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MEETING OF INVESTIGATORS ON POPULATION BIOLOGY OF ALTITUDE

A Summary

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A Summary

During the past two years, three separate international conferences have been convened to discuss man at high altitude. This may seem excessive in light of the apparently highly specialized nature of the subject. However, the rationale for so many conferences is in major part explained by the very important findings which have been emanating from the study of high altitude man. One might select findings such as the almost total absence of ischemic heart disease or the differences in prenatal development, but indeed it now appears that at higher elevations men are biologically unique from conception through death. As this conference showed, we cannot assume that human populations at high altitude will respond like low altitude men in any aspect of their structural or functional development.

This uniqueness, of course, offers an unparalleled opportunity for scientists of any discipline to gain insight into our favorite subject -- ourselves. With such a sharp comparison we can hope not only to understand processes better but to intervene in them in order to cure some of the health risks from which men suffer.

The goals of this particular conference were to review our knowledge about high altitude populations in the most interdisciplinary manner possible and from this review to develop a list of the most promising and pressing research needs. The results of this conference were to serve,

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therefore, as a guide and justification for high altitude research programs in the International Biological Programme, the World Health Organization and I hope also for the Pan American Health Organization.

The final list of over 50 participants from 12 countries fulfilled the goal of being both geographically diffuse and heterogeneous in scientific discipline. For convenience the research reports were organized into four topics. These were:

(1) General Aspects of Altitude Biology
(2) Physiological Adaptation and Acclimatization to Altitude
(3) Human Biology of Altitude Populations
(4) Health Aspects of Altitude.

Again for convenience rather than with any intellectual confidence in this taxonomy, I will follow this topical sequence in reviewing the conference results.

General Aspects of Altitude Biology. Fundamental to any study of the biology of human populations are the demographic and environmental parameters. Yet, as was pointed out in the conference, we cannot specify either very well at high altitude. It is estimated that between 20 and 25 million people live above 3000 meters, but this is a very rough estimate and we have no idea of the extent of migration in and out of the areas. More importantly we do not have good studies on fertility and mortality although some recent work strongly suggests that altitude may decrease fertility while increasing both pre and neo-natal mortality. Demographic research at high altitude will certainly involve us in the social sciences. At the present time, no firm conclusions about the effect of altitude per se on demographic structures can be made because adequate research designs have not been

applied taking into consideration socio-economic factors.

We usually assume that the biologically significant factor in the high altitude environment is the reduction in barometric pressure, but as was repeatedly pointed out in the conference, the high altitude areas of the world are also lower in temperature and in vapor pressure, while higher in radiation of all wave lengths than most lowland areas. Any research design applied to human populations in these areas must take these facts into account.

Physiological Adaptation and Acclimatization to Altitude. It was highly apparent to the conference participants that a careful definition of the population under study must be made in order to study the processes of adaptation and acclimatization. This is essential since it now appears that the length of stay at altitude, the age of exposure and the genetic characteristics of the individual all affect not only his responses to hypoxia but also his responses when entering or reentering "normapoxia". Indeed it was argued that at least for the Peruvian high altitude native, a move to sea level produces a series of life long stresses on the individual not encountered by low level populations.

In assessing the information available on the various population subgroups, it appears that the most complete physiological information concerns the acclimatization process which occurs during a short term exposure of lowland populations to hypoxia. Here the changes in the oxygen transport chain have been carefully explored. However, the neurophysiological problems and changes in the central nervous system are poorly understood in part because adequate methods are not available. Information on capillary and tissue changes are also in need of elaboration. Finally

it should be pointed out that information on the physiological consequence to this population of returning to sea level is incomplete.

Our knowledge of the physiology of high altitude natives is primarily derived from Andean populations, but even here the samples have often been poorly defined in terms of genetic history and exposure to altitude. The other high altitude population with long generational sequences are the natives from India and Nepal. We also now have some data on groups from the U.S. and Ethiopia who are either first or second generation natives to altitude. Unfortunately, the two latter groups are from rather low elevations of 3000-3300 meters.

From the evidence available at this time, it appears that these populations as adults arein many ways physiologically different from the lowland man who is exposed to altitude even after the lowlanders have been there for a year more. To briefly review the differences as they are known along the oxygen transmission chain, we may list the following:
(1) The Peruvian and Asian high altitude native may have a greater maximal O_2 consumption than sea level man. This has been questioned by some since sea level athletes can match the performance of natives tested. Only more careful sampling can resolve this question.
(2) Hyperpnea caused by hypoxia was reported to be absent in high altitude natives when PCO_2 is held constant. This seems to be characteristic of all people spending the early period of life in hypoxic conditions. It appears irreversible but more details on the topic are obviously needed since it has a variety of important health implications.

(3) At all work levels, Peruvian high altitude natives appear to have a greater oxygen extractive efficiency. This may be related to structural differences in the lungs, particularly a larger residual lung volume and to shifts reported in the oxygen dissociation curve.

(4) High altitude residents have pulmonary hypertension when compared to people at low elevations. However, there exists good evidence to suggest that the degree of hypertension may be lower in the Andean native than in the one generation resident.

(5) In the same nature, polycythemia characterizes all populations at high altitude but it is distinctly possible that the long term native in the normal state has a lower degree of polycythemia.

(6) At the capillary and tissue level, our knowledge is sparse but intriguing. It is well established that after a time at altitude, the capillaries and small blood vessels expand, but from recent work on rats, guinea pigs and human muscle biopsies, it appears that the number of capillaries per mm^2 of muscle may be greater in individuals born and raised at high altitudes. Whether this is entirely a developmental phenomenon or also partly genetic remains to be answered. At the tissue level, there may also be differences between individuals raised at altitude and those not. This has been suggested by studies on rats and cows but has not been investigated on men.

In this physiological resume, I have not dealt with many structural and functional differences which will be covered in the human biology and health aspects of altitude. I have also omitted in general a comparison of the South American high altitude native with the Asian because of the scarcity

of comparable data. However, I hope this has been enough to indicate the paucity of data on the subject, its importance and the stress placed in the conference on proper population description.

Human Biology of Altitude Populations. In the human biologists' search for the sources and significance of human variation, high altitude studies are of particular interest because of the obvious stresses placed on populations by the lowered oxygen tension and other environmental extremes of high mountains. The methods of the human biologist lead him to concentrate on carefully sampled population units in an attempt to uncover both genetic and developmental differences.

In contrast to the situation encountered with physiological data, human biological data are more complete on resident populations than on immigrant groups. However, it is clear that the data presently available are quite inadequate for all groups. In the Andean region, observers have persisted since early Conquest days in reporting that immigrant European and Negro populations suffered in both fertility and viability compared to the high altitude natives. This seems to be partially confirmed by the sparcity of immigrant populations above 3400 meters in the Andean range, but scientifically acceptable evidence on this subject is very incomplete. As reported at the conference some work has begun on fecundity related factors in a group of males exposed to altitude and fertility in a small group of immigrant couples. The data support the hypothesis of reduced fertility but is based on too small a sample and too short a study time to be conclusive. For a wide variety of reasons, research on this subject is a pressing need. In the Andean

regions, suitable populations exist in both Peru and Bolivia. When such studies are undertaken, they should also include analyses of genetic characteristics, growth, mortality, disease, etc., since we have very little data on how altitude affects these processes in immigrants. The small population in the United States at high altitude is also highly suitable for such studies and it is indeed from this group that we first learned that neonatal mortality is generally increased at high altitudes. The only recent immigrant population currently being intensively investigated is in Ethiopia where studies are under way with British IBP endorsement. These studies are disclosing a number of differences from more permanent high altitude groups but because of the major genetic and environmental differences between Ethiopia and other high altitude areas, it seems unsafe to generalize these findings until comparative data are available on other immigrant groups.

A beginning has been made toward defining the genetic characteristics of high altitude men and it appears that the Andean native is unique. It was suggested by one investigator that long term populations in the Andes have partially lost genetic resistance to infectious disease. However, it was agreed that a major problem at this time is to discover whether the physiological and morphological uniqueness of high altitude populations has a genetic base. No studies of this nature exist except as based on population comparisons.

The biological fertility of the high altitude native is probably somewhat impaired in spite of relatively high reproduction rates. This is suggested by the facts that: (1) Puberty is reported to be two to four years later in

high altitude populations than in comparable groups at low altitudes. This has been reported for three Andean groups and one from the Tien Shan mountains in Russia. These findings should mean a shorter time of pregnancy risk for these women if menopause is not delayed and indeed the available data do suggest a late first pregnancy considering the mating structure. (2) A high placenta to newborn weight has been reported in natives at altitude and this may produce increased pre and neonatal mortality, a suggestion which remains only partially confirmed.

After birth, the high altitude native clearly follows a different pattern of development. It is reported that physical growth is slower, chests grow larger, and the types of both congenital defects and infectious diseases encountered are different from lowland groups. In all cases, it is probably not safe to identify the specific environmental or genetic factors involved, but at this stage of investigation, hypoxia appears to be a primary factor in most of the differences. It was even reported that hypoxia may slow psychomotor development in the Andean Indian. While this was disputed, psychologists at the conference were optimistic that methods for testing potential differences in psychological characteristics can be devised. Reports on the sensory motor effects of short term hypoxia clearly indicate the need for more studies of this nature. In one paper it was suggested that the effects of hypoxia and ageing were similar on psychophysiological measures. This was one of many suggestions which induced the conferees to recommend strongly the study of ageing at altitude.

In summary discussions, the human biologists at the meeting agreed that although knowledge was at this moment

quite sparse, the available data indicate that in general altitude probably had as dramatic effect on human populations as originally suspected, and therefore remains a very promising direction for research concerned with human adaptive mechanisms.

Health Aspects of Altitude. The medical problems encountered at high altitude are in many aspects unique. Thus there are diseases which are altitude specific and the environmental effects appear to structure disease manifestations so that diseases common in lowland areas are often rare while the rarer problems at sea level are sometimes common at altitude. There also exist some unique therapy problems particularly in surgery and in the use of drugs.

Despite a high degree of individual and exposure variation almost all individuals display some symptoms of altitude sickness when rapidly introduced to altitudes of 4000 meters or above. These symptoms include headache, lassitude, difficulty with sleep and numerous minor complaints. A variety of studies indicated that the degree of physical fitness and the use of some drugs may modify the development of symptoms and certainly slows or prevents some of the physiological changes common to individuals rapidly ascending to high elevations. However, the most effective method of preventing symptoms is a transitional exposure of one to three days at an intermediate altitude of 2500-3300 meters before proceeding to higher elevations.

In a small percentage of cases, the temporary symptoms develop into a more serious situation of progressive pulmonary edema or acute mountain sickness. Among high altitude natives who are returning from low altitudes this response is most common in young adolescents and for all

individuals it is a more likely response if extreme exercise is undertaken within a short time after reaching altitude. Several studies suggested that it is directly related to the pulmonary hypertension common at altitude but there was also the suggestion that a rise in fibrinogen may be the precipitating factor. The theories of treatment include diuretic drugs and oxygen administration, but the majority of cases show spontaneous remission with bed rest.

High altitude Andean natives also suffer the problems of the lowlander if they go to low altitude for an extended period of time and then return. In addition, some develop chronic mountain sickness or Monge's disease which resembles in its hemotological, pulmonary and cardio-vascular syndrome a condition similar to that seen in extremely obese individuals at low altitude. As might be expected the major diseases among natives are bronchio-pulmonary and prognosis is generally poorer than at sea level. However, surgical intervention is usually successful provided that there is careful attention to the greater tendency for bleeding and the fact that sedatives and anesthetic procedures must be adjusted to the normal hypoxic conditions of altitude. Occupational diseases such as silicosis appear to have an earlier onset and there may be some differences in nutritional responses particularly in glucose disappearance rates.

At this time perhaps the most interesting finding is in the area of cardio-vascular disease. Congenital cardiopathologies particularly <u>patent ductus arteriosus</u> show a well documented rise with altitude such that the incidence of the <u>patent ductus arteriosus</u> is probably ten times as great at 4000 meters as at sea level. On the other hand, cardiovascular disease in the adult is extremely rare. Reports from the

Cerro de Pasco region indicated a total absence of arterio-sclerotic obstructions in the vessels and no cases of aneurisms. They also report phlebothrombosis and myocardial infarction to be extremely rare. A number of studies have now reported that systemic blood pressure is low in high altitude natives and almost never reaches hypertensive levels in older individuals. There is even one study which suggests that systemic blood pressures gradually fall in individuals who migrate from low to high altitudes. As previously cited, some animal studies suggest that the lack of old age cardio-vascular disease at altitude may be directly associated with chronic hypoxia.

In summary discussions it was emphasized that only some of the findings on Andean natives were common to all high altitude peoples and since high altitude health presented so many unique problems, a coordination of research using common methods is highly desirable.

In this brief summary of such an extensive conference I have only touched on those points of information which were striking to me as a participant. Doubtless other participants would have selected other aspects of the deliberations to stress. This will be corrected since publication of the papers presented and other results of the conference is in process.

Research Needs on Man at High Altitude. Aside from a review of knowledge on the topic, a second major conference goal was to develop a prospectus for the most promising research in the topic. To accomplish this goal, the conferees were divided into three groups, each of which developed a document describing the research needs in their area. These documents were then reviewed and amended by the entire group of conferees before final approval. This is rather an extensive document but I feel it would be highly presumptuous of me to try to select from it. The complete prospectus is, therefore,

appended to this report. As can be seen, the quantity of research recommended is quite extensive and beyond the ability of any single organization to support. Fortunately for the future of high altitude research no such requirement exists since the subject matter crosses the boundaries of basic and applied research, the boundaries of countries and encompasses a multiplicity of scientific disciplines.

For the purpose of IBP endorsement a research program must be concerned with populations, must be international in character and must relate to a pressing problem in human adaptability. A great percentage of the research proposed for high altitude fulfills these criteria and indeed many of the ongoing research programs are part of the present International Biological Programme. I am sorry to say that such endorsement does not always mean financial support.

Another portion of support will be derived from countries where altitude constitutes a significant health problem and the World Health Organization has recently also begun research support in this topic. All this might be considered an adequate level of support if the research proposed was likely to produce results significant only to that small percentage of humanity which resides or will visit high altitudes. However, I believe this conference made it clear that a thorough knowledge of what happens and has happened to men at high altitude may be of vast importance in health related problems of world wide significance.

For these reasons I believe the Pan American Health Organization should maintain a high level of interest in the area. It will not, I think, be disputed that there are more scientists who are skilled and interested in high altitude man to be found in the Americas than in the rest of the world and without in any way depreciating the great importance of the comparative work underway and planned in the rest of the world,

I believe that much of the sophisticated and extensive research called for must be done in the Americas. Finally I would like to note that with the increasing geographic mobility of men and with the changes occuring in some of the populations needed for study, there is some urgency about the research needs on high altitude populations.

Research Prospectus Prepared by Conference Participants

1. Physiological Adaptation and Acclimatization to Altitude

Introduction

Several studies have indicated that there are important differences in a variety of structural and functional characteristics among people who can be identified as: 1) highlanders for many generations, 2) lowlanders acclimatized to altitude, 3) new arrivals at altitude, 4) highlanders acclimatized to sea level, and 5) lowlanders.

It is not clear what these differences mean. We do not know, for example, whether these differences reflect simple adaptations to a new environment, or are the result of selective adaptive processes, or even, in some instances are detrimental to the individual.

For the more than 25 million people who now live at high altitude, and for those who will move there, the most important area of altitude physiology is that which has to do with natural and acquired acclimatization. Study of these processes should direct particular attention to the functional adaptation of people of both sexes, of all ages and of those living under different working conditions.

Of lesser importance to human populations as a whole is the study of the acute adaptive mechanisms which are of concern to the much smaller groups of people moving between high and low altitude and for whom residence at high altitude is usually brief.

a. Physiology of Exercise and Work Capacity at Altitude

There are, at present, a number of human populations at various levels of altitude who for many generations have lived and worked while exposed to low levels of ambient O_2 content, although they have not necessarily been exposed to continued tissue hypoxia. The physical performance capacity of these populations is not adequately established.

Studies were suggested on:

1) The basic work capacity of highlanders
2) The maximum oxygen consumption of altitude populations
3) The metabolic response to work in various highlander populations
4) The effect of age and sex on work capacity in altitude populations
5) The relationship between heart rate and oxygen consumption in indigenous highlanders.

b. Altitude Limits for Acclimatization

There is a need to specify altitude tolerance limits for humans and other animal species. The temporal maintenance of normal functional integrity of organ systems, behavioural activity, and physical and mental performance should be evaluated.

c. Environmental Factors

Studies are needed to determine the significance of environmental factors other than hypoxia in altitude acclimatization such as the climatic conditions and the socio-economic environment.

d. Respiration

An important adaptation of the resident to altitude, which is different from the lowlander, is his pulmonary ventilatory response to different concentrations of both O_2 and CO_2

in the air he breathes. The native highlander is relatively less sensitive to low levels of O_2 in alveolar air than is the lowlander. It is not clear whether this decrease in the native highlander in sensitivity to breathing low concentrations of O_2 is an advantage or a disadvantage at altitude.

Analysis of the important adaptive respiratory process should include study of: age and sex differences, neurological factors, acid-base factors, chemoreceptor sensitivity and thresholds, as well as tissue responses to hypoxia. In addition it would be of importance to study regulation of ventilation during the performance of physical work at altitude and during sleep. Apnea and associated periodic hypoventilation as well as performance of hard exercise, increase hypoxic exposure.

e. Circulatory Mechanisms of Altitude Acclimatization

Although circulatory responses in man at altitude have received more study than other physiological responses we do not know the criteria upon which we could advise healthy people whether they should or should not live at high altitude, or at what stage of morphological or functional alterations they should move to low altitude. The following areas of investigation are of importance to answer this problem.

A) Epidemiology - Much needs to be known about the prevalence and incidence of cardiovascular disease at altitude. Ecological factors other than altitude should be identified which affect normal cardiac function in highlanders. In addition we do not know the circulatory response to physical work at different ages.

B) Cardiac Muscle Metabolism - The basic inability of cardiac muscle to work under anaerobic conditions makes it vulnerable to hypoxia induced by high work loads at altitude. Before optimal and maximal levels for work at

altitude could be recommended further studies are necessary on coronary blood flow and cardiac muscle metabolism during work and rest at altitude.

C) Microcirculation - Whether increased capillarity and anastomotic vascularity in cardiac or skeletal muscle is an anatomical feature of the acclimatization process needs further study. The possible role of changes in the microcirculation in the development of chronic mountain sickness has not been determined.

D) Pulmonary Hypertension - Longitudinal observations are needed in highlanders who develop pulmonary hypertension and right heart hypertrophy. Control measurements are needed that cover both sexes and a wide age range. Special study is needed of the factors which lead to high altitude pulmonary edema.

E) Circulation Dynamics - More information is needed on the expected changes in cardiac dynamics at altitude. Included under this heading are observations on cardiac output, cardiac work, peripheral resistance heart rate, stroke volume, blood pressure as well as the role of changes in blood volume, hematocrit levels and pulmonary circulation. Partitioning of blood flow through vital organs under various conditions at altitude is also an important area to be studied.

f. Cellular and Tissue Mechanism of Altitude Acclimatization

The biochemical mechanisms underlying high altitude acclimatization are inadequately understood. Respiratory and vascular adaptations to altitude which permit an adequate delivery of O_2 and removal of metabolites at the cellular level during rest may not be adequate for sustained hard work by healthy men, or for that matter, sedentary life in the elderly and infirm. There is a need to determine the adaptive processes at the cellular level in the highlander

as well as in newcomers to altitude.

We need to know what role is played in these cellular responses by changes in the amount of myoglobin, the number of mitochondria and the capacity of the cytochrom and electron transporting system. More information is needed on possible adaptive increases in ensymes favouring both aerobic and anaerobic metabolism. We need to know the degree to which rate-limiting neurohumoral-endocrine mediators affect these cellular functions. And finally we need to know whether genetic factors are operative in the adaptation at the cellular and subcellular level.

g. Other Areas of Altitude Physiology Requiring Further Study

It became apparent that the knowledge available is inadequate concerning nutritional requirements of those with natural or acquired acclimatization or in those acutely exposed to altitude. Further nutritional and metabolic studies are necessary to establish optimal nutritional allowance for high altitude residents and for those who wish to reside at altitude.

The factors regulating redistribution of fluid and electrolytes among the various fluid compartments need further elaboration.

In the long-time resident at altitude we need to know more about the possible role of adaptive tissue and vascular responses in the ageing process. It is also possible that high altitude residence has an effect on man's immunological responses and on the types and frequency of infections that he harbours.

The sequential changes which occur during the period of adaptation of the newcomer to high altitude are poorly understood. Accurate time tables are not available that show rate of adjustment for each organ system including the respiratory, cardiovascular, digestive, endocrine, renal

and neuromuscular systems.

The time course of the de-acclimatization process should also be studied particularly in those who are exposed intermittently to altitude.

The working group suggested that a handbook of physiological values be developed which uses standardized terminology. A collection of data on normal and abnormal biological values for different altitudes is urgently needed.

2. Human Biology at High Altitudes

The working group considered the problems posed by the biology of human populations living at high altitudes. They concluded that as well as characterizing such populations and their adaptations to their particular environments, such studies could also, and equally importantly, be of relevance to many fundamental problems of human biology in general.

It seems appropriate to present the recommendations for these two approaches separately, although in practice the methods used and observations made will be closely similar.

a. The Characterization of High Altitude Populations

It was agreed to recommend that using compositive methods of approach and standardised procedures, information could be obtained in the following categories:

A) Fertility and the Components of Fertility i) By demographic methods; ii) Using methods in the reproductive physiology of man and of animals which could be applied to human population studies.

B) Growth, Development and Ageing i) Age changes and variability in characteristics thought to be of adatpive value at high altitude; ii) Age changes and variability in characteristics related to the somatic fitness of

individuals; iii) Such studies should not be divorced from the psychological and intellectual changes which occur during development.

C) Nutrition In all cases the nutritional assessment of the populations studied should be made in as detailed a manner as possible, commensurate with the resources available. Such assessments should include i) The nutritional status of individuals; ii) Detailed nutritional surveys, where possible; iii) Biochemical studies related to nutrition.

D) Special Problems Relating to Work Capacity Both physiological and psychological methods should be used.

E) Epidemiology i) In all cases the pattern of disease distribution in populations should be studied. Where additional demographic information is available it is highly important that more vigorous epidemiological studies should be made; ii) It is of great importance that demographic methods should be developed which would enable the relationships between age, disease and morbidity to be ascertained.

F) Genetics Further information is required on: i) The distribution of polymorphic systems in high altitude populations; ii) The hereditability of quantitatively varying traits, particularly those presumed to be adaptive in nature; iii) Congenital defects, especially those presumed to have a genetic component.

G) General In all these studies the following are essential: i) There is as precise as possible an analysis of all biological and physical aspects of the environment; ii) Adequate precautions must be taken to ensure statistical representation and control situations. This will often mean the study of lowland populations. iii) The demographic background of the populations under study must be ascertained in as great a detail as possible.

b. Altitude Studies in General Human Biology

It was unanimously agreed that the ecological situations of high altitude populations often afford unique opportunities for the study of fundamental human biology. In particular the following problem areas can be ideally investigation.

A) Developmental Flexibility The determination of the magnitude and biological significance of normal environmentally induced responses.

B) The Genetic Structure of Human Populations - Especially as seen in isolated groups, where it may be presumed that factors such as genetic drift may be operative. Problems involving gene flow and the effects of selective migration may also be encompassed.

C) Natural Selection Of the variety of ways by which the problem of the detection of natural selection may be approached, it was thought that particular attention should be devoted to the analysis of the comparative fertility and mortality of different phenotypes and, where possible, genotypes. Such investigations could be made most appropriately in both stable high altitude populations and in those which have recently changed their altitude.

D) General This deals with fundamental problems of human biology and is in conflict with the objectives of categorising the biology of high altitude population, as discussed in (a). However, it demands a large-scale multi-disciplinary approach in selected areas, in which the various characteristics itemized in (a) are measured on the same subjects.

3. Health Aspects of Altitude

a. Ischemic Heart Disease at High Altitude

There is evidence that the incidence of ischemic heart disease in high altitude populations is lower than at sea level. Experimental studies indicated increased resistance to myocardial necrosis in altitude acclimatized animals. A controlled epidemiological study of the incidence of ischemic heart disease in high altitude populations will be carried out using suitable sea level controls and standardized techniques of investigation. Risk factors for ischemic heart disease will be evaluated and correlated with necropsy data. Adaptive mechanisms of the heart to high altitude pertinent to acute cardiac necrosis will be examined in experimental animals. Careful investigative techniques of population analysis will be employed and, depending on initial results, preventive trials may be initiated.

b. Development of Prognostic Tests for Altitude Sickness

It is important to be able to identify individuals who are likely to develop acute or chronic mountain sickness or high altitude pulmonary edema. Simple laboratory methods for determining the sensitivity of the carotid body and respiratory responses to various stimuli including hypoxia should be devised. Other screening tests should be avaluated on sea level subjects who will later be exposed to high altitude.

c. Epidemiology, Therapy and Prevention of High Altitude Pulmonary Edema

By means of questionnaires and interviews the importance of factors such as re-ascent, length of stay at sea level and slow ascent upon the occurrence of HAPE will be assessed. Field trials of prophylactic drugs using a double blind technique will be carried out preferably in troops. In selected patients during the acute stage the hemodynamic

effect of selected drugs will be investigated. Ventilation-perfusion characteristics will be examined sequentially in the acute stage and during recovery.

d. Congenital Malformations of the Newborn at High Altitude

Preliminary studies have shown that the incidence of congenital abnormalities of the heart and other structures is increased at high altitude. Whether this is a genetic abnormality or due to maternal hypoxia at a critical stage of fetal development is not known. Since maternal hypoxia can be prevented or minimized, studies at high altitude are indicated. By employing a standard, highly objective method of examination in a prospective study of newborn infants and school children at selected levels of altitude in different countries the causative factors can be evaluated. Countries to be included are those where the appropriate facilities are available. The administration of oxygen to newborns should be carried out at high altitude with suitable controls to determine its late effect on the incidence of PDA and the cardiovascular system.

e. Preparation of a Book on High Altitude Medicine

Despite the fact that over 25 million people live at altitudes of over 3,000 meters no information regarding special medical problems at high altitude is available. The following subjects should be presented by a selected group of physicians specialists who are experienced in high altitude medicine. 1) High altitude diseases such as acute and chronic mountain sickness and high altitude pulmonary edema. 2) Modification by high altitude of diseases which are common at sea level such as pneumonia, coronary disease and shock. 3) Action of drugs and anaesthetics that are modified by high altitude such as opiates and anaesthetics. 4) Occupational diseases at high altitudes. The book

should be organized by a single editor. It should be small condensed and highly selective with a bibliography. It should be designed for frequent revision. The emphasis should be on clinical medicine rather than physiology.

f. Evaluation of the Effect of Pulmonary and Cardiac Disease upon Cardio-respiratory Function at High Altitude

Pulmonary function and hemodynamic studies should be carried out in high altitude residents with silicosis, stanniosis and following pneumonectomy. The working capacity of such patients should be evaluated by appropriate methods. Techniques of early detection of industrial pulmonary disease at high altitude should be evaluated and applied to workers.

g. Factors Affecting Biliary Cholelithiasis in Native Highlanders

Cholesterol stones are commonly observed at high altitude with probably a different sex incidence than usually observed at sea level. Since this is an important cause of illness the causative factors should be studies. The study should include an investigation of dietary habits and serum lipids of patients with proven cholelithiasis compared to control subjects living in the same area with normal cholecystograms.

h. Drug Action at Different Altitudes

Drug action is probably significantly modified in the hypoxic high altitude environment. Toxicity may be enhanced or diminished and the therapeutic effect may be altered. Studies should be made and known information collected regarding the effect of selected drugs at various altitudes in the world. Drugs such as narcotics, anesthetics, analgesics, opiates, pressor drugs and cardiac glycosides should be investigated.

i. Vital Statistics in Relation to Altitude

Vital statistics of WHO are arranged for countries according to many categories such as geographical location

but information regarding the incidence of diseases or deaths is not arranged according to altitude. Such information is necessary in order to determine the effect of altitude upon the incidence of disease and mortality and efforts should be made to collect this information from countries contributing vital statistics to WHO.

j. Functional and Intellectual Correlates of Altitude Hypoxia in Children.

It is important to determine if the development and function of the central nervous system is adversely affected by the chronic hypoxia of high altitude. Suitable physiologic tests should be developed to quickly determine the degree of chronic hypoxia in children. Tests of central nervous system functions that could be affected by chronic hypoxia should be designed that would be suitable for field studies. A planning conference should be arranged with the appropriate specialists to develop an effective protocol. Field studies should then be made in Peru and other high altitude areas on a trial basis. If preliminary results justify continued study on a broader scale this should be carried out.