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HIGH ALTITUDE PHYSIOLOGY:
CARDIAC AND RESPIRATORY ASPECTS
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Preface

The subject for this symposium was first suggested to us by Professor Peter Harris, Director of the Institute of Cardiology, London. It seemed that studies on the structure and function of the cardiorespiratory system, particularly work on the chemoreceptors and on myocardial metabolism, at high altitude had now reached the stage at which anatomists, physiologists and clinical investigators working in the subject could usefully meet to discuss their findings. The Ciba Foundation was especially pleased to take up Professor Harris's suggestion because so much of this work had been done by Professor Alberto Hurtado and his group in Peru, and the meeting provided us with the opportunity of honouring his pioneering and continuing work on physiology at high altitude. We were delighted that Professor Hurtado, who has been a member of the Ciba Foundation's Scientific Advisory Panel for many years, and two of his colleagues from Peru, were able to come to the symposium.

We hoped that a Soviet scientist working on high altitude would also be able to participate in this meeting, but unfortunately, in spite of considerable help from the World Health Organization and the International Biological Programme, none of the appropriate scientists in the USSR was able to accept our invitation. We would like to thank Dr Z. Fejfar of WHO and Professor J. Weiner of the IBP for their help in this connexion. We would also like to thank Professor Harris and Dr Philip Hugh-Jones for their help in planning the meeting, the latter for his skilful chairmanship, and Peter Harris, yet again, for help in editing the proceedings which now form this volume.

The value of Professor Hurtado's work was repeatedly demonstrated during the symposium. Over thirty years ago, when he started his research on high altitude physiology, he first formulated many of the questions that are still being worked on today. He has provided some of the answers during the following years, but many of the problems remain for future research.
Nomenclature


\[ P_{O_2} = \text{oxygen pressure} \]
\[ P_{CO_2} = \text{carbon dioxide pressure} \]
\[ P_{A_{O_2}} = \text{alveolar oxygen pressure} \]
\[ P_{A_{CO_2}} = \text{alveolar carbon dioxide pressure} \]
\[ P_{a_{O_2}} = \text{partial pressure of oxygen in arterial blood} \]
\[ P_{a_{CO_2}} = \text{partial pressure of carbon dioxide in arterial blood} \]
\[ P_{I_{O_2}} = \text{pressure of oxygen in inspired gas} \]
\[ \dot{V}_E = \text{expired ventilation per minute} \]
The Ciba Foundation

The Ciba Foundation was opened in 1949 to promote international cooperation in medical and chemical research. It owes its existence to the generosity of CIBA Ltd, Basle (now CIBA-GEIGY Ltd), who, recognizing the obstacles to scientific communication created by war, man's natural secretiveness, disciplinary divisions, academic prejudices, distance, and differences of language, decided to set up a philanthropic institution whose aim would be to overcome such barriers. London was chosen as its site for reasons dictated by the special advantages of English charitable trust law (ensuring the independence of its actions), as well as those of language and geography.

The Foundation's house at 41 Portland Place, London, has become well known to workers in many fields of science. Every year the Foundation organizes six to ten three-day symposia and three or four shorter study groups, all of which are published in book form. Many other scientific meetings are held, organized either by the Foundation or by other groups in need of a meeting place. Accommodation is also provided for scientists visiting London, whether or not they are attending a meeting in the house.

The Foundation's many activities are controlled by a small group of distinguished trustees. Within the general framework of biological science, interpreted in its broadest sense, these activities are well summed up by the motto of the Ciba Foundation: Consocient Gentes—let the peoples come together.
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CHAIRMAN’S INTRODUCTION

P. HUGH-JONES

It is both a pleasure and a privilege to be at this symposium on high altitude physiology, particularly as it is being held in honour of Professor Hurtado, who pioneered so much of the work on high altitude adaptation.

It is now over fifty years since physiologists first described, during the classical expedition in 1913 to Pike’s Peak at about 14,000 feet, how the human body becomes adapted. On this expedition J. S. Haldane, C. G. Douglas, Miss Fitzgerald and others (Douglas et al. 1913; Fitzgerald 1913) were able to show that as they themselves went up to the summit of the mountain the hypoxia progressively stimulated their ventilation so that their alveolar carbon dioxide tension fell, and they demonstrated this effect with remarkable accuracy using quite simple apparatus, but a great deal of ingenuity. After those original observations there was a plethora of work on acute adaptation to altitude but very little work in Europe or the United States about the chronic effects; it is in eliciting these effects of chronic adaptation that Professor Hurtado and his colleagues in Lima have done so much. Most of the now well-known work on the changes in haemoglobin, in electrolytes, and on the effects of giving either additional oxygen or carbon dioxide to natives born at high altitude or others who are permanently resident there, was initiated by him.

Between two extremes of acute and chronic adaptation, Dr Griffith Pugh and others attending this symposium studied the interesting intermediate stage of how one goes from the acute to the chronic phase, on the 1960/61 Himalayan Scientific and Mountaineering Expedition. We meet here now with all this work on altitude adaptation behind us, but with many interesting problems still outstanding. Three main problems are to be discussed: (1) acute pulmonary oedema at altitude; (2) chronic mountain sickness and its effects; and (3) the effects of high altitude on the heart and blood vessels. These three, together with papers on the changes in the anatomy of the lung and on the chemoreceptors, form the basis of this symposium which Dr Peter Harris initiated and for which the Ciba Foundation has provided its excellent facilities.

REFERENCES

A high altitude environment imposes on the human body certain difficulties and limitations in the maintenance and successful coordination of its physiological processes. In such an environment the air density is decreased, the temperature and humidity are low and, if the level of altitude is extreme, there is some increase in radioactivity. But the main factor, and the most studied, is a condition of hypoxia or oxygen deficiency. As a consequence of the reduced barometric pressure, the partial pressure of the oxygen in the inspired air is low and, under these circumstances, the haemoglobin of the blood circulating through the lungs becomes less saturated with this gas. This fact, together with the decreased tension of the fraction physically dissolved in the plasma, makes its diffusion and utilization at tissue level more difficult.

To compensate for these limitations, the human body places in operation a variety of coordinated mechanisms, which have been investigated intensively in recent decades, both in regions at high altitude and in low-pressure chambers. In this regard it is important to note that the simulated altitudes frequently used in chamber observations probably exceed by a large amount the possibilities of tolerance or adaptation by the human body, so it is not justified to interpret the findings in terms of acclimatization. They correspond rather to deterioration. In addition, there is enough evidence to indicate that acclimatization only reaches a useful degree of effectiveness after very prolonged exposure and, even under these circumstances, it is not as complete as that observed in the man born and raised in this environment.

In the Andean region of Peru, the native resident has been under the influence of altitude environmental factors for millenia. P. Cardich, a Peruvian anthropologist, discovered human skeletons in Lauricocha, at 4200 m, which were shown by radioactive carbon studies to be approximately 9500 years old. This implies that the investigation of Andean man corresponds to what has been called 'natural acclimatization', in contrast to 'acquired acclimatization', and his characteristics represent not simply
adaptive processes present since foetal life or birth, but also genetic influences through many generations.

It has also been observed that the physiological characteristics of this native man, whether of a morphological, functional or chemical nature, in spite of some individual variability, have reached a higher degree of the so-called steady state, in comparison to what is found in newcomers, regardless of the length of their exposure. It seems then logical to consider this man as the best source of information on how an altitude environment modifies advantageously physiological characteristics and regulation. In other words, it is justifiable to rate acclimatization in any particular case in terms of similarity to what this native man exhibits, rather than from the point of view of modifications from what was present before exposure.

The adaptive processes which constitute 'natural acclimatization' may be broadly classified into two categories. In the first we may include those processes which act along the $P_O_2$ gradient, from the inspired air to the tissues, introducing an economy in its fall to compensate for the initial low value, and also facilitating the acquisition and transport of oxygen. The other group of processes operates at tissue level, favouring diffusion and utilization of oxygen in cellular metabolic activities. I shall attempt to discuss, very briefly and in sequence, these two series of processes.

The healthy native man at high altitudes hyperventilates, both at rest and during physical activity, and in this way partially compensates for the lower tension of oxygen in the inspired air. This is an almost constant finding, but its mechanism is actually subject to some controversy. We think that the respiratory centre, which regulates the level of pulmonary ventilation, shows an increased sensitivity to chemical stimulation by carbon dioxide in this environment. Experimental administration of carbon dioxide for a given period results in a ventilatory response much greater than at sea level, and the ventilatory response curve is moved to the left. Whether hypoxia is an additional stimulus for the increased ventilation is also a matter of controversy among investigators. In our experience, administration of oxygen does not usually affect ventilation significantly, but if the oxygen tension is experimentally reduced, in relation to the ambient pressure, ventilation increases in most cases. Sleep and body posture modify the ventilatory level.

In the lungs, we have found the $P_O_2$ A-a gradient to be considerably reduced. Probable related factors are the greater size of the alveoli (the residual volume of air is increased), and the dilatation of the alveolar capillaries, both of which facilitate diffusion.

It is interesting to notice that the native of high altitudes shows a moderate degree of pulmonary hypertension, and perhaps this condition produces a
better distribution of the blood in the vascular bed of the lungs. The pulmonary hypertension appears to be mainly the result of peculiar morphological characteristics in the walls of the lung arterioles, and hypoxia may be a contributing factor.

In the circulating blood, the absolute polycythaemia, associated with a definite increase in the number of red cells and in the amount of haemoglobin and the haematocrit, represents an increased transport capacity for oxygen. A given volume of arterial blood in the native resident of high altitudes contains a greater amount of oxygen than is found at sea level, in spite of the decreased saturation. The high altitude polycythaemia is the consequence of increased erythropoiesis, as has been demonstrated in the study of bone marrow biopsies, and of iron metabolism and utilization (Merino and Reynafarje 1949; Merino 1950; Reynafarje, Lozano and Valdivieso 1956). It is worth mentioning that hypoxia does not influence the production of white cells or platelets.

The modifications in oxygen transport in acclimatized natives are not only quantitative in nature. It was found in investigations made in Peru that the affinity of haemoglobin for oxygen is decreased or, in other words, that the oxygen dissociation curve at a given pH is displaced to the right, thus facilitating the release of this gas to the tissues. Studies showing that an increase in 2,3-diphosphoglycerate in red cells is responsible for the change in affinity (Lenfant et al. 1968) have provided a chemical basis for understanding this important adaptive process. And, in reference to the circulating blood, it may be added that the decrease in $P_{CO_2}$ resulting from hyperventilation is compensated by a lowered bicarbonate concentration, so the pH is maintained within the normal limits observed at sea level.

One of the most fundamental developments in the understanding of successful acclimatization to high altitudes relates to characteristics at tissue level. There is still ample opportunity for further contributions in this field, but we already know of important adaptive processes and we are inclined to believe that the basic difference between 'natural' and 'acquired' acclimatization lies in the presence and quality of the adaptive tissue processes found in 'natural' acclimatization. The greater number of capillaries per given unit of tissue, demonstrated in man (Valdivia 1956) and in adapted animals at high altitudes, favours the diffusion of oxygen. In addition, there are important chemical adjustments. Myoglobin is increased (Hurtado et al. 1937) and there is evidence of higher activity of the mitochondrial DPNH-oxidase system and transhydrogenase and of the TPNH-cytochrome $c$ reductase. All these changes are interpreted as indicating a higher rate of oxygen utilization through enzyme pathways.
linked preferentially with the production of high-energy phosphate bonds (Reynafarje 1962).

The remarkable degree of efficiency observed in ‘natural’ acclimatization, in compensation for the adverse environmental factors at high altitudes, has been strikingly demonstrated in the study of native man under the added stress of physical activity, when oxygen supply and utilization must necessarily be increased. In comparative investigations with healthy residents at sea level, we have found that the native subject, in his high environment, has a better average tolerance time to a maximal period of exercise, and somewhat paradoxically, his oxygen debt and lactate and pyruvate production are definitely lower, indicating a more aerobic than anaerobic source of energy. This fact also has a protective significance, on account of the decrease in available buffer base in the circulating blood.

It is not possible to discuss here some of the other important physiological stresses which demand adaptive mechanisms at high altitudes. One such condition is pregnancy, which together with the fertility rate, is being investigated by a group of endocrinologists in our institute. The data being obtained, including the histological characteristics of the placenta, are of considerable interest.

Before I leave the subject of adaptation to a low ambient pressure, it is important to point out that we do not yet know with precision the level of altitude at which tolerance or acclimatization is no longer possible because physiological reserves have become exhausted. One example may illustrate this point. We have observed in cases of silicosis, studied at high altitudes, that the level of polycythaemia begins to decrease when hypoxia reaches a very severe degree on account of the pulmonary lesions. This finding seems to indicate that hypoxia stimulates erythropoiesis up to a certain degree, beyond which it has a depressive action. It is possible that the same phenomenon could be observed in relation to other adaptive processes.

A high altitude environment not only modifies physiological patterns. It may be responsible, per se, for pathological conditions. For centuries, acute mountain sickness, known as soroche in Peru, was the only clinical disturbance described in direct relation to altitude. It corresponds to the symptomatology frequently observed in newcomers to this environment. Although this syndrome fundamentally represents the consequences of an acute hypoxia, we still do not understand clearly the immediate pathogenic mechanisms and the great individual variability in its occurrence. The clinical field of high altitude disease was expanded with the description, by Monge (1928) in Peru, of chronic mountain sickness, which represents
a loss of acclimatization in a native or in a long-term resident. The pathogenesis of this illness is still a matter of investigation but we have found, in most cases, a condition of hypoventilation and a loss of sensitivity and response of the respiratory centre to the chemical stimulation of carbon dioxide. The decrease in pulmonary ventilation, associated with a higher A-a oxygen gradient, acting on the descending part of the dissociation curve, causes a significant increase in the degree of blood unsaturation. In consequence, erythropoiesis is further stimulated and polycythaemia reaches a high level, and the acid–base balance shows some degree of respiratory acidosis, which is not compensated.

Another clinical condition related to a high altitude environment is pulmonary oedema occurring during the first hours of exposure. Since its original description in Peru in 1937 numerous cases have been reported. In the recent Indian–Chinese conflict, which occurred in the high Himalayan region, a large number of cases were observed. The immediate factors responsible for its occurrence are not well understood, but it is interesting that the incidence appears to be higher in apparently healthy high altitude natives who are returning to this environment after a short stay at sea level; that is, while they still have some degree of pulmonary hypertension and polycythaemia.

Further clinical investigations at high altitude are urgently needed. Extensive epidemiological studies are very few, but attention has been called to an apparently greater incidence, in this environment, of congenital heart defects, peptic ulcer, colelithiasis and liver disease, among others. On the other hand a low occurrence of systemic hypertension, cardiac infarct, diabetes and certain types of malignant processes has been noted. This field of research is highly interesting on account of the racial, genetic and environmental factors which come into play.

In concluding these brief comments, I should like to express my belief that high altitude research is no longer an isolated field of scientific medical endeavour, or an occasional physiologist’s hobby, as it was in the past. It helps toward a better understanding of many millions of men, native and permanent inhabitants of elevated regions. In addition, it must be remembered that a condition of hypoxia is not exclusive to a high altitude environment. Many pathological processes, frequently observed at sea level, may disturb the acquisition, transport or utilization of oxygen. An understanding of how a healthy man is able to tolerate and compensate for hypoxia, and maintain a successful physiological adjustment, may help the clinician in his efforts to alleviate the harmful effects of oxygen deficiency, when it is a consequence of disease.
DISCUSSION

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DISCUSSION

Harris: I have always wondered about the role of myoglobin at high altitude and how it works in the cell, because its dissociation curve is so very hyperbolic. Is the dissociation curve changed in the tissues at high altitude? Normally myoglobin won’t liberate oxygen until a rather low Po2 is reached, and I wonder whether the dissociation curve is shifted to the right for myoglobin at high altitude, as it is for hemoglobin. Does 2,3-diphosphoglycerate (DPG) affect myoglobin?