longer time to reach the possible maximal level. This is demonstrated by the diagram of Figure 8a. Very little evidence was available when this statement was made. It has recently been confirmed by Consolazio et al. (62), and Grover (63) that in fully trained individuals the decline of maximal physical performance found at the beginning of altitude exposure did not improve with further stay at that altitude. As far as physical training is concerned, the adjustments from maximal training provide maximal altitude resistance. This can also include the occurrence and length of duration of subjective symptoms at high altitude (7), a situation well known in the European Alps where the same mountains can be reached by train and by climbing. Mountaineers have few or no symptoms while visitors ascending by train show a much higher incidence of complaints which last for some time.

With cold stress the process of adjustment to altitude is hindered in both trained and untrained individuals, but in the trained less than in the untrained ones (Figure 8b). The excess oxygen consumption becomes immediately small when the BMR increases. If adjustments are insufficient, body temperature will decrease (79). For the time being, evidence for the two hypotheses concerning the impairment of adjustment to altitude with cold and work stress acting simultaneously is such that neither possibility excludes the other. It might well be that concomitant with the shortage of oxygen in the muscle and the increased heat loss through the peripheral vasodilatation at altitude, the temperature regulation center responds with lowering the set temperature as an energy and oxygen saving measure, similar to the decrease of the heart ceiling rate as a possible response to avoid cardiac muscular hypoxia. Investigations of this dimension are rare and many more must be performed as soon as the problem is clearly formulated.

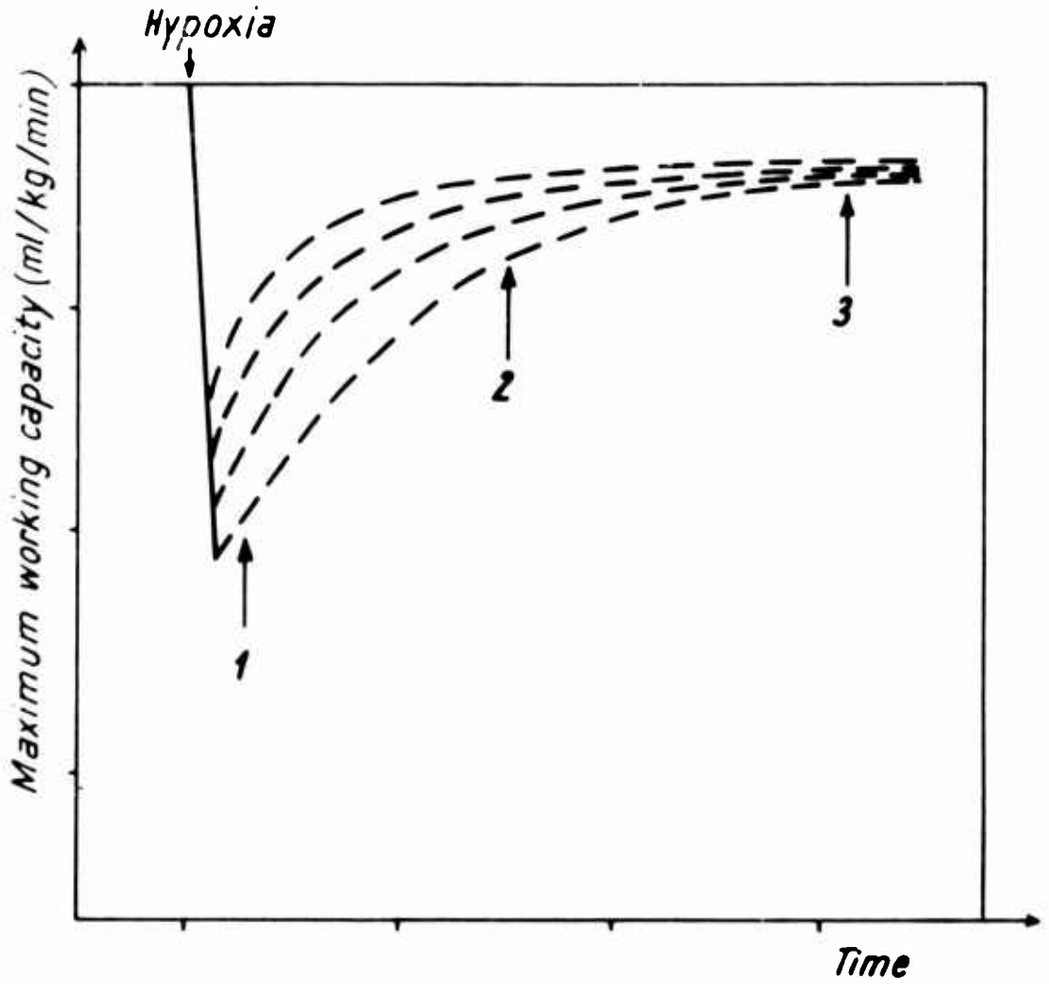


Figure 8a

Time course of adjustment of maximum working capacity to high altitude. The dotted lines from left to right demonstrate that with increased physical training before altitude exposure the time needed for maximum possible adjustment becomes shorter.

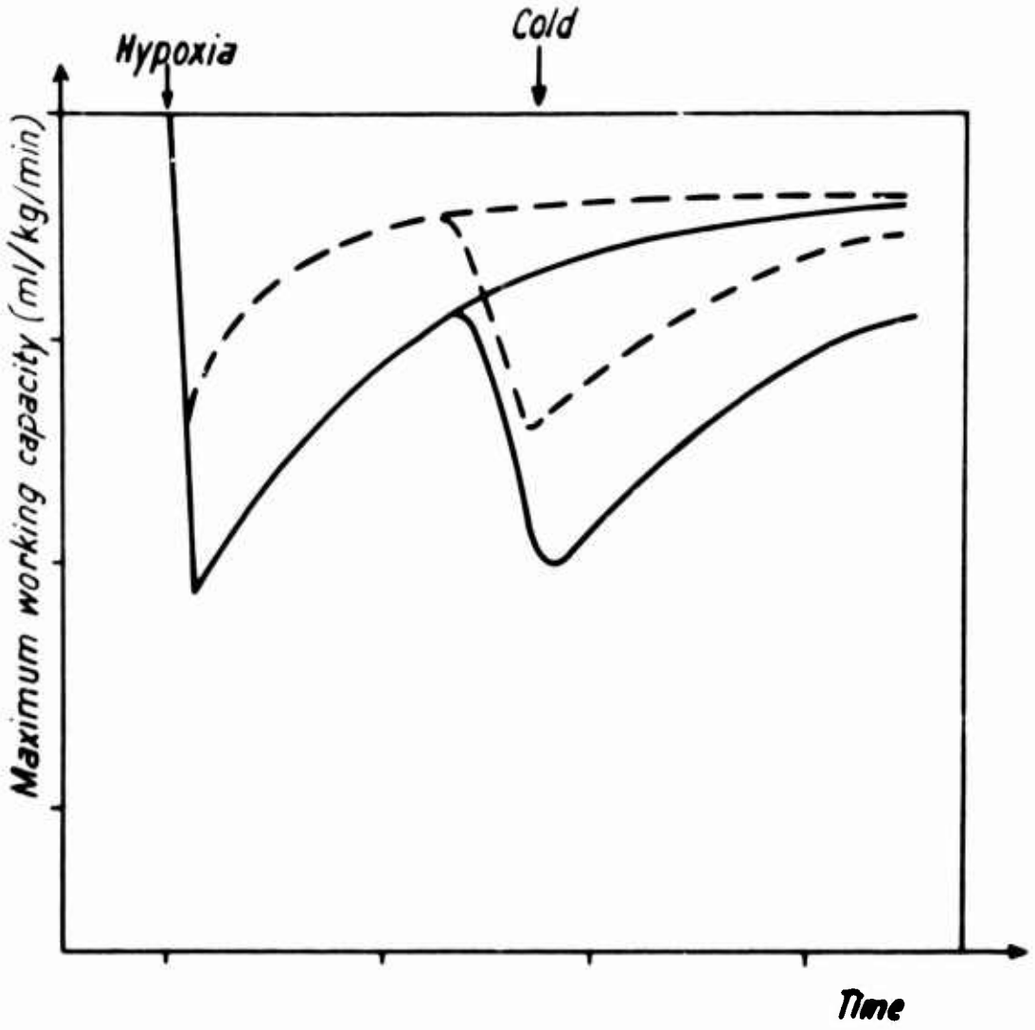


Figure 8b
When cold affects the untrained (solid line) and trained (dotted line) body during adjustment to high altitude maximum working capacity decreases and the time (weeks or months) needed for adjustment is delayed.

Conclusion

In summary, the inter-relationships of the adjustment patterns to cold, work, and altitude can be depicted in simple diagram form. The metabolic rate above the basal rate (excess oxygen consumption) increases with work, where heat is produced as a by-product of which the body must rid itself, and increases with cold, where heat is the wanted product. Both processes are hampered by hypoxia (Figure 9). On the other hand when maximum oxygen consumption

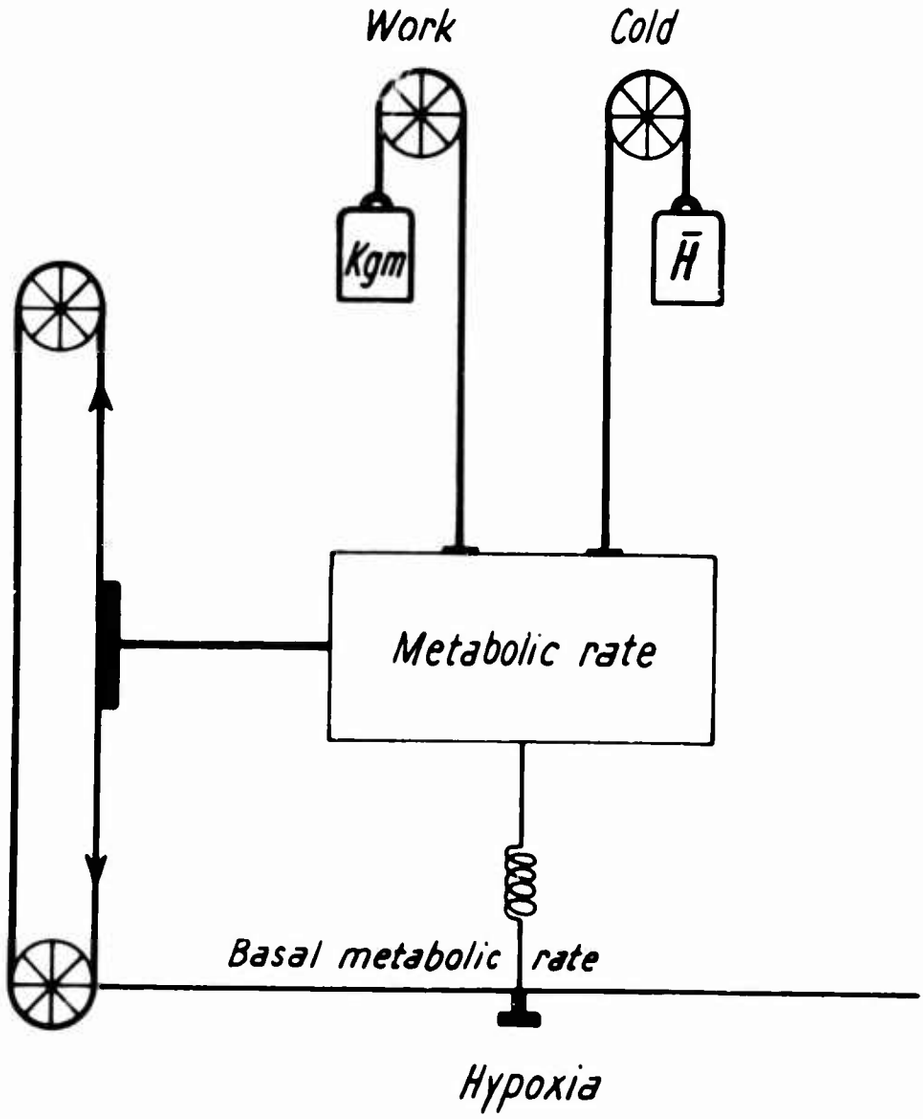


Figure 9
Diagram of the dynamics of the effect of work, cold and altitude on the metabolic rate of man. The increase of metabolic rate with work (kgm) or in response to cold (total body heat loss, H) is hampered by hypoxia.

(maximum working capacity) is considered, both cold and hypoxic environmental conditions, though in a different fashion, hamper nearly synergistically the improvement achieved by training (Figure 10). Much research will be necessary in the future to identify the various mechanisms taking part in the interrelationships of adaptive patterns to the stressors cold, work, and altitude.

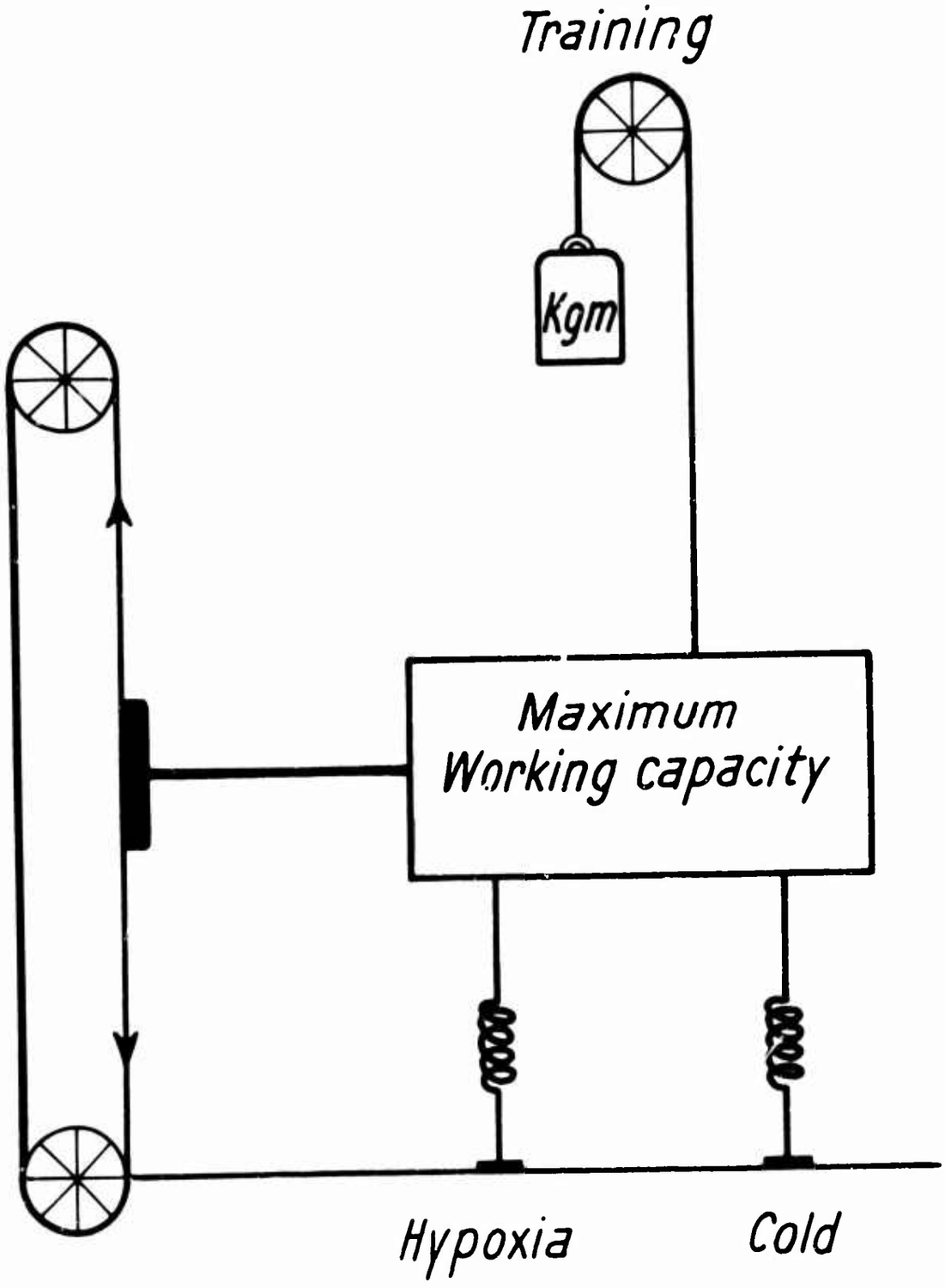


Figure 10

Diagram of the effect of training on the maximum working capacity of man during exposure to hypoxia and cold. Maximum working capacity which is hampered by hypoxia and cold can be improved by training.

DISCUSSION

DR. DILL: Let me point out that the hardest work reported in this country was the old study of the Maine lumberman who worked twelve hours a day with a caloric intake of 8,000 calories, which they digested, so I don't think there was much follow-up in their blood supply to their gastrointestinal tract. How can a man digest his meal, then, when he's doing hard work?

DR. SALTIN: There is a reduction, when the work is around 90% of the maximum.

DR. DILL: Well, that's practically over here in this maximum level.

DR. SALTIN: Roll's data showed 1,600 ml at rest and decrease down to 400 milliliters at 98% of maximum.

DR. DILL: My question was if in a working man there is any reduction in the blood supply to the gastrointestinal tract until you do get up to this, say, 80% level or something like that.

DR. SALTIN: But I think these lumberjacks take most of their calories in the evening, at least the Swedish lumberjacks eat a very heavy dinner, around 4,000 to 5,000 calories, then they have the night to digest it.

DR. EVONUK: You told us that the cross country skiers had to eat on the way or they won't make it?

DR. SALTIN: Yes, but if there is some absorption from the intestine, this is true.

DR. REYNAFARJE: I have a slide which shows pigments in the sartorious muscles and in the blood of subjects, normal subjects from high

altitude and sea level. In the first column would be the age in years, 28.8 the average for sea level and 24.3 years for altitude. The second column shows the hematocrit, 43 against 62 and the blood hemoglobin is 14.4 and 17 at high altitude and the third column is myoglobin, 16 milligrams per gram of tissue at sea level and 7 milligrams at high altitude.

DR. WEIHE: And this change is . . .?

DR. REYNAFARJE: It is significant, and in the fourth column is the blood content of fresh muscle tissues, the hemoglobin content of the tissues, which is much greater than what could be evaluated by the blood hemoglobin, which could mean that there is more blood in the tissues at high altitude than at sea level.

DR. BRAUER: These are the biopsy tissues that you were referring to?

DR. REYNAFARJE: Biopsy.

DR. BRAUER: What is the altitude?

DR. REYNAFARJE: These are natives from 4,200 meters.

DR. HANNON: Some of your data certainly doesn't agree with the experience we've had. Last year as I mentioned earlier, our laboratory took 16 subjects to the top of Pikes Peak, half trained and half not trained, and we continued the training before altitude exposure and during altitude exposure, and the weight loss was identical in both groups. The decrement in performance relative to their sea level performance was identical in both groups. There was no evidence that training improved their tolerance to altitude, whereas if you look at sickness or at the early decrement in performance at altitude versus the three week decrement at altitude performance, they were identical.

DR. DILL: I was thinking of your demonstration, Dr. Saltin, that those

who show the greatest decrease in maximum oxygen consumption are the best trained men, isn't that right?

DR. SALTIN: Yes, that's right, but here I think this training program was not sufficient to increase maximum oxygen uptake more than say five milliliters at sea level, and so you can't expect to get any big differences in these two groups. Still your conclusion I think is right, that a short training program will not change the story very much.

DR. HANNON: This training program started three weeks before they went to altitude and it was continued during altitude. There was a difference in maximal oxygen uptake.

DR. DILL: Another point. I don't remember the figures you gave on these cross-country skiers, but I know you said that when it gets to minus 20 Centigrade you have to stop because they freeze their feet. But what about the records of their performance at let's say down to 15, does it fall off?

DR. SALTIN: I want to discuss it a bit more, to say that the working capacity must decrease in cold. This is perhaps true if they can't protect themselves through clothes and so on, but these cross-country skiers they . . . I will not say that they perform better in cold, but you get very high work levels, 90%, for hours, down to minus 20 degrees Centigrade, suggesting unchanged performance capacity.

DR. WEIHE: Yes, but these people are in an optimal balance between heat loss and heat production, and I think you mentioned this, they just opened their shirts but just enough. We all know that when we got out and work very hard that we will sweat, but we have now to find the right balance. You mentioned that you swim in your suits afterwards.

DR. HORVATH: Not only that but in acute exposure to cold, you have to separate these things. This is an acute exposure, the man comes in from the

warmth, he's out—he's warm, he gets dressed, then he goes out. We might keep our terminology and concepts together—acute exposure to cold and a prolonged exposure to cold. They may be entirely two different problems. In fact I am pretty sure they are.

DR. SALTIN: I agree completely with that, but the high work levels that people are able to do in cold, and I think you have the same experience up here, those with top aerobic capabilities, they're all way down, but if you just think of acute exposure to cold, then it's no problem if you can keep up the work level.

DR. WEIHE: But to come back to this observation that the top level athletes showed a higher decrease of work capacity than less trained athletes. This doesn't matter, concerning time course, this is only the decline that we find. More important is, how long does it persist?

DR. BUSKIRK: Well, what evidence do you have that the time course changes?

DR. WEIHE: Yes, but we said there is no further change, it's the only . . .

DR. BUSKIRK: What evidence do you have that the time course adaptation to altitude is any different for the trained than the untrained?

DR. WEIHE: This is based on animal experiments. For example, I showed this decline in body weight—when you take an animal which has free access to the running wheel, and is fairly well trained, you don't have this weight loss, at least not at the altitude of 3,500 meters.

DR. BRAUER: But this may be a difference in body composition, couldn't it?

DR. WEIHE: No. We measured the food intake as well as the water intake.

DR. BRAUER: I'm talking about lipid content, body fat content, before you stop—I would bet that your untrained animals have a far higher—if they're rats, have a far higher fat content than the animals that have had exercise.

DR. WEIHE: Yes, but the point is still, how do they adapt on exposure? Do they maintain their energy intake or do they decrease it? This could be used as a barometer for acclimatization.

DR. BUSKIRK: This may work to man's advantage if he does this. I mean if he's lighter and he has to do a fixed amount of work at altitude, since he's transporting less weight, this is an advantage to him.

DR. WEIHE: This could be, yes, but other indicators besides maximum working capacities are subjective syndromes. Do they appear as quickly as they do with an untrained person? There is enough evidence which we have that they disappear quicker.

DR. HANNON: We have no evidence of this.

DR. WEIHE: But we have seen this many times.

DR. EAGAN: What is the difference in the food intake in these two groups?

DR. HANNON: I don't recall what these were.

DR. EAGAN: I am just wondering what the difference in training level was, how many calories did you pump through their systems?

DR. HANNON: I don't recall this, I would have to go back to the data.

DR. EAGAN: Because you can see from our data there was a considerable difference in food intake on a per kilogram basis.

COL. GOLTRA: Was data on yourself included in this calculation?

DR. EAGAN: Yes, I'm one of them.

COL. GOLTRA: Was this disputed?

DR. EAGAN: No, I know I gained one kilo during the two weeks and—

COL. GOLTRA: Yet your food intake was what, twice what the other people's was?

DR. EAGAN: No, no, on a per kilogram basis, I think I was second or third.

DR. HANNON: Now the other point you made, if I heard you right, is that in cold exposure, the metabolic increment needed to offset the decreased temperature was at the expense of work ability, is that correct?

DR. EAGAN: Yes.

DR. HANNON: I believe there's good evidence out of Hart's laboratory that rats, at least after they are acclimatized, maintain their ability to do work and build up their capacity for heat production. I think this was shown in Dr. Chiodi's slide. This is in acclimatized animals, though. It is probably not true in acute exposure. In acute exposure they do it at the expense of work capacity but in acclimatized animals they have regained that work ability. I am not at all sure how much really in the way of cold acclimatization, a true cold

acclimatization, you see in people. You just don't expose them to the temperatures to which we expose rodents.

DR. SALTIN: May I turn over to the finding that the hemoglobin content in the tissue was increased in the native at high altitudes? I just wonder if you can give the reason or the mechanism behind it, because there is great benefit for oxygen transport, but—

DR. BRAUER: Do you think perhaps we could have a little bit more description of methodology, because I frankly don't quite clearly see how you would do this in a subject without forcefully training him and I think—

DR. SALTIN: This is one point, but the other point is that the data as shown are very interesting just in respect to oxygen transport and if you said there was an increase of blood in that tissue, well an increase of red cells, so there must be a selection, again, and that must be very important at altitude.

DR. BRAUER: Why must it be?

DR. SALTIN: You have the hemoglobin concentration increased in the tissue.

DR. BRAUER: Why must it be selective?

DR. SALTIN: If you have the information on the hemoglobin content of the whole blood—

DR. BRAUER: Yes, but I lack the plasma figures. What do you mean by selection? Perhaps I misunderstood. The tissue contains more erythrocytes, but if you compare plasma—

DR. SALTIN: But if you compare the figures from sea level with high

altitude, the difference is much bigger in the high altitude and that's why I think this difference and a selective shift of erythrocytes to the tissues. And then have you any explanation for the mechanism?

DR. REYNAFARJE: The only mechanism is that there's more capillaries per unit of–

DR. WEIHE: Surface?

DR. REYNAFARJE: Surface, enlargement of the surface.

DR. HORVATH: Do you actually mean, I think there has been some concern about more capillaries, actually of course there is–

DR. REYNAFARJE: There are more capillaries.

DR. HORVATH: There's no question that you have more blood in the capillaries, more of them are dilated.

DR. REYNAFARJE: I actually wrote on resting subjects. During rest there was more blood.

DR. CHIODI: And also that has been shown in brain myopics; there are more capillaries. I think that the eye, the retina, also shows an increase of size and the number of capillaries. I remember when we looked at the rat that has been at high altitude for one year, there was a striking difference in the brain.

DR. BUSKIRK: Does this happen in an isolated muscle, let's say that's isolated, that still is viable, and that is perfused, and one perfuses this now with a

hypoxic mixture, will it change in volume? Have simple experiments like this been done?

DR. BLATTEIS: Hasn't somebody shown a different number of capillaries in puppies born at altitude as opposed to puppies born at sea level, puppies of the same breed?

DR. BRAUER: It's been done with guinea pigs, it's been done with dogs, an attempt has been made to correct it too for hematocrit, and we're waiting for further data to tell us whether new capillaries are or are not sprouting in that.

DR. SALTIN: May I comment that if you tried to measure muscle blood flow in the very well trained, with the Xenon method, you actually get exactly the same maximal value as for the untrained, 49.5 for the untrained and 48.9 for the well trained, so I really doubt about the blood-

DR. BRAUER: This is not volume, of course, this is flow.

DR. SALTIN: This is flow, yes, but they're talking about greater vascularization or capilarization.

DR. BRAUER: Actually with the same method using the inter-arterials, you should be able to get maximum flow at times which under those conditions then would give us the volume.

DR. SALTIN: Yes, but still during maximum exercise you probably open all your capillaries and you get exactly the same flow.

DR. EAGAN: Of course there may be a greater flow through the muscles of the leg because the point you made is that you have hypertrophy of the muscle and of course the measurement is on a per hundred grams of tissue.

DR. SALTIN: Of course, the well-trained, his cardiac output is around 25, rather than 18-19 liters, so the blood has to go somewhere, and then there is the increased muscle volume.

DR. TODA: I want to say that if you compare low calorie fat diet, and low and standard diet, and low calorie diet and standard diet, and low protein diet and standard diet, and low fat diet, and on the same subject, that the efficiency of work is not so different. However, in case of low calorie diet, low protein diet, or low fat diet, the duration of work times becomes very shortened.

DR. EAGAN: Yes, this is really Dr. Saltin's thesis, that diet is important.

DR. BLATTEIS: With respect to the body weight changes, the newborn at altitude is often born at smaller weight than we see in his counterparts, but there doesn't appear to be any difference in the rate of growth, in weight gained, and eventually the slopes of the two curves are often parallel.

DR. HORVATH: Let's clarify this, what do you mean by often? They're often smaller or larger - are you talking in terms of 80% or 90% or what?

DR. BLATTEIS: It's dependent on the species. If you talk about the rat, then the two curves are parallel. If we talk about the calf, then after about three weeks as I recall, the calf at high altitude gains weight a little bit more rapidly than his sea level counterpart, but the adult animals of the same species and of the same strain are approximately of the same weight.

DR. WEIHE: It depends of course on the energy supplied by the mother, do they get enough milk.

DR. BLATTEIS: Well, this is taking it beyond the weaning period.

DR. GROVER: There was a control experiment done at the school of Veterinary Medicine at Fort Collins where they took two groups of ten growing

steers, one was kept at five thousand feet and the other was taken to ten thousand feet. Both were kept corralled to limit activity and given exactly the same diet and over six months the animals at ten thousand feet were 20% behind their "litter mates," so to speak, at low altitude, and when they were killed they had much less fat on the carcass.

DR. BRAUER: Isn't this what you were saying this morning about the rats having to be big before they get retarded?

DR. GROVER: Didn't they what?

DR. BRAUER: When we were talking about the cold retarded rats, didn't you argue that the rats had to be pretty big before you got good retardation?

DR. HANNON: You're talking about altitude.

DR. BRAUER: Yes.

DR. HANNON: No, we got essentially the same thing in rats at altitude, reduced body fat content.

DR. WEIHE: Do you know the ambient temperature in these studies?

DR. GROVER: It did tend to run lower at ten thousand feet.

DR. WEIHE: Of course this is the common observation in the Alps; the cattle, when they were brought up to the meadows in the summer period, lose weight. This is due to exercise, of course. They had to walk around all day at reduced temperatures. But they put on weight, the important thing is this: they put on weight very rapidly on returning to low altitudes, much faster than

animals which had been kept there at low altitudes during the summer.

DR. CHIODI: What about the food intake, did you check how much they eat at 10,000 and 5,000?

DR. GROVER: This was kept track of, and it was also offered ad lib, but I don't recall whether they ate more or less.

DR. BLATTEIS: I have one other comment which refers to the importance of the habitual environment in nature, in animals particularly. There was a control experiment run about two years ago I think at Oxford, at which time newborn rabbits right from birth were kept in a slightly cooler environment than their thermoneutral environment, and animals from the thermoneutral environment were tested at three days of age in the environment of the cooler animals. The newborn that had been living at thermoneutrality showed a metabolic response to cold, I believe it was five or ten degrees below their thermoneutral, whereas those that had been living at this environment for the first few days of their lives no longer showed a response to cold in that environment. It's sometimes important to consider what the history of the environment is, or the species that one is working with. Oftentimes these animals are not kept in the environment which is really the neutral environment for the species.

DR. BRAUER: In the case of your cold-adapted rats, you are really making–conducting–a study of heat adaptation when you put them back into your so-called thermoneutral state?

DR. BLATTEIS: If they were adults, yes.

DR. DILL: I'd like to ask a question about Dr. Reynafarje's table which you used. I was surprised at the small difference in both myoglobin and hemoglobin at sea level versus 4,200 meters. The myoglobin was up 1 milligram in seven which would be about 13% and the hemoglobin was up about three in

fourteen which would be about 20%. Don't you usually have a higher hemoglobin in residents at 4,200 meters?

DR. CHIODI: I think it depends upon the individual. I found that there was much individual variation in the amount of hemoglobin from one individual to another.

DR. HANNON: I'd like to toss out the one about Eskimos that was alluded to here earlier. Nothing has been said since then, but I think the body of literature indicates that Eskimos do have a higher metabolic rate than Caucasians.

DR. CHIODI: Well, we showed that.

DR. WEIHE: I think Rodahl found out this was due to the protein diet.

DR. HANNON: I'm not too sure that is necessarily true. I'd like to mention one experiment we did here—Dr. Milan was in charge of it—and that's exposing Eskimos versus Indians and soldiers to various temperatures in the bath calorimeter so we could change the metabolic rate. At the thermo-steady state and metabolic steady state, Eskimos were always higher in terms of heat production and heat loss, and I think there is data, probably Dr. Eagan can comment on it, from Eskimo students who have been in a non-Eskimo environment for a period of a year and they saw a similar type of difference.

DR. EAGAN: This was an experiment done by our laboratory a couple of years ago when Dr. Milan and Dr. Evonuk and I went down to the Chinawa Indian School. We did many measurements on six Indians who were normally from Alaska, six Eskimos normally from Northern Alaska, and six Navajo Indians who were normally from Arizona and New Mexico. They were living at the Chinawa Indian School and had been there for the previous eight months. They were leading a sedentary life and subsisting on an ordinary mixed diet. In keeping with an objection that Dr. Brauer made that there are no control

studies, we did have controls from the University of Oregon. The groups were equal in age, and roughly equal in body composition, although the Eskimos turned out to be very slightly leaner. The Alaskan Indians and the Eskimos were not different from each other in metabolic rate, and the Navajo and Caucasian controls were not different from each other, but there was a highly statistically significant difference in basal metabolic rates between the Alaskan subjects and those from the temperate zone, and this difference had persisted at least through eight months.

DR. EVONUK: They still had resistance to cooling also.

DR. EAGAN: Yes, and in most of our cold tolerance tests, the differences by most of our criteria were significant at the one percent level.

DR. BUSKIRK: What happened to the metabolic rates in the cold? Did you do that?

DR. EAGAN: Well, our metabolic rates—it's hard to compare, measurements were made in one place and then in the other with different apparatus, and the conditions of measuring our basal metabolic rate were to wake the subjects up so that they are measured early in the morning—the Alaska natives gave sort of normal BMR values, while the Navajo and the controls gave sub normal values.

DR. BUSKIRK: You didn't expose these people to total body cold stress then?

DR. EAGAN: No, it was purely basal.

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SUMMARY

DR. HORVATH: I sat down for quite a time and thought of what I ought to say about the summary of the conference, and I have come to the following conclusion: this conference is not difficult to summarize—it is just impossible. I did have a few points which I thought would be well worth while reconsidering, though. I felt that the major point of this conference was quite straightforward; namely, that we had such a wide discrepancy in the results which have been obtained by various people at various times under various conditions, poorly controlled or well controlled, so that it is impossible at the present state of affairs to do much more than to hazard a guess as to the significance of the changes that occur. There are certain aspects on which most people seem to agree, but it is rather surprising—to me at least—that in the more recent studies, some things which looked like they were in good agreement were now suddenly going off in the other direction. There seems to be a considerable difference in the methods that are used by different groups to obtain potentially the same sort of information. Now whether this is a good thing or a bad thing I haven't as yet been able to decide, but it did appear to me that one of our important contributions made during the conference was to point out the need to define clearly the methods that are being utilized in these studies. We should also clearly define data and information on subjects so that these things which have now been so beautifully shown by Dr. Dill's work will continue. He has been able to identify a difference in pattern just because somebody happened to put in his records the absolute raw data or at least some portion of the raw data. I think if we had more such information in our records we might very well come up with some better conclusions than we did this time. Dr. Buskirk's observations would have been helped a great deal if all of the data he attempted to correlate on the blood volumes, the fluid volume balances, had been documented in terms of individual data, times at which the data were obtained, that is, if date, year, and the conditions were more precisely stated, something more about the weight of the subject—all these things probably would have made it easier for him to have come up with what might have been a very clear cut delineation of what happens to the fluid balances in man under conditions of work and altitude.

There are several other points which are really quite appropriate for us to consider; for example, the definition of what may be called a series of critical altitudes. By this I mean we should be able to agree, as we apparently have at least on one point, that somewhere above 6,200 meters is the point at which the physiological deterioration is greater than the physiological improvement. In other words, it's impossible for people to live successfully for any extended

period of time above 6,000 plus meters, but we have not established a delineation of the very critical altitudes below this. For example, where does the first modification of man's performance occur? Some of you have implied that it's somewhere around three thousand meters, but this is undoubtedly a mistake because we know from earlier studies of psychological deterioration that the critical altitude is somewhat closer to fifteen hundred meters, where there are a number of changes that occur in the ability of men to respond to make critical judgments. All of this suggests that somehow or other we are not using, again, adequate enough, precise enough, subtle enough tools to delineate this. We have to set criteria, and Dr. Weihe has shown this in a sense in some of his charts, where he is relating altitude, cold and the natural selection. We need to know a great deal more about these critical altitudes, where do these changes occur, in what direction is the change at certain altitudes, how long does an individual have to be at that altitude before he can more successfully go up to a higher altitude—in other words is it best to stay at 3,000 meters for two weeks, three weeks—is it better to stay at 3,000 meters doing (a) a minor level of activity, (b) a very strenuous level, or (c), a series of extraordinarily vigorous activities—which is best?

We should not limit ourselves to the standardized, simplified physiological approaches. We somehow or other must combine the physiological and the psychological approach. We ought to know whether or not the work periods that we are requiring of the human organism are going to be those which are for short durations, for maximal work output, or whether they're to be for sustained operations. We really should devote a great deal of our attention now to studies of man working for what may be considered a necessary optimum, an eight-hour day: can he work at fifty percent of his maximal capacity, or maximal for that altitude? If the maximum capacity is reduced twenty-some-odd percent, should we then expect that the individual who prior to this had been able to work say fifty percent of his maximum at sea level, will we now expect him to work at fifty percent of his maximum at 3,000 meters or 4,000 meters for the same length of time? We have no idea whether this is even possible, because we have not spent any time working on this problem. We have ignored cross-adaptation because the data was not sufficiently precise to enable us to make what we had hoped to come out of this conference, namely a suggestion that it is possible to adapt to altitude by working at some lower level, or that exposure to cold at some lower level would make it possible for one to adapt to altitude better. The reason we haven't been able to provide this sort of answer, and the reason we're going to leave it as a question, is that the few data we have on this are

completely inadequate. So cross-adaptation is something we've got to consider seriously as one of the major projects for the future.

A major problem that faces a man at sea level as well as at altitude in cold conditions is dehydration. A man working at a level let's say of about 350 calories per hour is going to produce–wearing the normal standard arctic clothing issues–he's going to produce a tremendous amount of water which he will lose in addition to that which he'd lose if he's just up there being dressed and working. Most of the experiments have been done, not out at the actual temperature up at the altitude where we have been, but in the beautifully safe confines of the little laboratories that we install at these temperatures and these altitudes.

It's perfectly evident, from what we have been discussing today and yesterday and the day before, that we need to know more about the influences on the central nervous system of these hypoxic states and how they are modified by the additional load on the oxygen requirements of the tissues when we work an individual. Now, we have some evidence that the central nervous system is markedly impaired at these altitudes, and we must consider this much more carefully than we have. We need to know a great deal more about the regulation of acid-base balance, and this of course consequently relates to water balances and so forth. It is also quite important for us to evaluate the influence of a large psychological factor, namely motivation, because most of you who have been up at altitude have this motivation to a degree which is not present in the ordinary individual. The only reason you're up there suffering, if I may put it that way, is because you are highly motivated, you are performing at a level which is considerably in excess, I am sure, of that of some other individual who is only told to go up there and does not necessarily respond in the same effective fashion. We must therefore very carefully evaluate the motivational drives of all the people who go to altitude, not just the subjects but the experimenters also. I think another factor which we touched on, and to me at least it seems to become more and more important, is the problem of sensory deprivation. We are beginning to see a number of facts for example on water balance, where in the hypodynamic state the individual is essentially suffering from a series of deprivations in his sensory input, and these in turn affect his osmo-receptors and therefore his water balance. This same sort of situation apparently does occur in some of the prolonged studies where sensory deprivation has been the prime concern of the investigator. I think this now comes into the picture because there is I am sure in most situations at altitude and cold, a combined situation which does induce a state of sensory deprivation.

SUMMARY

I could go on and on, but actually you covered so many of these things that it's sort of ridiculous for me to keep on mentioning them. I would like to end up with one statement, and I have tried to bring this out but everyone has by-passed me in considering it, and that statement has to do with this: Over the years I have become quite convinced that there is no such thing as a return to normal after a stress. I think the fact that we say that the cardiac output returns to normal, the plasma volume returns to normal, the blood volume returns to normal, and that we get a stabilization of the erythropoetic response, this to me does not mean that the individual is the same individual that he was before he went to this situation. I ask you to consider the question: does not the frequent occurrence of mountain sickness indicate the residuals of some alteration which has not been noticed by us because of our delight that everything has reached a point of homeokinesis, a point of stabilization? I would like to have the people who are going to work in this field spend a little more time considering the potential degree of alteration in the homeokinetic mechanisms which can only be deduced if we provide another stress to the individual.

This therefore, Colonel, provides you with an opportunity for another conference which will not be entitled "Cold, Work, and Altitude," but will be "—Something—cold, work, and altitude," and it is up to you to find out what that "something" is before the conference begins. Thank you very much for your kindness in listening to us. I know I haven't done a very good job of summarizing this, but I think my initial statement is true, namely that this has been a conference impossible to summarize. It is always easy for a chairman to get out of this sort of thing because all he has to do is call upon a friend to help him out at the last moment, and I'm going to call upon Colonel Goltra to take over and save me.

COL. GOLTRA: Thank you, Dr. Horvath. I am in the enviable position of flatly disagreeing with you. I think you have summarized it extremely well.

I would first like to express the official gratitude of General Jones, his staff, and the Yukon Command, and of the United States Air Force, the sponsoring body for this conference. I know that it was in some instances an imposition upon the critically short time that some of you men have to participate in this kind of thing, but again thank you for helping us. You have pointed up an enormous number of problems which are in very definite need of scientific exposure. I would also like to compliment the participants in this conference for their obvious erudition—I am impressed. I think also this symposium visibly demonstrates and reflects a need for this kind of continuing

scientific cooperation between investigators both in the United States and between investigators of the United States and elsewhere in the world, South America, Europe and so on. This is a salubrious and necessary thing for scientific progress. You have made pertinent contributions to the understanding of our mission requirements and the requirements which are placed upon us by our Command and our military needs. You have pointed out many operational military problems of importance, particularly for our environment up here.

I must agree and perhaps amplify the remarks of Dr. Horvath concerning the need for experimental design. I think perhaps the approach to a problem of the evident complexity which is demonstrated by this conference enforces the need for a very careful experimental design, probably of a rather sophisticated multi-factorial type, a need for a very careful definition of terms, an exquisite qualification of methodology, the value of raw data you talked about. It is perhaps unnecessary to debate this further. Raw data is sometimes absolutely invaluable for an unbiased evaluation of an experiment. The complexity of the problem you have all completely demonstrated to my satisfaction. The way you have approached it I wish to compliment you on. Also a thing that was evident to me was the need for cooperation and working together of many disciplines–physicists, physiologists, mathematicians, engineers, physicians, botanists, nutritionists, you could go on forever. Many of you men in this room have these skills–no one of you has all these skills, nor does any single individual that I know, therefore I think it imperative that you continue this type of cooperative approach to work. Again, thank you for helping us, please feel free to come back to help us some more. We would like to see you back.

DR. HORVATH: I know that we have been very pleased to come here, and I think one of the reasons that we were so very free in our exchanges was because of the fine attitudes that you have here. So may we thank both you, Col. Goltra, and especially you, General Jones, for the very nice things that have happened to us here. I am sure that we will remember them for a very long time.

DR. MORRISON: May I express on behalf of the University of Alaska our appreciation to Col. Goltra and to Dr. Evonuk for their cordial inclusion of our staff as observers in this conference? As they well know, we highly regard the Aeromed Lab as a group of fellow scientists, and the advantage for us of their proximity is nowhere better expressed than on the occasion of these conferences. It's a very important asset to our people to be able to participate.

DR. HORVATH: I want to thank you, Dr. Evonuk, too, for the very nice things you have done for us.