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ADVISORY COMMITTEE ON MEDICAL RESEARCH

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Item 23.2 of the Agenda

REPORT OF THE WHO/PAHO/IBP MEETING OF INVESTIGATORS ON POPULATION BIOLOGY OF ALTITUDE

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PAN AMERICAN HEALTH ORGANIZATION
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Washington, D.C.

REPORT OF THE WHO/PAHO/IBP MEETING OF INVESTIGATORS ON POPULATION BIOLOGY OF ALTITUDE

Washington, D.C., USA
13-17 November 1967

Contents

FOREWORD

The WHO/PAHO/IBP Meeting of Investigators on Population Biology of Altitude was held in Washington, D.C., at the Headquarters of PAHO, from 13-17 November 1967.

The meeting was opened by Dr A. Horwitz, Director of PAHO. In his opening address Dr Horwitz directed attention to the multidisciplinary nature of this meeting and emphasized the importance of synthetizing the knowledge on altitude adaptation already available in the different branches of science. Man has to be studied as a whole, as a complex biological and social entity. Knowledge about the mechanism of interaction between man and his environment is necessary to understand the pathogenesis of disease so as to improve preventive and curative techniques.

Dr Fejfar and Professor Baker emphasized in their introductory remarks the contribution of altitude research to knowledge in human biology and also to solving medical problems of general significance.

The 50 participants (see p. 32 of this report) discussed the 30 working papers which had been prepared and which were presented by their respective authors (see Agenda p. IV) during the first two days and on the morning of the third day.

The papers were divided into 4 topics as follows:-

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

The Chairman for the first two topics was Dr Hurtado, for the third Dr Andersen and for the fourth Dr Severinghaus.

The Rapporteur for the first two topics was Dr Buskirk, for the third Dr Harrison and for the fourth Dr Hultgren.

A panel discussion on altitude research facilities and available population samples was the next item on the Agenda. Dr Grover was the Moderator and he asked the participants to present a short report about

their laboratories and subject material. The reports were received with great interest and a recommendation was accepted as to establishing a centre for information on altitude research in relation to man where this information could be compiled, up-dated and made available to scientists (see p. 30).

On the afternoon of the third day the participants were divided into three working groups (see p. 31) to identify needs and opportunities for future research with particular emphasis on topics where multinational collaboration is desirable.

The first working group dealt with physiological adaptation and acclimatization to altitude and was moderated by Dr Buskirk. The second working group dealt with human biology of altitude populations and was moderated by Dr Harrison. The third working group dealt with health aspects of altitude and was moderated by Dr Hultgren.

One member of the Secretariat was delegated as adviser to each working group (see p. 31).

On the last day the Rapporteurs presented their session reports and the research recommendations of their working groups to the plenum. The reports of topics 3 and 4 and the research recommendations of working groups 2 and 3 were accepted after minor modifications. The report of the first two topics and the research recommendations of working group 3 had to be redrafted. The new draft report and research recommendations were subsequently submitted to the participants for comment and approval by mail. The report on topics 1 and 2 and the research recommendations of working group 3 are now finalised on the basis of the comments obtained.

WHO/PAHO/IBP MEETING OF INVESTIGATORS
ON POPULATION BIOLOGY OF ALTITUDE

Headquarters Building
Conference Room B
Pan American Health Organization
525 Twenty-third Street, N.W.
Washington, D.C.

13-17 November 1967

A G E N D A

Monday
13 November

9:30 a.m. Opening address - A. Horwitz

Selection of Chairman, Vice-Chairman and Rapporteurs

Orientation remarks -

For WHO: Z. Pejfar

For IBP: P. Baker

Topic 1. GENERAL ASPECTS OF ALTITUDE BIOLOGY

10:00 1.1 The demography of high altitude populations - G.F. De Jong: 15 mins.

1.2 The incorporation of the concept of biometeorology into high altitude medicine - W.H. Weihe: 15 mins.

Discussion, 5 mins. maximum per person.

10:45 C o f f e e

Topic 2. PHYSIOLOGICAL ADAPTATION AND ACCLIMATIZATION TO ALTITUDE

11:00 2.1 Natural acclimatization to altitude - A. Hurtado 30 mins.

2.2 Acquired acclimatization to sea level - T. Velasquez: 30 mins.

Discussion, 5 mins. maximum per person.

Monday
15 November (cont'd)

12:30 p.m. — L u n c h

2:00 — 2.3 Muscular exercise at altitude - R. Margaria: 15 mins.

2.4 Physical performance capacity at altitude - K.L. Andersen: 15 mins.

2.5 Problems of aging at altitude - R.A. McFarland: 15 mins.

2.6 Some pressing issues in psychophysiological research at high altitudes - D.B. Harris: 15 mins.

Discussion, 5 mins. maximum per person.

3:30 — C o f f e e

3:45 — 2.7 Respiratory regulation in man with lifetime hypoxia - S. Lahiri: 15 mins.

2.8 Respiratory function and aging in native high altitude Ethiopians - G.A. Harrison: 15 mins.

2.9 Nutritional aspects of sea level natives during acute exposure to high altitudes - F. Consolazio: 15 mins.

2.10 The food requirements of high altitude Peruvian natives - E. Picón Reátegui: 15 mins.

Discussion, 5 mins. maximum per person.

Tuesday
16 November

Topic 3. HUMAN BIOLOGY OF ALTITUDE POPULATIONS

9:00 a.m. — 3.1 Comparisons between high and low altitude populations in Ethiopia - E.J. Clegg: 15 mins.

3.2 Genetic characteristics of high altitude populations in Chile - R. Cruz-Coke: 15 mins.

Tuesday
14 November (cont'd)

3.3 Observations on the indigenes of the Bolivian Andean region - J.A. Vellard: 15 mins.

3.4 The high altitude resident of North America - R. Grover: 15 mins.

Discussion, 5 mins. maximum per person.

10:30 Coffee

10:45 3.5 Hemotypological study of Amerindian populations of the Amazonian forest and the Andes' high plateaus - E. Carles-Trochain: 15 mins.

3.6 Fertility at high altitudes - L. Sobrevilla: 15 mins.

3.7 Peculiarities of vegetative functions and somatic development of the aborigines children in the altitudes of Tjan-Shan - M.T. Turusbekov: 15 mins.

3.8 Lactation in the goat during chronic discontinuous hypoxia - Stickney: 15 mins.

Discussion, 5 mins. maximum per person

12:30 p.m. Lunch

Topic 4. HEALTH ASPECTS OF ALTITUDE

2:00 p.m. 4.1 Medical problems during short exposure to high elevations - J.T. Hansen: 15 mins.

4.2 Studies of high altitude physiology and pathology in Tjan-Shan and Pamirs - M.M. Mirrakhimov: 15 mins.

4.3 Clinical problems at high altitude - I. Singh: 15 mins.

4.4 Health problems at altitude - K. Hallriegel: 15 mins.

Discussion, 5 mins. maximum per person

3:30 Coffee

3:45 4.5 Congenital cardiac malformations in high altitude populations - J. Espino Vela: 15 mins.

Tuesday
14 November (cont'd)

4:00

4.6 Cardiopulmonary studies in acute and chronic mountain sickness - D. Penaloza: 15 mins.

4.7 Cardiopulmonary pathology at high altitude - E. Marticorena: 15 mins.

4.8 High altitude and acute cardiac necrosis: an analysis of an epidemiological model - O. Poupa: 15 mins.

Discussion, 5 mins. maximum per person.

Wednesday
15 November

9:00 a.m.

4.9 Irreversible ventilatory sensitivity to hypoxia in high altitude natives - J.W. Severinghaus: 15 mins.

4.10 Pathophysiology of high altitude miner populations - H. Salguero-Silva: 15 mins.

4.11 Abnormal responses to high altitude - H.N. Hultgren: 15 mins.

4.12 Mountain sickness in fit and sedentary subjects exposed to high altitude - C.B. Favour: 15 mins.

Discussion, 15 mins. maximum per person.

10:30 C o f f e e

10:45 Panel Discussion

High altitude research in human populations: opportunities, research facilities, available population samples and outline of proposed studies.

(10 mins. maximum per person)

12:30 p.m. L u n c h

2:00 Panel Discussion (cont'd).

Thursday
16 November

9:000a.m.-
5:00 p.m. Group Discussions

Working Group I. Physiological adaptation and acclimatization to altitude

Working Group II. Human biology of altitude populations

Working Group III. Health aspects of altitude

Working Groups meet concurrently to identify needs and opportunities for multinational collaborative research, to define population samples and methods and to suggest ways for improving research communication and coordination.

Friday
17 November

9:00 a.m.-
12:30 p.m. Final Session

Concurrent meetings of (a) Rapporteurs and Moderators to write reports and of (b) Subgroups to plan international collaborative research for IBP/PAHO/WHO endorsement.

12:30 p.m. L u n c h

2:00 Review and approval of reports.

5:00 Closure of the Meeting.

WHO/PAHO/IBP MEETING OF INVESTIGATORS ON POPULATION BIOLOGY OF ALTITUDE

Washington, 13-17 November 1967

A. REPORT OF THE PLENARY SESSIONS

1. Physiological Adaptation and Acclimatization to Altitude

People born at a high altitude can be referred to as being naturally acclimatized. According to the evidence presented the native highlanders have a degree of tolerance to the altitude environment not found in those not born there, even though the latter may have resided at altitude for extended time periods. A study of skeletal remains indicates that man has lived in the Peruvian Andes for at least 9,000 years.

Physiological factors associated with O_2 transport from the ambient air to the tissues were discussed, particularly as they affect residents at altitude. It was pointed out that the slope of the O_2 gradient from alveolar air to tissue is reduced at altitude. Compensatory mechanisms operate to ensure adequate supply of O_2 to the tissues. The relationship between these compensatory mechanisms are only partially known, particularly at the cellular level.

Data were presented on populations naturally acclimatized at altitude who then moved to sea level, either temporarily or permanently. The available evidence indicates that these people retain a characteristic physiological identity, no matter where they reside thereafter. There

may be analogous affliction to chronic mountain sickness, namely chronic sea level sickness; this, however, is speculative.

Chronic mountain sickness, reported in South American mountain dwellers, has not been observed in Indian soldiers or in Sherpas of the Himalayas. Regression of altitude induced changes after return to sea level were different in the Indian soldiers than in the Andean dwellers. Right ventricular hypertrophy and central blood volume were reduced and arterial saturation increased as expected, but these changes took up to twenty weeks to be complete in the Indian soldiers. Only persistence of right ventricular hypertrophy was reported in Andean residents moving to sea level whereas arterial saturation returned to normal sea level values within two weeks.

Elevation in pulmonary arterial pressure occurs upon ascent to altitude and persists during the time spent at altitude. Pulmonary arterial pressure is also elevated over sea level values in high altitude dwellers. Administration of O_2 as well as movement to sea level causes prompt reduction of these pressures; however, the mechanisms responsible are unknown.

Maximal work capacity at altitude is limited, as evidenced by a reduced maximal O_2 intake. Less intensive efforts, even though prolonged, do not appear impaired. Delivery of O_2 to tissues during performance of hard work involves many factors. However, the limiting factors remain obscure. More information is required on such questions as diffusion of O_2 at various levels of O_2 transport, the relationship

of the elevated hematocrit to pulmonary and peripheral perfusion, alterations in stroke volume, increased capillarization of tissues, and oxidative processes at the tissue level. Little is known about work performance capabilities of women, children and the aged. Information on nutritional state, physical fitness, and existence of pathology is needed in order to interpret observed work performance. It was emphasized that, in studying exercise capacity in people at various altitudes, comparable methodology be used in order to achieve a valid comparison between different population groups.

The effects of hypoxia on the nervous system are poorly understood. Despite the fact that O_2 consumption of the brain remains constant when arterial O_2 content varies, it is possible that changes in arterial PO_2 may produce subtle changes in the responses of the central nervous system. There are practically no methods for detecting suspected impairment although changes in light perception and in dark adaptation may provide important clues. Psychological evaluation of indigenous populations and newcomers to altitude is possible if appropriate tests are developed.

Alterations in diet, especially with elevated carbohydrate content, have been suggested as possibly beneficial in the acclimatization process and for relief of acute mountain sickness, but confirmation is required. Similarly vitamin requirements may be different at altitude but this has not proven satisfactory either.

The question of regulation of fluid balance was raised, particularly of those ascending to or returning from altitude. The redistribution of fluid and electrolites among the various fluid compartments seems to play an important role in acclimatization to altitude but the underlying mechanism is unknown.

Experimental results were presented which suggest that the sensitivity of the respiratory chemoreceptors to hypoxia is diminished in indigenous populations of the Andes and in Sherpas of the Himalayas. However, it is not clear whether the diminished respiratory response to low O_2 tension is common to all residents at high altitudes and what the meaning might be of this apparent loss of sensitivity, i.e. does it reflect adaptation or deterioration. Similarly, related ventilatory drive mechanisms during rest and work at altitude are not satisfactorily understood.

The importance of biometeorology in the physiological and clinical investigations at high altitude was emphasized. The group felt that in many investigations the environment has been incompletely described. This may partly be due to lack of suitable equipment for recording of meteorological parameters under extreme conditions of high altitude. There was enough recognition of the fact that the effective factor at altitude is not only the reduced partial pressure of oxygen but the entire physical environment characterized by meteorological and biometeorological parameters.

2. Human Biology of Altitude Populations

In this session attention was focussed on some of the current research which is in progress on problems of human variation in native high altitude populations, especially that concerned with genetics, physiology, developmental flexibility, fertility, growth and ageing. It was widely appreciated that much of this work is not only important to the study of altitude per se but has relevance to general aspects of human adaptability. In a number of ways variations in altitudinal environments afford favourable circumstances for studying the interaction between environmental and genetic factors in the development of human phenotypes.

By means of studies in Ethiopia, where populations at high and low altitude are contiguous, it has proved possible to control for genetic variety, and demonstrate that environmental variation in altitude can produce directly, even in adult subjects, not only marked physiological differences but also many morphological changes as well.

There are now considerable data available on the physical characteristics of Andean populations. Some of these populations which are exposed to unique conditions of altitude stress afford excellent opportunities for human biology investigations. Furthermore, the genetic structure of these populations often provide favourable circumstances for analyzing the interaction between various evolutionary forces, such as gene flow, genetic drift and natural selection.

The problems of recognizing such selective forces in altitude populations are many. One of the crucial concerns is the determination of the extent to which genetic variety accounts for apparent differences between populations in their physiological responses to altitude. Within the known genetic marker systems there does not appear to be a constant association with altitude. It is presumed that other ecological variables and historical factors account for the heterogeneity in these marker systems. When data are available on the heritability of the physiological components of altitude adaptation, it should become possible to analyze in real terms the role of natural selection, and genetic factors in determining the biology of high altitude populations.

Demography forms the basis for studies on human population biology concerned with genetics, development, and physiology. Too little is known, however, about the demographic structure of most high altitude populations. Populations which have received the most study are in certain mountain communities at temperate latitudes. In the Andes work has begun in measuring fertility and mortality rates. Already promising studies of the effects of high altitude on reproductive physiology are underway. The evidence from the Andes indicates that among indigenous populations fecundity is not impaired by altitude; but the comparatively high levels of pre- and post-natal mortality raise important practical and theoretical problems. It cannot be doubted that further study of the causes of this mortality, and also of the distinctive growth and

developmental patterns that characterize all high altitude populations should be rewarding.

There is also clear evidence that studies of ageing in high altitude populations are deserving of attention, not only for their own intrinsic interest but also because these studies may help to elucidate more general problems in gerontology. Such, however, is the dearth of demographic information for altitude that little is known about life expectancy and longevity in most high altitude populations where non-literate societies are of little help in determining the age of subjects. These latter difficulties not only handicap demographic studies but also present problems to the physiologist and geneticist.

Since the human population biologist is faced with complicated sociological as well as biological variables in any ecological study, it can be strongly argued that parallel animal experimentation is often desirable. The Ethiopian studies on the genetics of man at altitude arose directly from laboratory studies on temperature and barometric pressure effects on the growth and functional development of the mouse. Further study of animals under comparable climatic regimes not only may shed light on components of human adaptability but also may be of practical economic value, especially when such a study is performed with domestic animals.

Of some general importance to all those participating in this session were problems of sampling and the choice of controls. The

human biologist, in his concern with the origin, development and causes of human variability is, by definition, invariably dealing with populations from which he has to make population samples. The dangers of introducing bias into selection procedures were recognized. It was felt that for IBP purposes some detailed review of this problem was urgently required. However, it was also appreciated that there was no categorical answer to this sampling problem. Usually the nature of a sample is dictated by the particular problem under consideration.

3. Health Aspects of Altitude

In this session important new observations were presented regarding clinical and physiologic abnormalities arising as the result of acute and chronic exposure to high altitude as well as the effect of high altitude upon disease states commonly observed at sea level.

Two investigators reported studies of acute mountain sickness in healthy young men subjected to rapid ascent and to heavy exercise at elevations of 11,400 ft. and 14,100 ft. Symptoms were established by questionnaire or clinical observation. Interval acclimatization at an intermediate altitude reduced the incidence and severity of symptoms in both studies. Prior physical conditioning did not reduce the severity of acute mountain sickness but in one study physical performance on the third day of altitude exposure was improved.

Acetazolamide reduced the incidence and severity of symptoms but resting arterial oxygen tension was not significantly altered. Exercise performance was not impaired by acetazolamide administration. It is apparent that the exact mechanism of action of the drug in alleviating symptoms is unknown.

Important clinical problems in troops brought rapidly to altitudes of 14,000 to 18,000 ft. in India were described with particular reference to acute mountain sickness, high altitude pulmonary edema (HAPE) and high altitude pulmonary hypertension. A marked rise in pulmonary blood volume occurred in the first few days at high altitude associated with a decrease in cardiac output, elevation of pulmonary artery pressure and no change in left atrial pressure. The value of diuretics in the prevention and treatment of acute mountain sickness and HAPE was emphasized. Oxygen was frequently found to be ineffective in the treatment of HAPE and may not be accompanied by any significant rise in arterial oxygen saturation. Cerebrovascular accidents may occur as part of the picture of acute mountain sickness but late cerebral angiograms may be normal. Cerebral edema with an elevation of cerebrospinal fluid pressure was frequently encountered. Chronic mountain sickness was not observed even after 2 to 5 years of altitude exposure. Indigenous highlanders of the same area exhibited a high cardiac output, a normal pulmonary vascular resistance and only slight polycythemia. These data are unusual since they are at variance with studies that have been previously

made in the United States and Peru. The reason for this variation should be examined.

The hemodynamic features of 9 patients with chronic mountain sickness studied in Peru were presented. Pulmonary hypertension, arterial unsaturation and marked polycythemia was observed. Filling pressures were normal. Systemic diastolic hypertension was common. Pulmonary artery pressure was rapidly lowered on descent to sea level. Hemodynamic studies have been made in 2 additional patients with HAPE and the increased pulmonary vascular resistance in patent ductus arteriosus at high altitude has been confirmed by hemodynamic studies. To date only a small number of patients with chronic mountain sickness have had complete hemodynamic studies. Further similar studies are needed to understand the abnormal physiology of this important high altitude disease.

An important clue to the cause of chronic mountain sickness was provided by the report of studies comparing the respiratory response to hypoxia in persons born at high altitude and at sea level. Subjects born at high altitude have a diminished response to hypoxia which persists for many years after they move to sea level. Similar persistence of a diminished hypoxic response was observed in sea level children who are born with congenital heart disease which produces hypoxia from birth. Late surgical correction of the cardiac defect does not alter the diminished response. The data, therefore, suggest that this is not a genetic defect despite the

prevalence of this characteristic in the highland resident.

Another paper listed the following clinical abnormalities occurring as the result of acute or chronic exposure to high altitude: 1. Acute mountain sickness. 2. High altitude pulmonary edema. 3. Subacute mountain sickness. 4. High altitude pulmonary hypertension. 5. Chronic mountain polycythemia. 6. Chronic mountain sickness. Current research on HAPE was discussed. Pertinent clinical features which may provide clues regarding etiology were presented and the important hemodynamic characteristics of the syndrome were reviewed. It was shown that an important feature was the elevation of pulmonary artery pressure without a rise in "wedge" pressure. The early stage of HAPE appears to be an elevation of pulmonary arterioler resistance and a disturbance of the pulmonary circulation which results in an increased gradient for oxygen between the alveolus and arterial blood. A possible hemodynamic model of HAPE was suggested in which overperfusion of non-obstructed portions of the pulmonary vascular bed may lead to an elevation of pulmonary capillary pressure and edema production without elevation of pulmonary venous or left atrial pressure. Pulmonary edema in pulmonary embolism may occur under similar circumstances. It is clear that further field studies of the epidemiology of HAPE are needed since it is an important health hazard to troops and travellers to high altitude. An animal model is urgently needed to permit informative experiments.

Experimental studies of the effect of acclimatization upon the

ability of the heart to tolerate oxygen lack were reported. Acclimatized hearts recovered more rapidly from acute oxygen deficiency and showed less necrosis of the myocardium following injection of isoproterenol than control hearts. Myoglobin was increased. The mechanism of the increased resistance to oxygen lack or ischemia is not clear but increased vascularity or intracellular enzyme changes could be involved. These data are relevant to the low incidence and benign clinical picture of myocardial infarction at high altitude.

A high incidence of patent ductus arteriosus (P.D.A.) and of ventricular and atrial septal defects in school children has been observed at high altitude in Peru. The highest incidence of P.D.A. is seen at the highest altitude. The incidence of various non-cardiac congenital malformations in the newborn infant is higher at high altitude. Further studies of systemic blood pressure at high altitude have been made. Those born at sea level, living for 5 to 15 years at high altitude do not show the usual rise in systolic pressure with advancing age, rather they gradually approach the lower levels seen in high altitude populations. Systemic hypertension in high altitude dwellers is rare. Coronary disease at high altitude is rare and no deaths from myocardial infarction have been observed. Bed rest alone in the treatment of HAPE was found to be accompanied by clinical recovery in 11 consecutive patients indicating that this factor must be considered in the evaluation of any therapy for HAPE. These studies provide further

data demonstrating the striking rarity at high altitude of two of the most common diseases affecting the sea level dweller - high blood pressure and coronary artery disease. Further studies are clearly needed to understand the mechanisms involved.

Medical and surgical observations in a company hospital at 12,200 ft. in the Peruvian Andes were summarized. Surgical closure of patent ductus arteriosus was frequently performed. Wound healing and callus formation appeared to be more rapid than at sea level. Phlebothrombosis and pulmonary embolism were rarely seen. Gastric ulcer was more frequent than duodenal ulcer. Data on gastric analyses are being collected. Volvulus of the intestine causing bowel obstruction is frequent and may be due to a large mesentery. It is suspected that this may be a genetic defect of the gastrointestinal system.

A high incidence of pulmonary hypertension was observed in patent ductus arteriosus and atrial septal defect at a large cardiac institute in Mexico City. Similar observations have previously been made at high altitude in the United States and Peru.

A report from Bolivia described clinical and laboratory studies performed in patients with pulmonary silicosis which is frequently found in miners in that area. Because of the high altitude the characteristics of this disease are different from those observed at sea level.

The observations summarized in this report indicate that a large number of unique health problems occur at high altitude. Many represent common diseases that are found at sea level but which have a different

incidence of variable features at high altitude. Some are unique to high altitude. In some areas of research different results have been obtained by groups of investigators in different parts of the world. Variations in methodology have been used in studies designed to investigate similar problems. International co-ordination of effort is indicated to develop methods of detection, prevention and treatment of high altitude disease. Studies of the mechanisms of modification by high altitude of disease states commonly seen at sea level are needed to provide more information about the pathogenesis of these conditions so that preventive and curative measures can be intelligently employed.

It was also clear from the discussions at this meeting that systematic investigation of several critical health problems should be carried out in several high altitude areas of the world using a similar methodology. Studies in India for example suggest that many of the medical problems encountered there are quite different from those observed in Peru. The assumption that observations made in one high altitude area of the world are applicable to all high altitude regions is equally invalid. This is an important opportunity for international co-operation and collaboration.

B. RESEARCH RECOMMENDATIONS OF WORKING GROUPS

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 adaptative 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 or 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. Sleep 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 enzymes favouring both aerobic and anaerobic metabolism. We need to know the degree to which rate-limiting neuro-humoral-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 should 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 adaptive 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 heritability 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 investigated.

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 evaluated 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 studied. 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.

C. GENERAL RECOMMENDATIONS

1. This meeting demonstrated that co-operation between WHO and IBP-Human Adaptability Section is possible and fruitful. It is hoped that such co-operation will continue and increase in working together on such projects as recommended by this meeting.

2. It was recommended that the proceedings of this meeting should be published in full.

D. RECOMMENDATION FOR A CENTRE FOR INFORMATION ON ALTITUDE RESEARCH IN RELATION TO MAN

In order to facilitate communication and research planning in problems of man's adaptability in relation to altitude, it is agreed that a centre should be established.

This centre should fulfil the following functions:

1. Compile a list of existing research facilities
2. Compile a list of scholars active in altitude research including their specialization and current activities
3. Keep record of active research projects in the pertinent subjects
4. Provide information on request
5. Provide such services as are required for improving communication among scientists in altitude research.

Such a centre should be set up by an international organization such as the WHO and/or IBP.

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