THE PHYSIOLOGICAL EFFECTS OF HIGH ALTITUDE

PROCEEDINGS OF A SYMPOSIUM
HELD AT INTERLAKEN SEPTEMBER 1962

EDITED BY W. H. WEIHE

The Physiological Effects Of High Altitude

proceedings of a symposium held at Interlaken, September 18-22, 1962

edited by

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High Altitude Research Station
Jungfraujoch, Bern, Switzerland

SYMPOSIUM PUBLICATIONS DIVISION
PERGAMON PRESS
OXFORD · LONDON · NEW YORK · PARIS
1964

PERGAMON PRESS LTD.
Headington Hill Hall, Oxford
4 & 5 Fitzoy Square, London, W.1.

PERGAMON PRESS INC.
122 East 55th Street, New York 22, N.Y.

GAUTHIER-VILLARS ED.
55 Quai des Grands-Augustins, Paris 6

PERGAMON PRESS G.m.b.H.
Kaiserstrasse 75, Frankfurt am Main

Distributed in the Western Hemisphere by
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PERGAMON PRESS LIMITED

Library of Congress Card No. 63–19887

HIGH ALTITUDE RESEARCH STATIONS

Ticlio, *Peru*	4880 m —	16,000 ft
Morococha, *Peru*	4540 m —	14,900 ft
White Mountain, *Summit Laboratory, California*	4340 m —	14,250 ft
Mt. Evans, *Colorado*	4300 m —	14,100 ft
Cerro de Pasco, *Peru*	4200 m —	13,770 ft
Mina Aguilar, *Argentine*	3990 m —	13,100 ft
White Mountain, *Barcroft Laboratory, California*	3800 m —	12,470 ft
Jungfraujoch, *Switzerland*	3454 m —	11,333 ft
White Mountain, *Crooked Creek Laboratory, California*	3090 m —	10,150 ft
Grossglockner, *Austria*	3000 m —	9840 ft
Cal d'Olen, *Instituto Angelo Mosso, Italy*	2900 m —	9514 ft
Westgard Pass, *California*	2220 m —	7210 ft
Obergurgl, *Austria*	2000 m —	6560 ft
Denver, *Colorado*	1600 m —	5280 ft
Salt Lake City, *Utah*	1500 m —	4930 ft
Jujuy, *Argentine*	1260 m —	4140 ft

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ABBREVIATIONS

RESPIRATION

Primary Symbols

V	gas volume
$\dot{V}$	gas volume/unit time
P	gas pressure in mm Hg
F	fractional concentration in dry gas phase
f	respiratory frequency
s	oxygen saturation of hemoglobin, per cent

Secondary Symbols

I	inspired gas
E	expired gas
A	alveolar gas
T	tidal gas
D	dead space gas
B	barometric
BTPS	body temperature and pressure, saturated with water vapor
STPD	standard temperature and pressure (0°C, 760 mm Hg), dry
ATPS, ATPD	ambient temperature and pressure, saturated (S) or dry (D) with water vapor
D	diffusion coefficient
a	arterial
v	venous
BMR	basal metabolic rate
b.w.	body weight
CNS	central nervous system
CSF	cerebrospinal fluid
ECG	electrocardiogram
Hb	hemoglobin
RBC	red blood cells (erythrocytes)
rpm	rotations per minute

THE editor wishes to express his gratitude to Dr. Gertrud Perl and to his wife Dr. Patricia A. Weihe, M.B.B.Chir. (Cantab.), D.C.H., for their invaluable assistance in editing this book.

INTRODUCTION

WHERE ARE WE?

A SHORT REVIEW OF HIGH ALTITUDE PHYSIOLOGY

ALEXANDER VON MURALT

AT 3 o'clock in the early morning of 15 September 1894 a strange group of men left the little village of Zermatt in Switzerland. About 60 men were walking slowly upwards towards the Theodulpass, among them two guides in front and seven scientists riding on mules. On reaching the lower Theodul hut the path became so steep that the mules had to be left behind and the seven scientists were seated in portable baskets each of which was carried uphill by six men. At 11.30 a.m. they reached the Theodulpass (3500 m) where the frequency and shape of the pulse, the vital capacity of the lungs, and the hemoglobin content of the blood of the seven scientists were measured. This was one of the first two systematically organized expeditions of physiologists up to high altitude and Hugo Kronecker, Professor of Physiology at the University of Berne, was its leader. He wanted to know whether the passive transport into high altitude (on mules and in baskets) had any special effects on humans, because at that time plans were being discussed for building a railroad to the top of the Jungfrau (4158 m) and the authorities had asked Kronecker for advice (Kronecker, 1903).

The second expedition in the same year of 1894 was led by Angelo Mosso and consisted of 12 Italian scientists and a large group of soldiers. They walked up by foot from Gressoney on the south side of Monte Rosa to the Punta Gnifetti on the Monte Rosa massif where the Italian Alpine Club had constructed a hut, Capanna Regina Margherita, at 4560 m. Mosso's interesting studies in connection with this and many following excursions were described in a book which appeared in 1899.

These new studies were stimulated and influenced by the fundamental work of Paul Bert who had published in 1878 a book, entitled *La Pression*

barométrique, in which he showed that oxygen deficiency is the main feature in all biological effects of a decrease of barometric pressure. He saw that the body responds to this oxygen deficiency by increasing the number of red cells in the blood. Viault (1890) made the first careful counts of red cells during his trip through the Andes of Peru and Bolivia and found that his red cell count and that of his companion had risen from 5 million per mm^3 at sea level to 7.5–8 million at Morococha (4540 m) and that this increase had occurred during a short time, whereas Paul Bert had thought that the change could only take place gradually through adaptation over generations staying at high altitude.

In the years following the first two organized expeditions of Kronecker and Mosso, the Monte Rosa became a center of physiological research and attracted such men as N. Zuntz and Schumburg (1895), A. Loewy, J. Loewy and L. Zuntz (1896), N. Zuntz, A. Loewy, F. Müller and W. Caspari (1901). In the year 1901 the Capanna Margherita was declared to serve as an international laboratory for high altitude physiology and was properly installed with the financial aid of Ernest Solvay. On 27 August 1907, a new international institute was opened as a base for the Capanna on Col d'Olm (2900 m) situated on the south side of Monte Rosa. In honor of Angelo Mosso this institute carries his name today. It can be reached by foot or on the back of a mule from Gressoney. Durig and three co-workers spent 4 weeks up there (Durig, Kolmer, Rainer, Reichel and Caspari, 1909; see also the excellent report by Loewy, 1932) and since that time Col d'Olm and the Margherita hut were visited regularly by many physiologists.

The English physiologists became interested in the problem at this stage and went first to the Pic of Teneriffe (Alta Vista hut, 3400 m) in an expedition led by Pannwitz in 1910 where Barcroft, Douglas and Zuntz were the principal members. At the same time the Pike's Peak (4312 m) was used for high altitude physiology by Schneider and his colleagues (Douglas, Haldane and Henderson) in the years 1907–1911 and by Haldane in 1912. And then the interest turned to the exceptional possibilities in the Andes of South America, where a railroad was available from Lima up to altitudes above 4000 m (Cerro de Pasco, 4200 m; Morococha, 4540 m). Barcroft went there in the winter of 1921–1922 (see Barcroft, 1927) with Binger, Bock, Doggart, Forbes, Harrop, Meakins and Redfield, and gave a very vivid description in two volumes of his famous book. Finally, the various excursions of Grollmann (1930) should be mentioned who worked mainly on the minute volume of the heart at Pike's Peak. In 1931 Hartmann (1933) led an expedition to the Himalayas and in 1935 Will, Christensen, Keys and Edwards went on a large expedition to the Andes, known as the International

High Altitude Expedition. And this closes what might be called the heroic period of high altitude research.

Permanent laboratories at high altitude were now being built and became the safe and efficient bases for high altitude physiology. The best known laboratories are: Echo Lake Laboratory, Colorado (3200 m), Hafelekar Station, Austria (2297 m), Jungfraujoch High Altitude Research Station, Switzerland (3450 m), Morococha Station, Peru (4540 m), Mount Evans Laboratory, Colorado (4300 m), White Mountain Research Station, California (3800 m). At the same time a vast increase in scientific publications occurred and through these new facilities the laboratory technique and the precision of the observations increased considerably (see *The Worlds High Altitude Research Stations*, edited by the College of Engineering, New York University, New York, 1954).

It requires a great deal of courage to make an attempt to pick out some of the results of all the careful and extremely exacting studies made up to the present time. If I try to do so, I must ask my readers to be generous about the shortcomings of such an attempt.

One of the well established facts of high altitude physiology is the development of acapnia (loss of CO_2) in the blood, leading to a respiratory alkalosis. This change which occurs rapidly is marked on the day of arrival, especially if the subject was transported to high altitude and did not climb. It disappears with acclimatization. The experimental observation is, that the driving force of CO_2 on respiration has increased. In other words, the linear relation between arterial P_{CO_2} and ventilation is shifted to the left. The current interpretation of this observation is, that hypoxia and hypoxemia increases the sensitivity for CO_2 in the receptor system, driving respiration. But this is not the whole story. Upon return to sea level, where there is no hypoxia, this increased sensitivity remains for weeks and even months (Becker-Freyseng, Loeschcke, Luft and Opitz, 1942; Wilbrandt and Sommer, 1944; Dejours, 1958). The observed reaction is well established, but the interpretation is far from being satisfactory. Opitz (1941) postulated the existence of a "tissue factor" in acclimatization.

A word may be said about hypoxia and hypoxemia. A normal subject at rest has an oxygen requirement of about 0.5g O_2 per min (350 cm^3). By going from sea level to Jungfraujoch the number of oxygen molecules per cm^3 is reduced by a ratio of 3:2 and the same is true for the partial pressure which these molecules exert on the alveolar membrane. We find at sea level a P_AO_2 of 96 mm Hg and on Jungfraujoch a P_AO_2 of 64 mm Hg, which corresponds exactly to this ratio. This subnormal condition of partial oxygen pressure at the level of the alveolar membrane should be

called alveolar hypoxia. It is produced by high altitude or by diluting the number of oxygen molecules per cm^3 by mixing the inspired air with other gases.

Now let us consider the passage of these molecules through the membrane into the blood. It is an experimental fact that only one fifth to one fourth of the available oxygen molecules are taken up by the blood. This is due to the diffusing capacity of the lung (D_{LO_2}). An enormous amount of work has been done on clarifying the conditions which govern this uptake and the names of Bohr, Barcroft, Murray and Morgan and Riley and Courant may be mentioned here. (A review of this important problem was written by R. E. Forster, 1957.) For a surface area of 2 m^2 the D_{LO_2} is between 20 and 35 cm^3 per min mm Hg, where the lower value refers to conditions at rest and the higher at moderate work. If the venous blood entering the lung is charged with the amount of oxygen which corresponds to the oxygen requirement of the body, even at a lower per cent saturation of the hemoglobin as is the case in acclimatization (due to the increase in red cells, i.e. hemoglobin) there is no hypoxia in the blood. If, however, the amount of oxygen taken up per minute in the lung is not adequate to the requirement of the body, we speak of *hypoxemia.* The same consideration may be applied to the periphery. If the arterial-venous difference and blood flow correspond to the oxygen requirement of the tissues, there is no hypoxia in the tissues, but if toxic phenomena interfere with the oxygen uptake, there is histotoxic *hypoxia.* I think that the oxygen requirement of the body and the consideration of whether this requirement is fulfilled at the level of the tissues or not, should be the governing thought in all studies of the effects of external subnormal oxygen pressure and the compensations occurring in the body.

Another well established fact is the increase of red cell count with altitude, the increase of reticulocytes in the blood (polycythemia), and the increase in viscosity (Hurtado, 1932). Injection of blood of human subjects at high altitude (especially taken on the fourth day after reaching high altitude) into control rats at sea level produced erythropoiesis in the receptor animals (Loeschcke and Schwartzer, 1939; Biber, 1957; Reynafarje, 1958; experiments by Merino in Peru see also the report by Gordon, 1959). It is only within the last ten years that reliable evidence has been presented for the existence of one or several circulating hemopoietines in the blood of subjects reaching high altitudes. Here, again, the slow disappearance of polycythemia after return to sea level (one to two months) seems to me an unsolved problem of great interest. It seems also established that the loading of the red cells with hemoglobin remains normal even with high rates of activity of the bone marrow, which is an astonishing fact.

Hard to understand is the increase in the number of platelets at high altitude (Webb, Gilbert and Havens, 1914) and the shortening of the blood coagulation time (Hurtado, 1932). But in remembering Cannon's experiments (1932) one is tempted by the idea that oxygen lack, being the most primitive danger to life, produces in the body an "emergency reaction". One of the components of this general reaction is the shortening of coagulation time as a result of sympathico-adrenal stimulation.

Studies on the reaction of the nervous system towards moderate hypoxia of high altitude (3500 m) fit well into this picture. With moderate hypoxia the nervous response is increased, whereas pronounced hypoxia or anoxia diminish or abolish all nervous reactions due to tissue damage.

Fleisch and his group have made an extensive study of the aspect of moderate hypoxia (von Muralt, 1944; Fleisch and von Muralt, 1948; Grandjean, 1948). At Jungfraujoch there is a significant lowering of the thresholds for touch during the first days of exposure. The same is true for the four qualities of taste (bitter, acid, salty, sweet), and the tactile sensitivity of the cornea. The tonus of skeletal muscle was increased slightly in the first two days and then diminished; the patellar reflex threshold was lowered and the intensity increased and the reaction time to optic stimulation was shortened. Visual sensitivity in general was increased (acceleration of dark adaption, smaller pupillary diameter at standard illumination, disappearance of pupillary oscillations), and the same was true in the regulation of blood sugar — tolerance is increased.

In a short paper I have tried to summarize what happens in the autonomic nervous system (von Muralt, 1957) and Fleisch and I proposed a new term in calling the reaction of body the towards moderate hypoxia: *amphotonic*. This means that the tonus in the both sympathetic and parasympathetic system seems to be increased under the influence of mild hypoxia.

In 1942 van Liere gave an admirable summary of our knowledge at that time and as a recent summary the proceedings of the Haldane Centenary Symposium should be consulted (Cunningham and Lloyd, 1963).

How fascinating the field still is became apparent in Interlaken in the fall of 1962, when we held the symposium which is summarized in this book. How diversified all the aspects of High Altitude Physiology are today will be evident in reading this book. As an old-timer, I may be permitted to say, that to my mind, high altitude, as a stimulus to the living body, is one of the finest experimental tools for the study of the efficiency of the regulatory systems within the body.

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