VIII.—*Observations upon the Effect of High Altitude on the Physiological Processes of the Human Body, carried out in the Peruvian Andes, chiefly at Cerro de Pasco.*

Report to the Peru High-Altitude Committee. *Drawn up by the Members of the Expedition, viz.:*—J. Barcroft, *F.R.S.*; C. A. Binger (*Rockefeller Institute, New York*); A. V. Bock (*Massachusetts General Hospital*); J. H. Doggart (*King's College, Cambridge*); H. S. Forbes (*Harvard Medical School*); G. Harrop (*Presbyterian Hospital, New York*); J. C. Meakins (*University of Edinburgh*); A. C. Redfield (*Harvard Medical School*).

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[Plates 19 and 20.]

Contents.

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INTRODUCTION.

What is reported in the following pages is an example of work achieved in a relatively short time by the co-operation of a sufficient number of institutions and individuals.

The venue of this research was in the Andes, and the work was carried out in the winter 1921–1922, yet its organisation only commenced definitely in the early summer of 1921, when a group of British and American physiologists secured the support of the various universities or other institutions to which they were attached. This support was given in the most ungrudging way. It included the liberation from immediate duty of the members of the party, often at considerable inconvenience to those who remained at home, the loan of apparatus, the contribution of substantial funds, and a great body of goodwill, which was perpetually translating itself into increased efficiency of the work actually accomplished. The following collaborated in one or more of the ways indicated above:—

The Department of Physical Chemistry of Harvard University.
The Proctor Fund of Harvard University.
The Elizabeth Thompson Fund.
The Rockefeller Institute of Medical Research, New York City.
Columbia University.—From a fund, to which contributions were made by Dr. Walter B. James, Mr. Cleveland H. Dodge, and a contributor who wishes to withhold his name, but to whom thanks are none the less due.
The Royal Society of London.
The Research Grant to the Physiological Department of the University of Toronto.
The Moray Fund, Edinburgh.
The Carnegie Fund, Edinburgh.
Sir Robert Hadfield, Bart., F.R.S.
Sir Peter Mackie, Bart.

Important apparatus was loaned to the Expedition by the General Electric Company, Schenectady, New York, and the Leeds and Northrup Company, Philadelphia, Pa.

The thanks of the Expedition are due to the Provost and Fellows of King's College, Cambridge, who at a critical moment in the organisation of the Expedition gave the financial guarantee necessary to its further promotion. Such success as the Expedition achieved was also largely due to the kindness of a number of companies or corporations in giving it facilities for work. These include the British and Peruvian Governments, the Pacific Steam Navigation Company, the Grace Line, the Peruvian Corporation, and last, but not least, the Cerro de Pasco Copper Corporation.

The names of the members of the Expedition are as follows:—J. Barcroft, C. A. Binger, A. V. Bock, J. H. Doggart, H. S. Forbes, G. Harrop, J. C. Meakins, A. C. Redfield. The ages varied from about 25 to 49.

I.—Acclimatisation.

The primary object which prompted the Expedition was a desire to investigate the physiological conditions which make considerable muscular and mental effort possible at high altitudes. The term "high altitude" is in practice a comparative one. The interpretation which we would put upon it is "the highest altitude at which a population is maintained and carries out the ordinary functions of life" (this in the Andes is 14,000–16,000 feet). The mining camps of the Andes afforded just the sort of venue which seemed desirable for such work. The town of Cerro de Pasco, the third largest city in Peru, has a population of 12,000* inhabitants, 8,000 of whom are natives and 4,000 floating. The staple industry of the place has for centuries been that of copper mining. Cerro is situated on an incline, the lowest point of which is 14,200 feet above the sea-level. Smaller camps are to be found at higher altitudes, reaching up to about 16,000 feet. The highest point on the Central Railway of Peru, which affords communication with the mining localities of the country behind Lima, is 15,860 feet high. Up to an altitude just short of 16,000 feet, then, this locality yields the necessary facilities for research—transportation, a native population, and a temperate climate. The sequel will show the extent to which it was possible to turn these facilities to account.

The following Table gives an itinerary of the various members of the party, giving the altitude, and, so far as they were observed, the barometric heights of the localities:—

Itinerary 1.

Date. 1921.	Binger.	Bock.	Forbes.	Harrop.	Redfield.
November 16	N.Y.	N.Y.	N.Y.	N.Y.	N.Y.
,, 23	Panama	Panama	Panama	Panama	Panama.
,, 28	Lima	Lima	Lima	Lima	Lima.
December 19	,,	,,	,,	,,	,,
,, 19	Oroya	Chosica	Chosica	Chosica	Oroya.
,, 20	,,	,,	,,	,,	,,
,, 21	,,	Oroya	Oroya	Oroya	,,
,, 22	,,	,,	,,	,,	,,
,, 23	,,	,,	,,	,,	,,

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* These and all similar data are only approximate, there being no exact statistics obtainable. There are said to be 8,000 natives, and a transient population of 4,000.

Itinerary 1—*contd.*

Date.	Binger.	Bock.	Forbes.	Harrop.	Redfield.
1921.					
December 23	Cerro	Oroya	Cerro	Cerro	Oroya
,, 24	,,	,,	,,	,,	Cerro
,, 25	,,	,,	,,	,,	,,
,, 26	,,	,,	,,	,,	,,
,, 27	,,	Cerro	,,	,,	,,
1922.					
January 12	,,	,,	,,	,,	,,
,, 12	Casapalca	Casapalca	Morococha	Casapalca	Casapalca
,, 13	,, (climb)	Matucana (climb)	Casapalca	Matucana (climb)	,, (climb)
,, 14	Lima	Lima	Lima	Lima	Lima
,, 15	,,	,,	,,	,,	,,
,, 16	,,	,,	,,	,,	,,
,, 17	,,	,,	,,	,,	,,
,, 18	S.S. Ebro	S.S. Ebro	S.S. Ebro	S.S. Ebro	S.S. Ebro

Itinerary 2.

Date.	Barcroft.	Meakins.	Doggart.
1921.			
November 17	Left Liverpool	Left Liverpool	Left Liverpool (S.S. Victoria)
December 18	Lima	Lima	Lima
,, 19	,,	,,	,,
,, 19	Chosica	Chosica	Chosica
,, 20	,,	,,	,,
,, 21	Matucana	Matucana	Matucana
,, 22	,,	,,	,,
,, 23	Oroya	Oroya	Oroya
,, 24	,,	Cerro	Cerro
,, 25	,,	,,	,,
,, 26	Cerro	,,	,,
	(January 5—Gollarisquisga for the day.)		
1922.			
January 12	Cerro	Cerro	Cerro
,, 12	Casapalca	Casapalca	Casapalca
,, 13	Matucana (climb)	,, (climb)	,, (climb)
,, 14	Matucana	Casapalca	Casapalca

Itinerary 2—*contd.*

Date. 1922.	Barcroft.	Meakins.	Doggart.
January 14	Lima	Lima	Lima
„ 15	„	„	„
„ 16	„	„	„
„ 17	„	„	„
„ 18	Sailed on S.S. Ebro.		

The positions of the principal localities visited are shown on the following rough map, whilst the silhouette diagram gives an idea of the levels at which the places mentioned are situated. The Andes in this part of South America run as two chains of mountains parallel to the coast. Of these the most westerly is somewhat the higher. Between the two chains is a broad valley, some 50 miles across, the level of which varies from 12,000 to 15,000 feet in the part of Peru where we were. The Central Railway of Peru starts from Callao and runs through Lima inland, ascending the Western Cordillera to a height of 15,860 feet—that is to say, to the snow line. At this point it evades the extreme watershed by passing through a tunnel and then

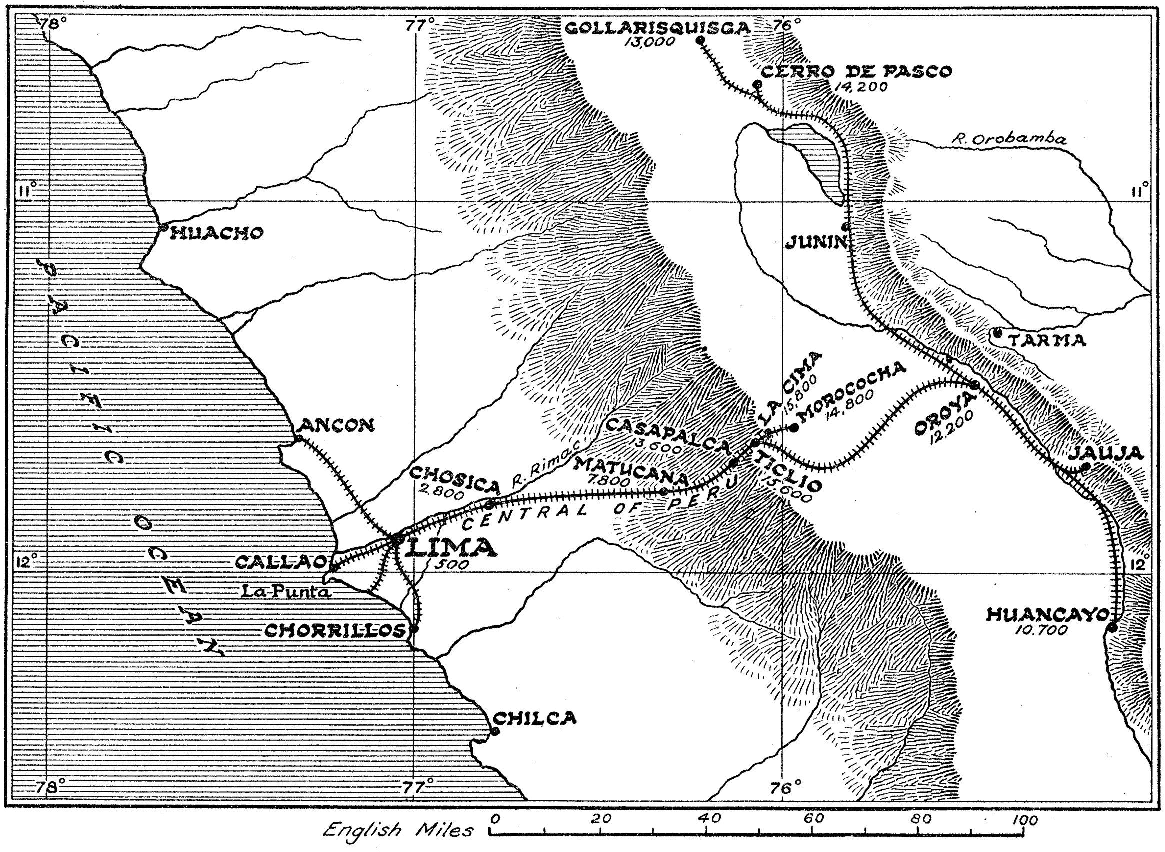

FIG. 1.—Outline map of Central Peru.

descends to Oroya (12,000 feet). In the immediate vicinity of the railway the highest peaks are between 17,000 and 18,000 feet. Up one of these, Mount Carlos Francisco, we walked. Further away the mountains are somewhat higher, the highest we saw being about 21,000 feet. This mountain, we believe, has never been climbed, and without considerable organisation it would not be available for high altitude physiological research.

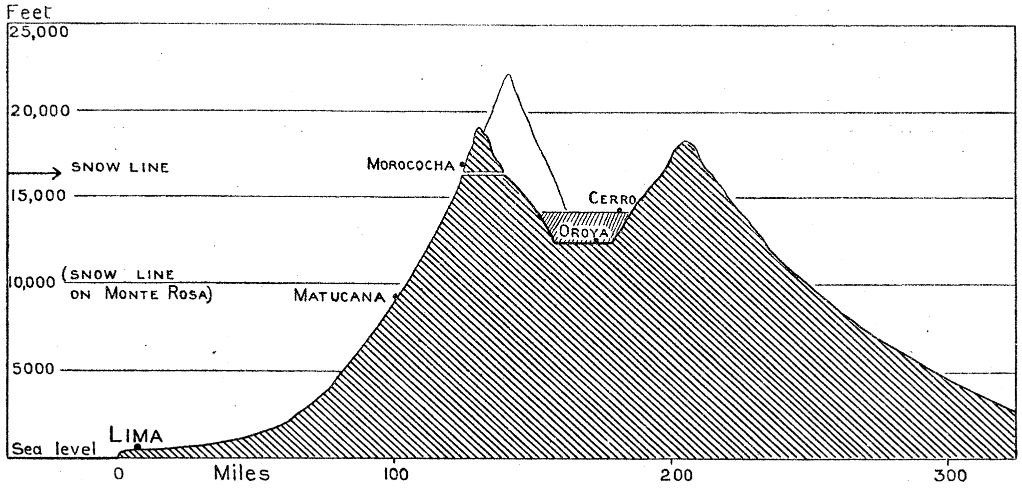

FIG. 2.—Profile diagram to show altitudes of places visited by the party.

Oroya is the headquarters of the Cerro de Pasco Copper Corporation. It boasts of smelting works on a very large scale—something like 700 tons of copper ore are being smelted daily—and is equipped with an excellent hospital. We cannot mention Oroya without expressing our thanks to the Cerro de Pasco Company for their kindness to us. The officials, executive, engineering and medical, one and all, placed their resources at our disposal, and whatever measure of success we attained in Peru we owe in great part to their kindness and to that of the Central Railway; of this latter we shall speak presently. Cerro de Pasco is about 80 miles from Oroya in a northerly direction and is situated at a higher altitude; it is a terminus of the railway and is the site of the most extensive copper mines in this district.

The laboratory was established in a baggage car furnished us by the Central Railroad of Peru. It was 45 feet long, of standard gauge width—the type of car called an "equipage" in Spanish, a "luggage van" in England, and a "baggage car" in the United States. A few minor modifications converted the car into a laboratory with extraordinarily good facilities for work. The problem of lighting was met by opening two of the large rolling side doors diagonally opposite each other, boarding up their lower halves, and setting in window-panes above. At Cerro the car was wired and we were provided with electric light as well as heat, which was very welcome. Work benches, 2 feet wide, were put in along the wall, and shelves at a convenient height, about 2 feet below the ceiling. Combined with cupboards and bins, with which this type of baggage car was already equipped, they furnished ample storage room for articles in use. Most of the apparatus was clamped to the benches to insure security in transit. The water supply was from a hogshead fitted with a tap. Besides, we carried a 10-gallon carboy of distilled water in the laboratory. Primus stoves and spirit lamps furnished the heating facilities.

The chief source of inconvenience in this type of laboratory was due to vibrations caused by walking on the floor of the car or by passing trains. This often made reading a meniscus difficult, because of oscillations in the mercury column. The obstacle was overcome by having the car jacked up on stilts.

Whilst upon the subject of laboratory accommodation, mention must be made of the laboratories which were improvised on the steamers "Victoria" and "Ebro," belonging to the Pacific Steam Navigation Company. This company, the Central Railway and the Cerro de Pasco Corporation, and W. R. Grace & Co., did everything which was possible to make our journey a scientific success, and we would like to express our thanks to the officers of the Pacific Steam Navigation Company, both ashore and afloat. On each of these steamers we had a cabin which served as a laboratory. The upper berth was folded up and formed a rack for Douglas bags, etc. On the lower one we retained the mattress to damp the vibration; on the mattress we placed boards which served as a bench. In moderate or calm weather we were able to do gas analysis, measure blood volumes, estimate the quantity of CO in hæmoglobin, and so forth.

Before examining the changes in the body which make for bodily and mental efficiency at high altitudes, it may be well to give a brief statement of what amount of labour can be accomplished. The ascent from the sea-level to the mountains produces some upset of the biochemical condition in all persons; this upset may be slight or it may amount to a definite condition of mountain sickness.*

After the system has re-established an equilibrium with its surroundings tasks can be undertaken which would previously have been impossible. Yet it must be distinctly understood that no one, whether he be a new comer, a resident of some years standing, or a native whose ancestors have lived at Cerro for generations, can do the amount of work above 14,000 feet that he could accomplish at ordinary altitudes. Everyone is to some extent immobilised; a surprising capacity for movement is, however, attained.

In giving some examples of the muscular work which can be and is performed at Cerro, a distinction may be drawn between exercise which is continuous and exercise which is spasmodic. The former presupposes a current of chemical events which runs at an even speed and maintains a constant level. The latter assumes a departure from this level for a short time, followed by a subsequent return. A considerable amount of continuous exercise may be taken on the level. To give a specific

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* To the condition of mountain sickness the term "Soroche" is applied in Peru. By this term it is known by both the Anglo-Saxon and the Spanish population there, we therefore propose to use it in the present paper.

example :—The New Year was ushered in by a ball near to Cerro; our party were honoured with invitations. Dancing commenced about 9.30 and ended at 2.30. Some of the party danced every dance except during supper, and had no difficulty in doing so. Many ladies present were enthusiastic dancers and probably missed very few dances.

Walking likewise can be maintained at the ordinary rate for a long time; lawn tennis is played. The native boys play football—fifteen minutes each way.

A hill presents quite unusual difficulties, however. One gets out of breath rapidly, and any considerable task of climbing tends to shift the form of exercise from the continuous to the spasmodic type. On our ascent of Carlos Francisco we had to resort to the latter form of exercise for about the last thousand feet. That is to say we took some steps through the snow, which was almost knee-deep, paused till we had regained breath, then took another score of steps and so on. The inwardness of this type of exercise no doubt is to be found in the recent observations of HILL and LUPTON, that a man can easily overdraw his oxygen account by about 4 litres and in extreme cases by 8 litres—that is, at the sea-level; what the extent of his oxygen credit at 17,000 feet may be is not known.

The greatest feats of exertion which we saw were of this type. They were performed by the porters who carried metal from some of the old Spanish mines. We were fortunate enough to visit one of these. The mine was said to be 250 feet below the surface, and the staircase which led down to it 600 in length. The porters varied greatly in age and stature, some being mere boys. One such said he was 10 years of age, but looked older. The load which he brought up was about 40 lbs.; another porter of perhaps 19 years, carried up a load of about 100 lbs. In every case the exercise was spasmodic. The respiration was of the most laboured description. It could be heard from far down the staircase before the man, or rather his light, came into view; the climb was very slow and consisted of the ascent of a few steps at a time, each spasmodic ascent being followed by a long pause. (See figs. 4–9, plates 19 and 20.)

The efforts of these porters seem on a small scale to resemble those of pearl divers who can remain under the surface, working for about 3 minutes, come up with their oxygen reserve exhausted, lay in a fresh stock, and dive once more (1). In the case of the miners the oxygen reserve is smaller and the amount they can undertake at a spasm is less.

Leaving on one side the question of spasmodic exercise, we will now proceed to the task of investigating the alterations, real or alleged, in the body which make for an adaptation to the conditions of life at high altitudes. The possibilities which we investigated were :—

(*a*) Oxygen secretion in the lungs.
(*b*) Increased total ventilation.
(*c*) Alterations in the chemical constitution of the blood.

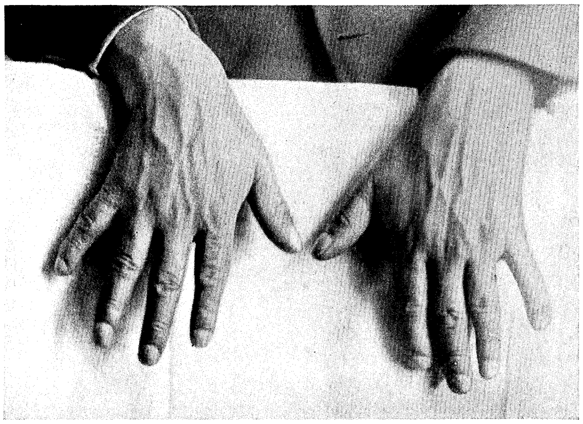

Fig. 3. Fingers somewhat "clubbed" in natives, unassociated with cardiac or pulmonary lesions (see p. 384).

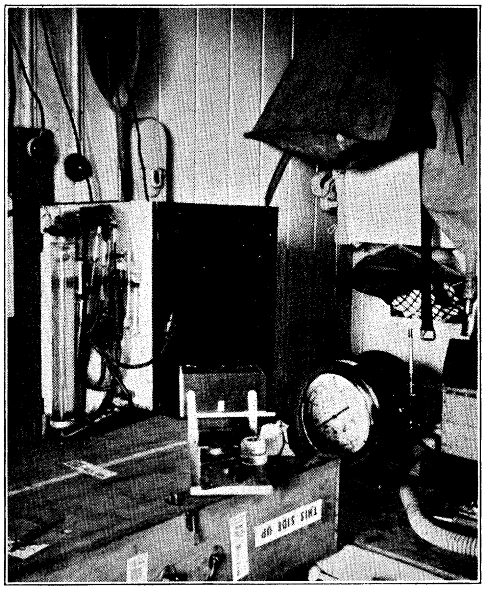

Fig. 4. Cabin on S.S. "Victoria" converted into laboratory.

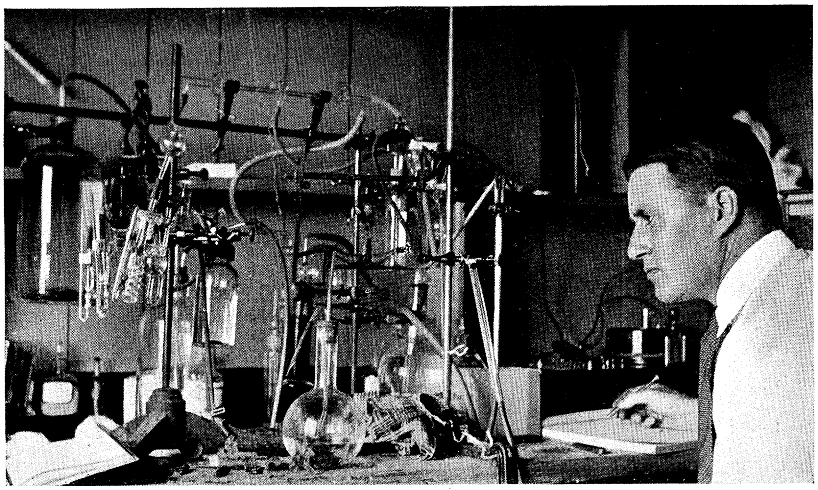

Fig. 5A.

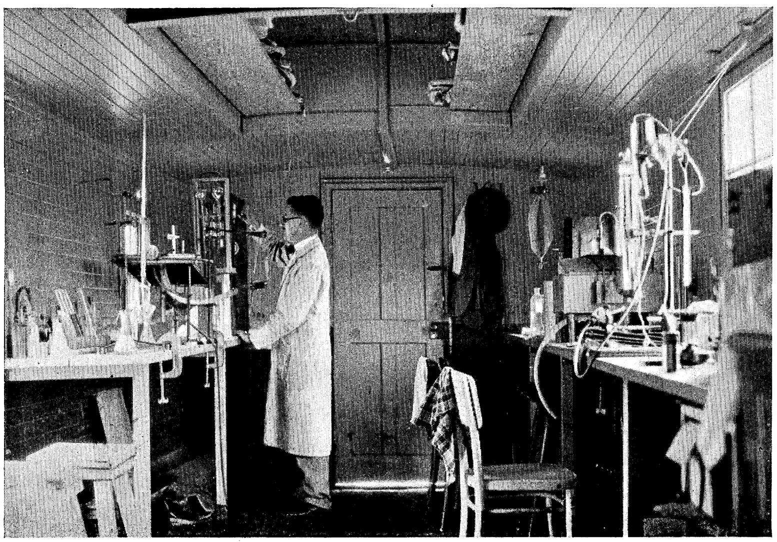

Fig. 5B.

Figs. 5A and 5B. Views inside mobile laboratory made from baggage car on Central Railway of Peru.

[*To face p.* 358.

Fig. 6. Woman of Cerro (14,000 feet) going uphill "at a double" with burden on back.

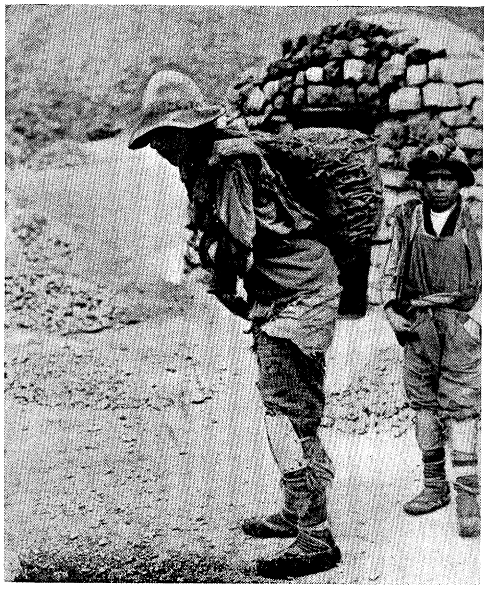

Fig. 7. Porter with load of about 80 lb. of ore which has been brought up from mine.

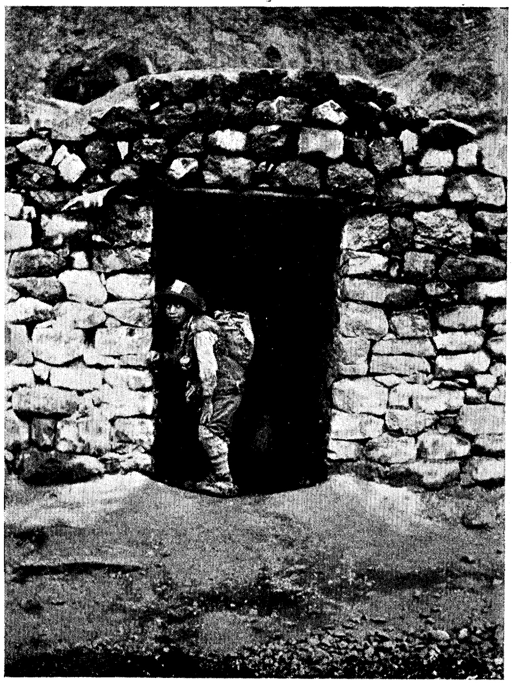

Fig. 8. Head of stairs leading to mine 250 feet below surface. Boy, aged 10 (?), with load of 40 lb.

Fig. 9. Piles of ore, each representing amount raised by one porter up to 11 o'clock on day of our visit.

(*d*) Alterations in the size of the chest.
(*e*) The vital capacity.
(*f*) The residual alveolar air.
(*g*) Diffusion coefficient as defined by Bohr.
(*h*) The number of red blood corpuscles and the quantity of hæmoglobin.
(*i*) The increase in the pulse rate.
(*j*) The increased minute volume of blood.
(*k*) Systolic output and radiograms showing the size of the heart.
(*l*) Alteration in blood volume.
(*m*) The relative importance in some of the observed factors in acclimatisation.

A. OXYGEN SECRETION.

It seems unnecessary to give a lengthy historical account of the work which has been done already at high altitudes (2), (3). As regards the immediate points which we intended to study, however, special reference must be made to the work of HALDANE and his associates on Pike's Peak (4). The most striking form of adaptation which those authors described was a rise in the pressure of the oxygen in the general arterial blood, so that, after a short residence at 14,000 feet, the arterial blood was described as having an oxygen pressure of the same order as that which normally prevails at the sea-level. HALDANE and his associates suggest that this being so, the arterial blood is of its normal red colour, and attains its normal degree of oxygen saturation. A chamber experiment (5), of which one of us was the subject, failed to corroborate the findings of the Pike's Peak Expedition. Before further work could be carried out profitably it was necessary to define the degree of anoxæmia which existed, not only by observations on the degree of cyanosis which may be seen, but by obtaining a definite answer to two questions :—

(1) What is the partial pressure of oxygen in the arterial blood ?
(2) What is the percentage saturation of oxygen in the arterial blood ?

The colour both of the countenance and of the arterial blood bears instructive testimony to the degree of saturation of the blood with oxygen.

(a) *Cyanosis.*—The colour of the blood when it entered the syringe from an artery was very striking. The arterial blood invariably looked more or less dark, a fact which explained the peculiar complexions of all who had any colour in their cheeks.

Many of the natives of Cerro are sallow, but the majority, and especially the children, have ruddy complexions. The red in their cheeks is, however, of a different hue to that of a full-blooded person at the sea-level. It contains an intermixture of blue, so that it would be almost more accurate to call their cheeks plum-coloured than rosy.

The same is true of the Anglo-Saxon residents. Those whose faces normally have little colour do not show much that is distinctive, but anyone whose complexion borders upon the rubicund has a distinctly cyanosed appearance. In one case we had the opportunity of comparing the complexion of such a subject at Cerro and at Lima, where the blue tinge at once disappeared, and his face presented a fresh and healthy appearance. In our own cases—a fact observed by most previous workers was apparent, namely, that the cyanosis, which at first was very marked in our faces, and especially in our nails, became reduced in degree. On arrival at Oroya, for instance, our nails were much more cyanosed than those of the residents with whom we compared them. In a day or two this difference had practically disappeared, and we acquired the same colour as the Anglo-Saxon of longer residence in the mountains. In our case the cyanosis which takes place on first reaching a high altitude could not be attributed to cold, as has been done elsewhere, for the houses were heated, as was the car in which we travelled. It must be clearly stated that neither we nor anyone else were the same colour as at the sea-level. We became accustomed to the altered aspect of mankind and ceased to notice it, but half-a-minute's respiration of oxygen at any time altered the colour either of ourselves, our fellow Anglo-Saxons, or the members of the indigenous population to whom the gas was administered.

(b) *Measurement of the Pressure and saturation of the blood with oxygen* were made by the application of the following methods to blood taken by direct arterial puncture from the radial or brachial arteries :—

(1) The "bubble" tonometric method described by BARCROFT and NAGAHASHI (6).

(2) The standard methods for the determination of the percentage saturation of blood with oxygen, namely, that of VAN SLYKE (7) for 1 c.c. of blood, of HALDANE (8) for samples of 2 c.c., and the differential method (9) for samples of 0·1–0·15 c.c. The persons observed for these, as for other purposes, were divided into three categories :—

1. The members of the Expedition ; 2. Anglo-Saxon residents ; 3. Persons born in the Cordilleras and who may be regarded as having such characteristics as are imprinted by the local conditions upon the race. Just what that race may be is, in some cases, a very difficult question to answer.

The following Table gives the partial pressure of oxygen in the arterial blood, as measured directly by the "bubble" method, as well as that in the alveolar air measured by the method of HALDANE and PRIESTLEY (2).

TABLE I.

Category.	Date.	Place.	Name.	Oxygen pressure	
				In arterial blood (error ± 4 mm.).	In alveolar air.
				mm.	mm.
I	July 28, 1921 . . .	Cambridge .	Meakins. . . .	99	100
	January 9, 1922 . .	Cerro . .	„	58	56
	March, 1922 . . .	Edinburgh .	„	100	101
II	December 31, 1921 .	Cerro . .	McQueen . . .	57	59
	December 31, 1921 .	„ . .	Philpotts . . .	48	55
	January 1, 1922 . .	„ . .	McLaughlan . .	47	56
	January 8, 1922 . .	„ . .	Cuthbertson . .	55	54
III	January 3, 1922 . .	„ . .	Zalada	50	51
	January 4, 1922 . .	„ . .	Baracoyle . . .	40	—
	January 4, 1922 . .	„ . .	Villareal . . .	50	—

A study of the above Table shows that there is never any great disparity at rest between the oxygen pressure in the alveolar air and the arterial blood. The analysis of the bubble is, of course, a much rougher process than a normal alveolar air estimation; on the other hand, the determination of alveolar oxygen in the case of persons in categories II and III are not at all so accurate as in the case of those in category I.

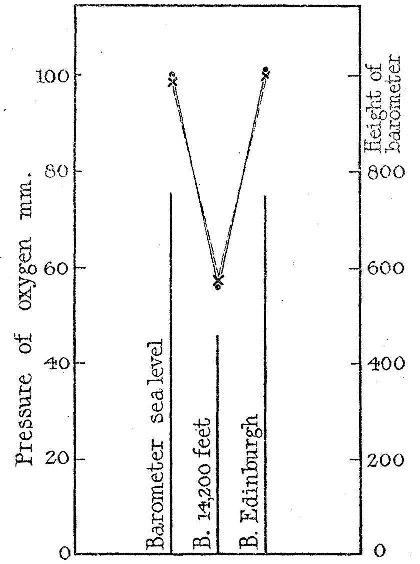

FIG. 10.—Relation of oxygen pressure in alveolar air (•) to that in arterial blood (×) at different altitudes (Meakins).

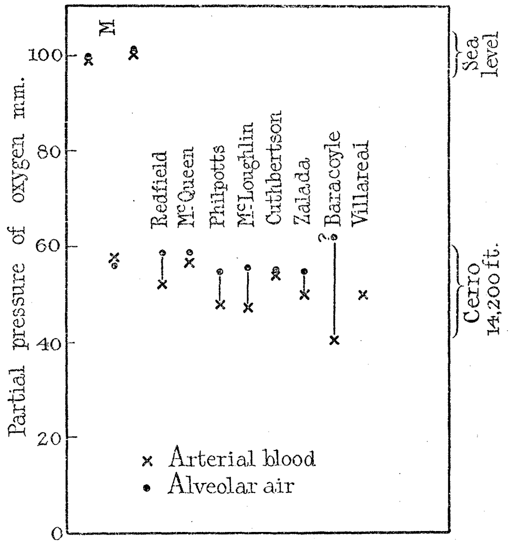

FIG. 11.—The same for different persons.

Apart, however, from small differences such as might be attributed, rightly or wrongly, to experimental error, the main facts stand out: (1) that there is no suggestion of oxygen pressures of 90–120 mm., such as have been alleged to exist in dwellers at high altitudes; (2) that the pressures of oxygen in the arterial blood are such as would naturally be brought about by diffusion, but which would only be produced accidentally by any other mechanism. It is very improbable that so many consecutive accidents should occur.

The low order of oxygen pressures ruling in the arterial blood is in general agreement with the low percentage saturations of oxygen found in blood withdrawn by direct arterial puncture.

Perhaps the most remarkable feature of the Table given below is the high degree of *un*saturation of the arterial bloods of those native to the mountains. The three examples showed their arterial blood to be but 82–86 per cent. saturated, and in this condition presumably they pass their lives.*

TABLE II.—Arterial Oxygen Saturation.

Name.	Date.	Altitude.	Condition.	Alveolar air.	Differential method.	Haldane method.	Van Slyke method.	Average.
				mm.	per cent.	per cent.	per cent.	per cent.
Meakins . .	—/ 7/21	Cambridge	Rest	100	95	—	—	95
	—/ 5/21	Edinburgh	,,	—	—	95	—	95
	25/12/21	14,200	,,	57	—	—	83	83
	9/ 1/22	14,200	,,	55·6	94	91	88	91
	9/ 1/22	14,200	Work	60·2	79	—	—	79
Redfield . .	18/12/21	Sea-level	Rest		—	—	97	
	7/ 1/22	14,200	,,	59	87	88	—	87·5
	7/ 1/22	14,200	Work	59	91	90	90·7	90·5
Binger . .	—	Sea-level	Rest		—	—	—	
	27/12/21	14,200	,,	47 (?)	—	85	83·3	84
Bock . . .	—	Sea-level	,,		—	—	95	
	19/12/21	14,200	,,	50	79	82	83·5	81·5
Harrop . .	—	Sea level Baltimore	,,	—	—	—	95	95
	30/12/21	14,200	,,	50	—	—	82	82
McQueen .	—	14,200	,,	59	86	—	—	86
Philpotts .	—	14,200	,,	55	90	90	92·5	91
McLaughlan	—	14,200	,,	56	86	88	84	86
Cuthbertson	—	14,200	,,	54	—	87	—	87
Zalada . .	—	14,200	,,	51	86·5 & 93	84	86	86
Villareal . .	—	14,200	,,	—	82·5	—	—	82·5
Baracoyle .	—	14,200	,,	62	82·3	—	—	82·3

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* Dr. GILDEA has kindly informed us of his confirmation on Pike's Peak of the above saturations. In a number of cases whose residence varied from a few hours to four months, he obtained saturations of 80–86 per cent. in every case except one. His cases will shortly be published in America.

B. Increased Pulmonary Ventilation, Causing a Reduction in the Oxygen Difference between the Inspired and Alveolar Air.

This factor has been observed by all workers who have studied the matter within recent years (10), (11), (12), (13), (14), (15), (4). It is best understood from the consideration of an example such as has been given by Haldane (4) and others.

At the sea-level the pressure of oxygen in dry air is approximately 160 mm. In air saturated with aqueous vapour at 37° C. it would be 150 mm., more or less, according to the barometric pressure. The pressure of oxygen in the alveolar air is about 100 mm., *i.e.*, 50 mm. lower than that in the inspired air saturated at 37° C. The CO_2 in alveolar air at sea-level is 40 mm.

Consider now what would take place at Cerro de Pasco if there were no change in the rate or depth of ventilation or in the degree of metabolism. The CO_2 pressure in the alveolar air would remain at 40 mm., while the oxygen pressure would remain 50 mm. below that in the inspired air saturated with aqueous vapour at 37° C. The barometer at Cerro was usually 458 mm. The oxygen pressure in the moist air at body temperature would then be 88 mm., and the pressure of oxygen in the alveolar air would be 38 mm. The effect of the increased total ventilation was to lower the partial pressure of the alveolar CO_2 from about 40 to something like 28 mm., and to raise the corresponding pressure of oxygen from 38 to 50–55 mm. on the average—a gain of some 15 mm. oxygen pressure.

The actual figures for the various persons studied are given in the following Table :—

Table III.—Alveolar Air at Rest.

Name.	Date.	Position.	Bar. pr.	CO_2 mm.	O_2 mm.	Time.
Meakins . . .	25/11/21	Sea-level	765	40·6	100	
	11/12/21	" "	762	37·7	103	
	14/12/21	" "	761	37·7	103	
	20/12/21	Chosica (2,800)	697	38·3		
	21/12/21	Matucana (7,790)	565	37·6	66·4	9 P.M.
	22/12/21	"	565	36·4	70·5	10 A.M.
	22/12/21	"	565	36·6	67·5	9 P.M.
	23/12/21	"	565	35·8	71·0	10 A.M.
	30/12/21	Cerro (14,200)	458	27·2		
	3/ 1/22	"	458	25·5	57·6	9.30 A.M.
	9/ 1/22	"	458	25·9	55·6	11 A.M.
	15/ 3/22	Edinburgh	761	40·2		
Barcroft . . .	30/11/21	Sea-level	761	39·3	103·0	
	6/12/21	" "	765	39·1	107·0	
	9/12/21	" "	764	39·1	106·0	
	15/12/21	" "	761	37·8	107·7	
	21/12/21	Matucana	565	41·0	64·5	9.30 P.M.
	22/12/21	"	565	38·2	67·5	8.30 P.M.
	22/12/21	"	565	38·9	70·9	11 A.M.
	23/12/21	"	565	39·1	67·5	9 A.M.
	29/12/21	Cerro	459	31·5	48·4	7 A.M.

TABLE III—*continued.*

Name.	Date.	Position.	Bar. pr.	CO_2 mm.	O_2 mm.	Time.
Harrop	16/12/21	Sea-level	757	40·0	—	2.30 P.M.
	20/12/21	Chosica	697	38·3	—	9 P.M.
	2/ 1/22	Cerro	458	29·1	49·6	7 A.M.
Redfield . . .	16/12/21	Sea-level	753	37·5	—	10 A.M.
	16/12/21	,, ,,	753	37·0	—	2 P.M.
	26/12/21	Cerro	459	24·2	57·5	7 A.M.
	6/ 1/22	,,	459	22·9	60·8	12 NOON.
	7/ 1/22	,,	458	22·8	59·3	12 NOON.
	3/ 2/22	Boston	747	31·0		
	5/ 6/22	,,	756	36·0		
Bock	17/12/21	Sea-level	757	38·3	—	10 A.M.
	28/12/21	Cerro	458	29·1	50·1	7 A.M.
	3/ 2/22	Boston	747	37·0	102·0	12 NOON.
Binger	17/12/21	Sea-level	757	40·6	—	12 NOON.
	17/12/21	,, ,,	757	40·4	—	2 P.M.
	27/12/21	Cerro	458	29·4	50·0	11 A.M.
	31/12/21	,,	458	30·5	46·7	7 A.M.
Cuthbertson . .	8/11/21	,,	458	24·5	52·6	
Philpotts . . .	31/12/21	,,	458	28·5	55·2	
McLaughlan . .	2/ 1/22	,,	458	26·8	55·3	
	14/ 3/22	Boston	755	37·0	110·0	
Bravo	2/ 1/22	Cerro	458	28·0	50·2	
Zalada	3/ 1/22	,,	459	28·8	51·3	
Baracoyle . . .	—	—	460	24·2?	62·4?	

At Cerro de Pasco our results confirmed those of previous workers. It was a matter of some interest to us to see whether there was any indication of shallow breathing with the degree of anoxæmia experienced. The following Table shows pretty clearly that, in healthy persons, partially acclimatised at all events, there was no constant effect produced which could be designated by the term "shallow respiration," although the arterial blood was in most cases below 90 p.c. saturation :—

TABLE IV.

Name.	Place.	Litres per hour, 37° (moist), local bar. press.	Litres per minute.	Resp. rate.	Litres per resp., 37°, local bar. press.	Date.
Meakins .	S.S. Victoria .	399	6·65	7	0·92	Dec. 5/21
	,, ,, .	427	7·12	7	1·62	,, 12/21
	Cerro	514	8·58	12	0·71	Jan. 3/22
Barcroft .	S.S. Victoria .	410	6·84	10	0·68	Dec. 4/21
	,, ,, .	460	7·67	10–11	0·73	,, 10/21
	Cerro	423	7·06	12	0·59	,, 29/21
Bock . .	Lima	371	6·18	13	0·48	,, 16/21
	Cerro	642	7·37	14	0·53	,, 28/21
Binger . .	Lima	328	5·48	8	0·69	,, 14/21
	Cerro	444	7·41	12	0·62	,, 31/21
Redfield .	Lima	389	6·49	17–18	0·37	,, 13/21
	Cerro	600	10·00	17	0·59	,, 26/21
Harrop . .	Lima	391	6·52	14–18	0·40	,, 12/21
	Cerro . . .	548	9·14	17	0·53	Jan. 1/22

The Mechanism of Increased Ventilation.

(*a*) *The Hydrogen-Ion Concentration of the Blood at Rest.*

Whilst the facts given above are a mere confirmation of those observed by previous workers, the mechanism which is responsible for them is a matter for further research. Two views have been put forward to explain the increase of total ventilation at high altitudes; of these, the one was that the excitability of the respiratory centre is constant, and that its activity is dependent upon the hydrogen-ion concentration of the blood, increased ventilation at high altitudes being due to an immeasurably small increase in hydrogen-ion concentration. "On Pike's Peak the respiratory centre was presumably reacting to a difference in cH corresponding to this very small difference in CO_2* pressure" (16). Later, HALDANE gave up this view, and took his stand with the Copenhagen School (20), who believe that the excitability of the respiratory centre is a variable quantity during health. He pointed out that the observed facts might be met on the hypothesis that the lack of oxygen increased the irritability of the respiratory centre, causing increased total ventilation; the secondary results would be loss of CO_2 by the blood and decreased hydrogen-ion concentration, which might or might not become wholly compensated by the kidney. The same view is held by YANDELL HENDERSON, who has demonstrated the order in which changes take place in animals (18).

Much doubt then has centred around the possible alterations in the hydrogen-ion concentration of the blood, and the extent to which they are responsible for a physiological adaptation under discussion, *i.e.* the increase in total ventilation which leads to an approximation in composition between the alveolar and expired airs.

It was shown by one of us in Teneriffe (13) that the actual affinity of hæmoglobin in the body was the same, within the limits of experimental error, at 7,000 feet altitude as at the sea-level. A few determinations seemed to show that the same was true after a stay of a night at 11,000 feet, and this fact was subsequently confirmed at Col d'Olen (15) (10,000 feet) and by the Pike's Peak Expedition of 1914 (4) at 14,000. In the latter case the length of residence before the determinations were made was not specified. The most probable inference was that, in the corpuscles at all events, the hydrogen-ion concentration remained unaltered, and subsequent work has borne this view out to the extent that it has been shown that small changes in the already large saline content of the blood do not produce any appreciable change in the dissociation curve. The average of a number of experiments of this nature pointed to a trifling change in the acid direction, but one too small to warrant any stress being placed upon it (15).

SCHNEIDER (19) quotes direct measurements by SUNDSTROEM of the hydrogen-ion concentration which point in this same direction. Chamber experiments, performed by HASSELBALCH and LINDHARD (20), however, though they also show the change

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* 0·8 mm.

in reaction in the blood to be very trifling, if it exists at all, point to a change in the opposite direction.

This result was confirmed by PARSONS and BARCROFT (21), who found that the hydrogen-ion concentration of BARCROFT'S blood at rest under normal conditions was $3 \cdot 72 \times 10^{-8}$ ($p\text{H} = 7 \cdot 43$), whilst that of his blood, after a week at gradually decreasing oxygen pressures, was $3 \cdot 63 \times 10^{-8}$ ($p\text{H} = 7 \cdot 44$).

In view of the above conflict of opinions and the importance of the issue, it seemed clear that further experimental data were urgently required in order to elicit a conclusion as to whether the concentration of hydrogen-ions in the blood varied or was the same at high altitudes as at sea-level and at (B), and in the event of its varying as to the direction in which variation took place. We have used two methods, firstly, a modification of the Dale-Evans method (22), and secondly, the determination of the ratio of free to combined carbonic acid. The last of these we have treated in two different ways. Firstly, we have used blood taken directly from arterial punctures as the basis of calculation. The blood withdrawn from the radial or brachial artery, into a syringe containing either carbonate-free oxalate or hirudin, was passed, in measured quantity, directly either into the Van Slyke apparatus or into the bottle of a Haldane apparatus. The total CO_2 was measured immediately, the alveolar air being taken as the measure of the free CO_2. The second way of treating the blood was to determine the CO_2 dissociation curve of the oxidised blood, and place on the curve a point marked A corresponding in pressure to pressure of CO_2 in the alveolar air, from which the concentration of hydrogen-ions may be determined by the construction of the type of diagram introduced by HAGGARD and YANDELL HENDERSON (23). The former method avoids the danger of *post-mortem* alterations in the reaction of the blood, and is therefore physiologically more accurate, though mathematically less accurate, than the Haggard-Henderson diagram.

The results which we have obtained did not seem at first sight to be completely concordant. We should like to take this opportunity of thanking Dr. LOVATT EVANS (24) for an act of courtesy and helpfulness which was much appreciated by our party. Having made certain observations on the rate at which the CO_2 content of the blood changes after withdrawal from the body, he at once acquainted us with them by mail.

Direct Determinations of Hydrogen-Ion Concentration by Titration against Indicators.

Fig. 12 shows two curves obtained on Binger's blood oxidised and reduced respectively. They delineate the relation between the pH and the CO_2 pressure. The points marked with a cross were determined at Lima; those with a ⊙ at Cerro de Pasco. So far as the number of determinations warrants a conclusion, it is that altitude has no appreciable effect upon the curve. The natural deduction would be that the blood in the body at Cerro de Pasco is more alkaline than at sea-level, precisely in proportion as the CO_2 pressure is less. On this showing, the change in reaction should be 0·04 *p*H as between Cerro de Pasco and sea-level. The determinations were as follows :—

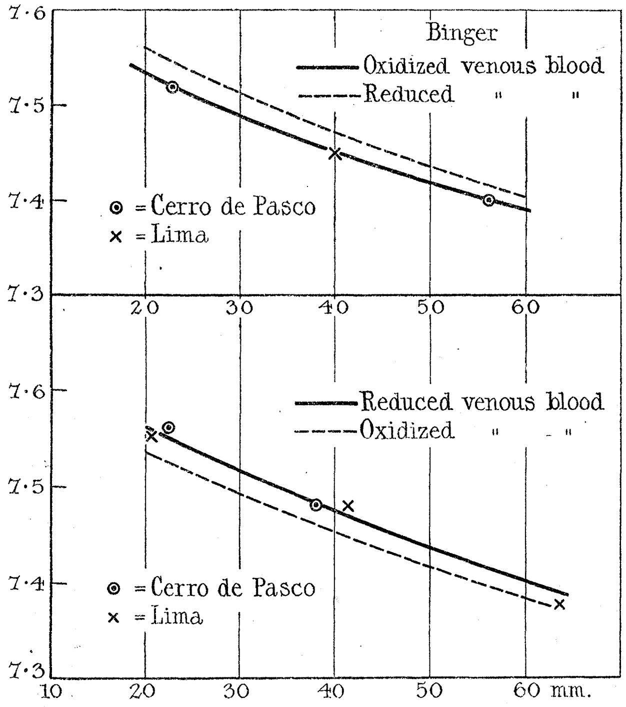

FIG. 12.

TABLE V.—Binger's Blood. Pressures in mm.

	*p*H.	CO_2.	O_2.
December 15/21, Lima	7·38	63·4	3·0
	7·48	41·6	4·7
	7·55	20·6	6·2
	7·45	40·1	Saturated
January 8/22, Cerro	7·52	22·8	,,
	7·40	56·0	,,
	7·56	22·4	8·0
	7·48	38·0	3·7

The results obtained from the titration of blood withdrawn by arterial puncture point also in the direction of increased alkalinity, the increase being greater.

TABLE VI.—Summary *p*H Data.

			Sea-level.		Cerro.
Bock	Cerro, Dec. 28/21 . . .				7·53
					7·51
				Mean	7·52
McLaughlan . .	Cerro, Jan. 1/22 . . .				7·48
					7·49
					7·52
				Mean	7·50
Forbes	Boston, Nov. 2/21 . .		7·48		
			7·49		
		Mean	7·48		
Binger	Lima, Dec. 18/21 . . .		7·44		7·72
			7·44		7·68
			7·44		
			7·48		
			7·50		
		Mean	7·46		7·70
Redfield	Boston, Oct. 27/21 . .		7·26		7·49
			7·36		7·56
			7·38		7·48
			7·38		7·42
		Mean	7·35		7·49
	Lima, Dec. 18/21 . .		7·53		
			7·56		
			7·50		
			7·53		
		Mean	7·54		
	Boston, May 6/22 . . .		7·49		
			7·40		
			7·50		
		Mean	7·49		

TABLE VI.—Summary *p*H Data—*continued.*

		Sea-level.	Cerro.
Harrop	Cerro, Dec. 30/21 .		7·56
			7·56
			7·54
		Mean	7·55

	Mean of all determinations.	
	Sea-level.	Cerro.
	7·48	7·42
	7·46	7·50
	7·35	7·70
	7·54	7·49
	7·49	7·55
Mean . . .	7·46	7·59

Passing from the method of titration to that of comparing the ratios of the combined fixed carbonic acid contents, we find that those measurements in which there was an immediate analysis of the blood from arterial punctures, show more or less of an increase in alkalinity in most cases. This is true, both when the carbonic acid content was measured by the Van Slyke apparatus and when it was measured by the Haldane method.

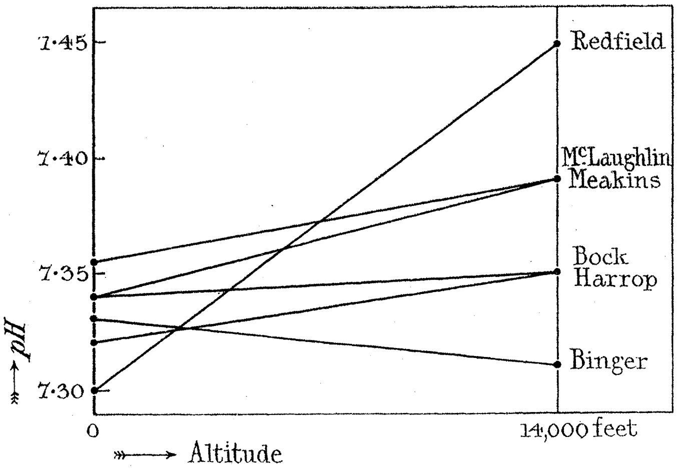

FIG. 13*a*.

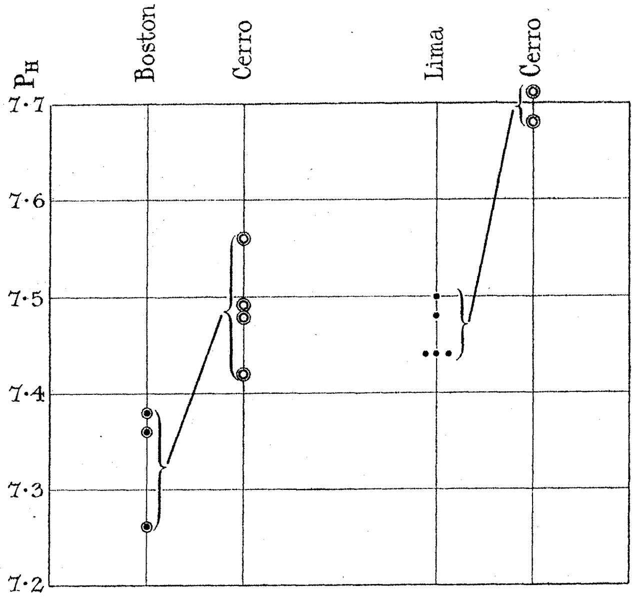

FIG. 13*b*.

FIG. 13*a* and *b*.—Comparison of apparent hydrogen-ion concentrations of arterial blood at sea-level and at Cerro de Pasco. 13*a* shows the extreme limits of change in reaction as shown by the Dale-Evans method in Redfield's and Binger's blood respectively. The actual change may be anything between nothing and the alteration indicated. 13*b* shows the measured changes in hydrogen-ion concentration by the CO_2 method uncorrected for any change in the quantity of hæmoglobins present.

Table VII gives the results which were obtained with what appears to be the limits of error. The general trend of the experiments is clearly seen from fig. 14. In the Table the letters V and H stand for the methods by which the total CO_2 was determined, V meaning Van Slyke's method, and H the constant pressure apparatus described by Haldane. In the figure, comparisons are only made between results in which the same method was used both at Cerro de Pasco and at sea-level.

The comparison of the values of "*p*H" at high and low altitudes shows that in no case was the concentration of hydrogen-ions appreciably greater at Cerro than at the sea-level. Usually the determinations at Cerro yielded a more alkaline figure, but only more alkaline by a very trifling amount, on the average about 0·2 *p*H. In making the calculations, there is the assumption that the constant pK_1 in Hasselbalch's formula has the same value in the case of the blood both at sea-level and at Cerro. This, however, would not necessarily be the case if the corpuscular content were markedly different, as in fact it was.

TABLE VII.—Corrected *p*H Figures.

Name.	Date.	Place.	CO_2 pressure.	Free CO_2.	CO_2* content.	Combined CO_2.	*p*H.	Remarks.
Meakins . . .	/ 5/21	Edinburgh	40·4	2·71	50·0 H	47·29	7·34	
	25/12/21	Cerro	28·0	1·88	32·5 V	30·62	7·31	
	9/ 1/22	„	26·0	1·75	36·0 H	34·25	7·39	
	9/ 1/22	„	26·0	1·75	29·3 V	27·55	7·30	
Redfield . . .	16/12/21	Lima	37·5	2·52	45·9 V	43·38	7·34	
	7/ 1/22	Cerro	23·0	1·54	36·0 H	34·46	7·45	
	7/ 1/22	„	24·6	1·65	30·0 H	28·35	7·34	Work.
	6/ 5/22	Boston	35·7	2·4	46·6 V	44·2	7·36	
	6/ 5/22	„	35·7	2·4	40·55 H	38·15	7·30	
	6/ 5/22	„	37·9	2·54	35·6 V	33·06	7·21	Work.
	6/ 5/22	„	37·9	2·54	34·36 H	31·82	7·20	Work.
Binger . . .	17/12/21	Lima	40·5	2·72	48·4 V	45·68	7·33	
	27/12/21	Cerro	29·4	1·97	36·0 H	34·03	7·34	
	27/12/21	„	29·4	1·95	34·5 V	32·55	7·31	
	2/ 3/22	Boston	37·0	2·48	47·0	44·52	7·35	
Bock	17/12/21	Lima	38·3	2·50	46·0 V	43·50	7·34	
	27/12/21	Cerro	29·1	1·95	37·0 H	35·05	7·35	
	27/12/21	„	29·1	1·95	36·3 V	34·35	7·35	
Harrop . . .	17/12/21	Lima	40·0	2·68	46·7 V	44·02	7·32	
	30/12/21	Cerro	29·1	1·95	37·0 V	35·05	7·35	
Philpott . . .	—	„	28·4	1·91	32·0 H	30·09	7·30	
McLaughlan .	—	„	26·5	1·78	37·0 H	35·22	7·40	
	—	„	26·5	1·78	35·6 V	33·82	7·38	
	14/ 3/22	Boston	37·5	2·52	48·5 V	45·98	7·36	
Cuthbertson .	—	Cerro	26·0	1·74	36·0 H	34·26	7·39	
Zalada . . .	—	„	28·8	1·93	27·0	25·07	7·21	
Villareal . . .	—	„	—	—	34·0	—	—	
Baracoyle . .	—	„	24·2	1·62	34·0	32·38	7·41	
Brava . . .	—	„	28·0	1·88	32·0	30·12	7·30	

Working formulæ—Free CO_2 = CO_2 pressure × 0·0672.
CO_2 combined = content − free CO_2.
*p*H − 6·1 × log CO_2 combined/CO_2 free.

* In this column V and H signify the methods by which this CO_2 was estimated. V = Van Slyke method, H = Haldane method. Results are comparable when done by the same method.

The ratio of the combined to the free CO_2 may be measured in another way (23), namely, from the HAGGARD–HENDERSON diagram. Results of two series of observations are given in figs. 14*a* and 14*b*. The diagrams are more complicated than is ordinarily the case, because it is necessary to obtain the CO_2 dissociation curve of the blood saturated with oxygen to the extent which obtains at the place. For this purpose the CO_2 dissociation curves of the blood, both fully oxidised and fully reduced, are obtained, and the arterial curve is interpolated (see the dotted lines).

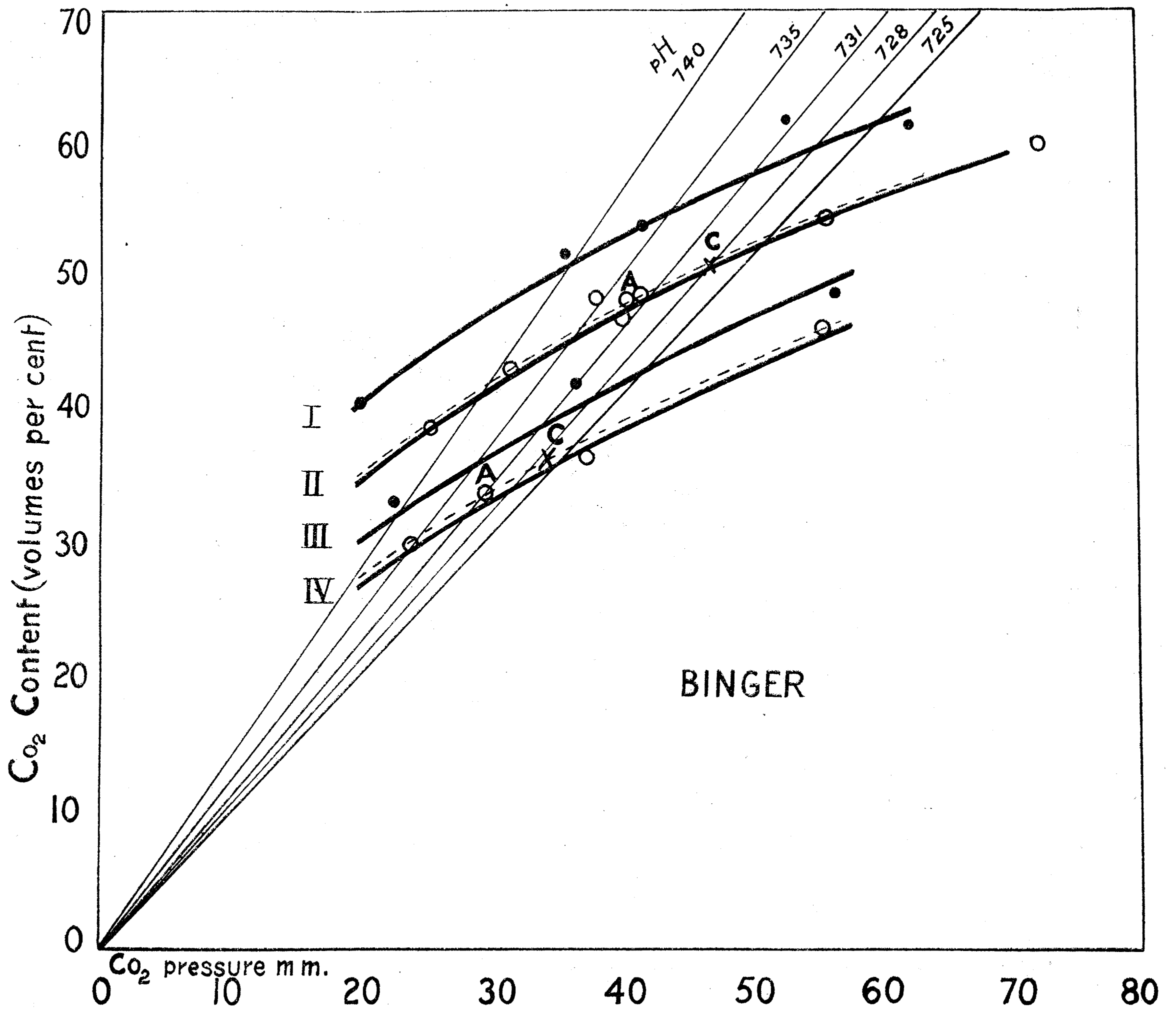

FIG. 14*a*.

FIGS. 14*a* and 14*b*.—● = fully oxidised blood. ○ = reduced blood. A⊙ = point corresponding to CO_2 pressure in alveolar. C × = point corresponding to CO_2 content in arterial blood. Curves I and II at sea-level; Curves III and IV at Cerro de Pasco. – – – – – – – = interpolated curves at oxygen saturation of arterial blood at the place.

The results show that :—

1. According to the diagram, there is little change in apparent hydrogen-ion concentration of the blood, whether (*a*) the carbonic acid pressure in the alveolar air

or (*b*) the carbonic acid-content of the arterial blood be taken as the point on the curve which indicates the ratio of combined to free CO_2.

2. There appears to be the same discrepancy between the points A and C as found by BARR and RULE. This discrepancy might be taken to indicate that the CO_2 pressure in the arterial bood was 5–8 mm. higher in the arterial blood than in the alveolar air. We hesitate to accept this reading of our results until we are more certain than at present that the discrepancy cannot be accounted for by *post-mortem* change in the blood from which the curves were determined. This blood, unlike that from which the content is determined, has to stand aside, and then be warmed up in the salivator for a considerable time; a development of acid equivalent to 0·3 *p*H in the process would account for the want of coincidence between the A and C points on the curve.

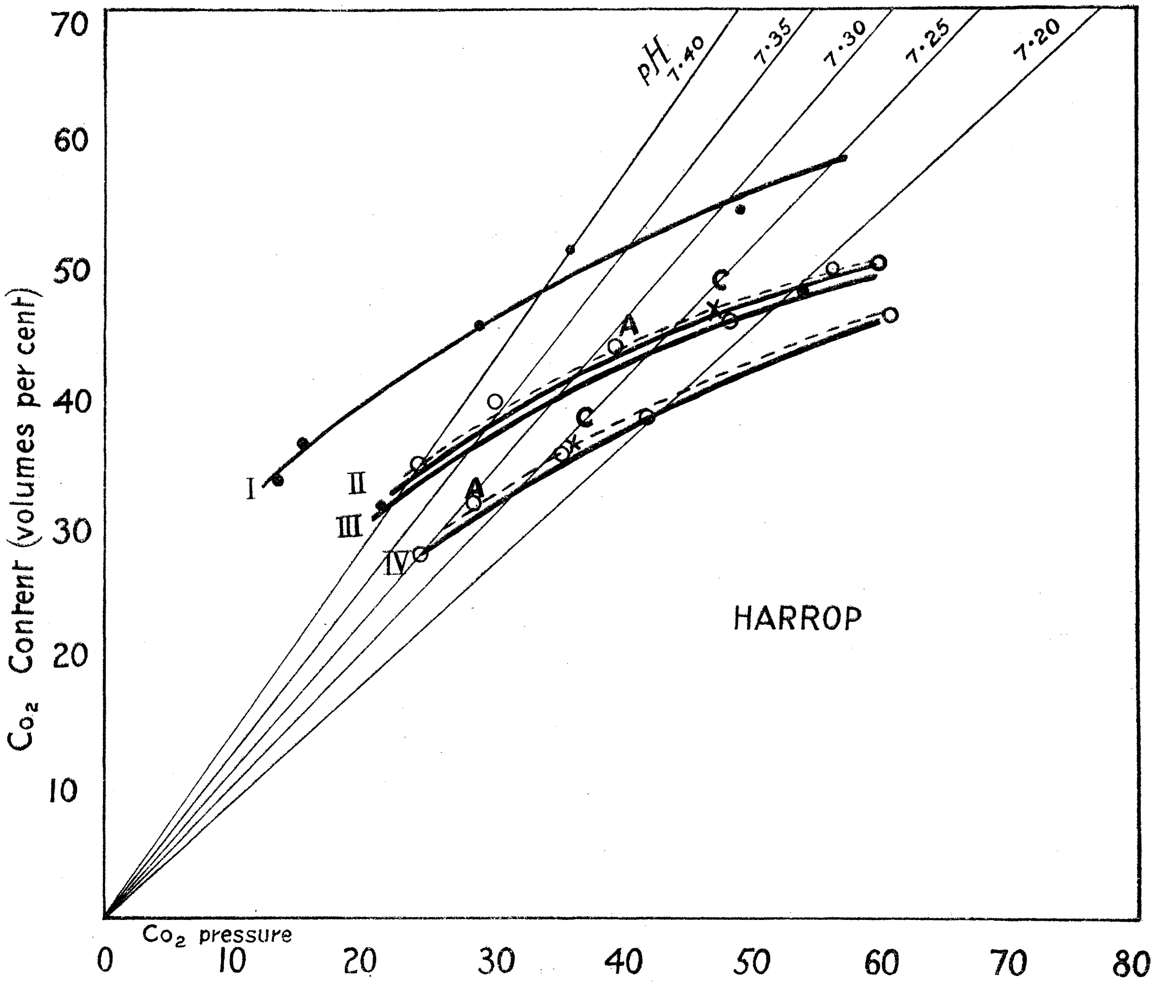

FIG. 14*b*.

(*b*) *The Hydrogen-Ion Concentration of the Blood during Activity.*

A single experiment was carried out at Cerro, in which the hydrogen-ion concentration of the blood was measured during work. The work was performed on a bicycle ergometer; the hydrogen-ion concentration was measured by the ratio of the free to the combined CO_2. At Boston, on the same individual, the experiment was repeated, the endeavour being to ascertain the quantity of work which would produce the same displacement in the hydrogen-ion concentration in the same time. The following are the data for the two experiments:—

TABLE VIII.

Boston.				Cerro.			
*p*H.			Work.	*p*H.			Work.
Before work.	After work.	Displacement.		Before work.	After work.	Displacement.	
7·30	7·20	0·10	750 kgrm. per minute.	7·45	7·34	0·11	193 kgrm. per minute.
7·36	7·21	0·15					
		0·12				0·11	

The above results agree with those obtained in the chamber experiment (21), in which at the end of six days' residence at a low and gradually diminishing oxygen pressure a somewhat similar result was obtained with the hydrogen electrode.

TABLE IX.

Atmospheric air.				Lower oxygen pressure.			
*p*H.			Work.	*p*H.			Work.
Before work.	After work.	Displacement.		Before work.	After work.	Displacement.	
7·43	7·35	0·08	640 kgrm. per minute for 36 minutes.	7·44	7·36	0·08	370 kgrm. per minute for 36 minutes.

Experiments in which the changes in the affinity for oxygen by hæmoglobin had suggested the change in hydrogen-ion concentration during exercise had given a similar result (15). These experiments were less reliable, for a number of reasons. In the first place, the change indicated by them took place in the corpuscles, and, in the second place, though change of reaction is the most potent cause of a shift in the value of K in HILL'S equation (26), it is not the sole possible cause. Such experiments could be regarded as indicating a change in the reaction of the plasma with a high degree of probability, but not with absolute certainty. It would seem that the probable interpretation of them was the correct one.

We have already alluded to the views put forward to account for the increase of respiratory effort at high altitudes; one of these views assumed that at a certain stage the blood became more acid, the other that at a certain stage it became more alkaline. These views were held by many to be mutually exclusive; the antithesis was heightened by the names given to them, for they were sometimes alluded to as the "acidosis" and "alkalosis" theories. The more thorough investigation which we have been able to give indicates that, so far from being mutually exclusive, they are complementary. The blood at rest is, if anything, more alkaline at high altitudes than at low ones—a change which would lead to apnœa but for the fact that the respiratory centre is rendered more sensitive by reason of deficient oxygen supply. The effect of change in reaction is, if it exists, more than balanced by that of the change in sensitivity, hence a somewhat increased total ventilation at rest. When exercise is taken a given increment in hydrogen-ion concentration is caused by a much less amount of exercise at the high altitudes than at the sea-level. Even, therefore, were the irritability of the respiratory centre the same, the subject would suffer from breathlessness on exercise. With a heightened irritability he suffers doubly.

C. THE MOVEMENT OF THE OXYGEN DISSOCIATION CURVE.

An examination of the blood of three natives of the mountains showed that the oxygen dissociation curve of the hæmoglobin as it circulated in the body was different from that of persons who have been examined hitherto, of whatever race and at whatever altitude. Briefly, the results of observations made hitherto have been as follows:—

(1) At or near the sea-level the oxygen dissociation curves of a great number of persons—American, British, German, Italian, Japanese, and others—have been determined and have fallen within the following limits of pressure for the percentage saturations specified below (26):—

Percentage saturation . . .	10	20	30	40	50	60	70	80	90
Limiting pressures (mm.) .	10	14	17	20	24	28	34	42	57
	12	17	21	24	29	34	40	51	72

These figures were obtained by the exposure of blood to the appropriate oxygen pressure in the presence of a partial pressure of CO_2 equal to that in the alveolar air of the subjects. Most of them were obtained by the differential method of blood gas analysis, some by the method of Barcroft and Haldane, as modified by Brodie. They were all obtained from defibrinated blood.

Many of the determinations in the present paper were carried out on blood which had been prevented clotting by the use of potassium oxalate, and the determinations were made in some cases with the Van Slyke apparatus. As a rule, however, hirudin was used for the prevention of clotting.

In order to eliminate the possibility of our conclusions being vitiated through the use of techniques which might not be strictly comparable, a series of determinations were made in the blood of a single person at sea-level :—

(*a*) By the Van Slyke method.
(*b*) By the differential method.

The results are shown in the figures given below.

It will be seen that the curves, as obtained by the two methods, are slightly different. It is not proposed here to discuss the cause of this difference, which is probably bound up with researches at present being carried on, on the action of ferricyanide on blood, by Drs. J. B. S. Haldane, C. G. Douglas and J. A. Priestley, of which they have been kind enough to tell us. We reproduce the curves merely as controls, for the purpose of comparison with the determinations made by similar techniques at high altitudes.

From fig. 15*a* it does not appear that the amount of oxalate used had any great effect on the position of the points. At the July (1922) meeting of the Physiological Society, a research, not yet in print, was communicated by H. O. R. Edmunds and T. Lanyon, which indicated that oxalate had a somewhat greater effect. The amount of oxalate which they used was not stated.

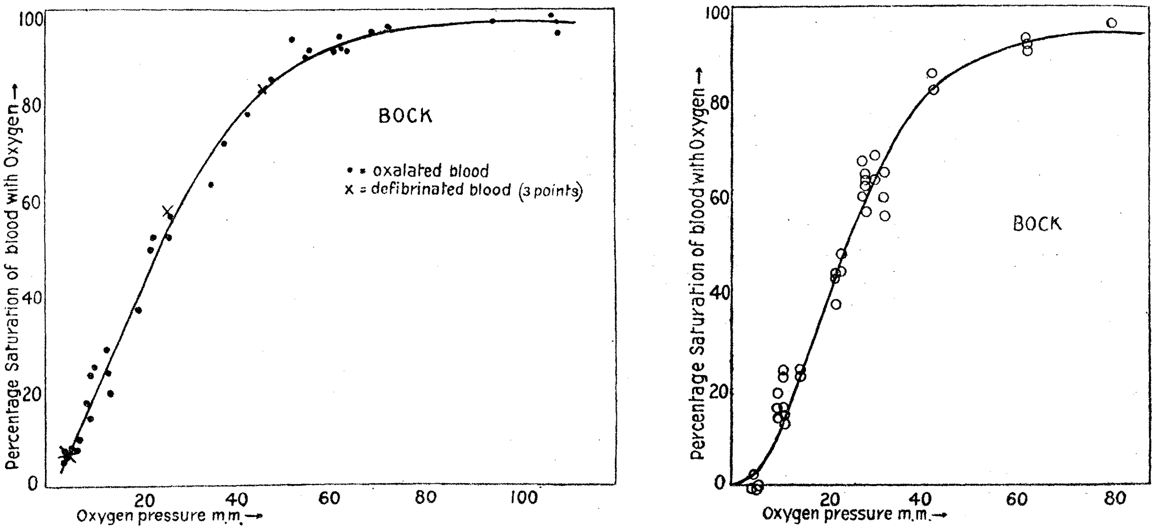

FIG. 15*a*. FIG. 15*b*.

FIG. 15*a*.—Oxygen dissociation curve of Bock's blood at 40 mm. CO_2 pressure obtained by the Van Slyke pump. FIG. 15*b*.—Points obtained by the differential apparatus on 0·1 c.c. of blood.

(2) Numerous experiments performed at the Cañadas, Teneriffe (altitude 7000 feet) (13) and Col d'Olen (Monte Rosa, altitude 10,000 feet) (15), showed that the dissociation curve at these altitudes remained sensibly the same as at the sea-level, *i.e.* that if at the sea-level the alveolar CO_2 was 40 mm., and at the Cañadas 32 mm., then the blood of the subject drawn at sea-level and equilibrated with

40 mm. CO_2 and 30 mm. O_2, or drawn at the Cañadas and equilibrated with 32 mm. CO_2 and 30 mm. oxygen, would give the same percentage saturation. At higher altitudes fewer experiments have been carried out, but such as have been done at the Alta Vista (13), Teneriffe (11,000 feet), Pike's Peak (4), Colorado (14,000 feet), and the Capanna Margherita, Monte Rosa (15,000 feet) (18), gave the same result. It is true that, averaging the portions of a great number of curves, there seemed to be the possibility of a slight shift, and that in the direction of increased pressure for a given content. This result, however, if it existed at all, was something so small as not to be discernible on any one curve.

The positions of the oxygen dissociation curves of the blood of three natives are given in the following diagrams. Their percentage saturations were determined in some cases by the Van Slyke apparatus, in others by the Haldane-Meakins The determinations by the different methods are distinguished in fig. 16*a*. This shift of the dissociation clearly enables the blood to pick up appreciably more oxygen than would otherwise be the case when the oxygen pressure is of the order of 40–50 mm. The question naturally arose whether the abnormal position of the curve was a racial characteristic or was merely a function of the altitude. This question was answered to some extent by the determinations made upon the Anglo-Saxon residents and on ourselves. Taking the former category first, Messrs. P. and McL. kindly allowed us to obtain blood from their vessels for our determination. In neither case was the curve so abnormal as in the case of Señor B. and probably of Señor V. Their bloods seemed to be both just near and probably just over the left-hand border of normality. It would be difficult to say that their blood had altered as the result of their residence.

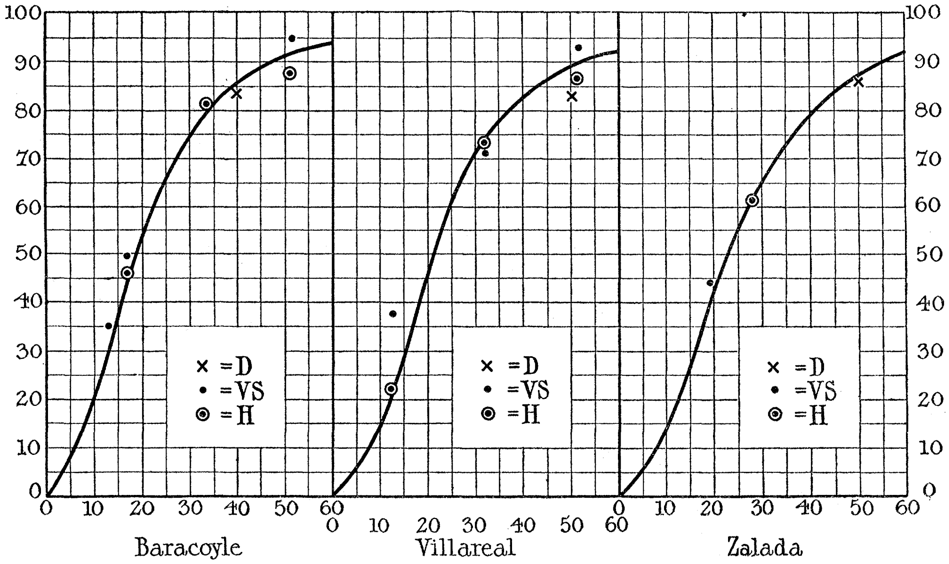

FIG. 16*a*.—Change in oxygen dissociation curve of natives. (Thick line, Cerro; dotted line, sea-level; D = differential; VS = Van Slyke; H = Haldane method.)

When we come to the members of our own party it becomes quite clear that their curves changed, as the curves (Fig. 16*b*), determined at Cerro de Pasco and at sea-level, show.

Summarising the observations which we have made on the reaction of the blood and on the dissociation curve and the alveolar CO_2, we arrive at the following statement:—

(1) The alveolar CO_2 drops from 40 to between 25 and 30 mm.

(2) The reaction of the plasma bears an unchanged relation to the CO_2 pressure, which suggests that at the lowered CO_2 pressure the reaction would become more alkaline (Dale-Evans method).

(3) The reaction of the plasma as measured by the Dale-Evans method does appear no less alkaline and possibly more so.

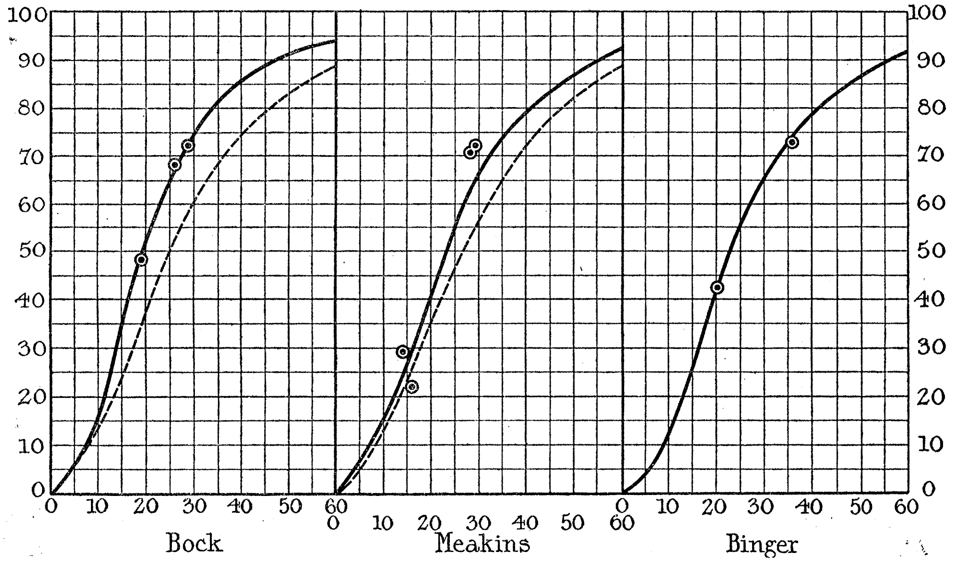

FIG. 16*b*.—Oxygen dissociation curve of members of expedition.

(4) Measured by the relation of free to combined CO_2, the blood appeared to be normal, or almost normal, in reaction. The measurements made in this category were numerous and consistent.

(5) The oxygen dissociation curve shifts in the direction of increased saturation for any given oxygen pressure.

The two most urgent questions which arise are: (1) Is there, or is there not, an alkalæmia? (2) If there is not, by what mechanism does the oxygen dissociation curve shift?

The second of these questions may be taken first, for the purposes of eliminating one possibility. Many observers (27) have supposed that carbonic acid has a specific action in turning the oxygen out of hæmoglobin. If that is true the problem presents no difficulty; its solution would be, the dissociation curve shifts because of the lowered CO_2 tension. The effect of CO_2 on the curve being a specific one, no assumption need be made with reference to the concentration of hydrogen-ions. Although this contingency seemed to go counter to previous work, in which the dissociation had been observed, in some cases, not to shift at lowered CO_2 pressures, there could be no excuse for leaving the matter in doubt. One of us, in collaboration with Mr. C. D. MURRAY, put the matter to the test of direct experiment, and found that CO_2 has no appreciable specific effect on the affinity of the blood for oxygen (see Appendix II). The change in the dissociation curve cannot be attributed to a specific CO_2 effect. Having eliminated that possibility, it becomes the more urgent to settle whether there is, or is not, an alkalæmia. At first sight there appears to be a conflict of methods—the Dale-Evans method against the $\frac{\text{Bicarbonate}}{\text{Free } CO_2}$ method. The latter method was applied in two ways: (1) by the determination of alveolar CO_2 and that of blood withdrawn by direct arterial puncture; (2) by the Henderson diagrams. In both cases the answer was the same, namely that the $\frac{\text{Bicarbonate}}{\text{Free } CO_2}$ was approximately unaltered.

If the data obtained by the Dale-Evans method are accepted, it is difficult to avoid the possibility of an alkalæmia.

The discrepancy might have remained, and the cause of the altered dissociation curve have been unexplained, but for a suggestion made by Mr. CECIL D. MURRAY (see Appendix III). As a result of it, we succeeded in reproducing a sample of blood, which has all the properties (including the apparent discrepancies) of the blood of the people at Cerro. This was accomplished in the following simple way: Blood was withdrawn from a vein in a syringe, and just sufficient oxalate added to prevent its coagulating. The blood was then shaken in a flask, and when the CO_2 had been in part removed the blood was centrifugalised. Plasma and corpuscles were mixed to imitate the concentration of corpuscles at Cerro, *i.e.* till the hæmoglobin value was about 140. The blood so obtained had the following characteristics:—

		Blood before centrifugalisation.	Concentrated fraction after centrifugalisation.
Composition of gas in saturation	O_2 mm.	19	17
	CO_2 mm.	19	27
	Hydrogen	—	—
Observed percentage saturation		40	65
1/K calculated from observed data		2400	620
1/K extrapolated to 27 mm. CO_2 pressure in each case by Henderson-Adair line		3400	620
Calculated percentage saturation at 17 mm. O_2 pressure and 27 mm. CO_2 pressure		37	74
Hydrogen-ion concentration (exponent) of plasma observed by hydrogen electrode at 29 mm. CO_2		**7·41**	7·37
Hydrogen extrapolated to 40 mm. CO_2, that of the body at sea-level		—	**7·31**

The reason for the concentration of corpuscles at high altitudes has in recent years been somewhat of a mystery (28). Formerly it was supposed that the object to be obtained by the organism was merely the transport of a certain quantity of oxygen in the blood. More recent workers have recognised the insufficiency of this idea. It would now seem probable that the extra degree of buffering which the blood acquires is an important factor. It allows of a more alkaline corpuscle at a given CO_2 pressure of 25 mm., a higher dissociation curve, and therefore a corpuscle which is more acquisitive of oxygen in the lung.

In a later section will be formed a discussion of the relative importance of the observed factors which make for adaptation. Here it need only be said that the factor of concentration of red blood corpuscles appears now in a new light. If no change took place in the properties of the corpuscle, the benefit which the increased corpuscle count seemed to confer on the body was small, out of all proportion to the magnitude of the concentration. That concentration of the corpuscles, coupled with alteration of the CO_2 tension, should give the blood a highly satisfactory oxygen dissociation curve greatly enhances the importance of the polycythæmia.

D. The Shape and Size of the Chest and Hands.

It is notorious that the population indigenous to the Pampas between the eastern and western Cordilleras has a chest development which is remarkable even to the naked eye. Efforts were made to study the chest in various ways which will now be taken in order.

X-Ray Measurements.—Chest.

Measurements were made from X-ray films used for examining the heart size of the chests of five members of the Expedition, both at sea-level and at Oroya or Cerro de Pasco, with the object of determining: (1) whether there was any observable difference in the dimensions of the chest as the result of temporary residence at a high altitude; and (2) whether any difference existed between the proportions of the chests of ourselves and members of the native population. For the latter comparison X-ray pictures were made of the chests of seven Peruvians who had resided for many years at a high altitude.

Measurement.—The selection of indices for measurement was guided largely by practical considerations, resulting from the fact that the Expedition was equipped with X-ray films for use in studying heart size, which were smaller (11 × 14 in.) than is desirable for chest measurement. The points to be measured consequently had to be chosen so that they could be found on the pictures made with these smaller films. They are indicated in fig. 17.

Height.—The vertical distance between the diaphragm and the junction of the clavicle with the first rib. A line is drawn through the mid-line of the vertebral column. Transecting it at A is drawn a line, *aa*, joining the points of intersection of the diaphragm and the right and left margins of the heart. Transecting it at B is drawn a line, *bb*, joining the right and left junction points of the clavicle and first rib. The distance AB is taken as chest *height*.

Width.—A line, C*d*, is drawn perpendicular to the mid-line from C, the outermost point on the inner margin of the eighth rib. A similar line is drawn on the opposite side. The sum of the lengths of these two lines is taken as the chest width. Owing to the size of the films employed, it was frequently possible to locate the point C on one side only. In such cases the chest width was taken as twice the length of the line C*d*.

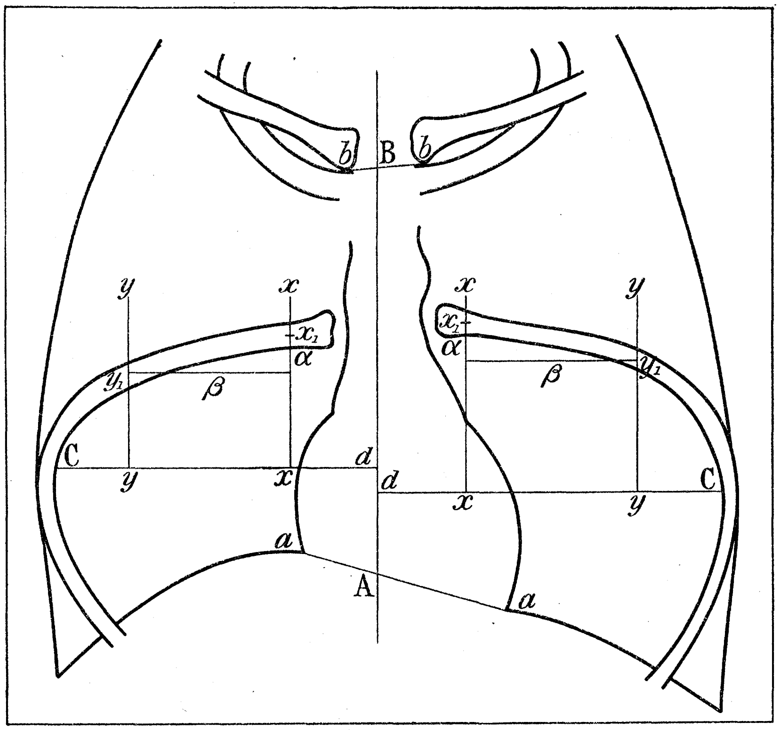

Fig. 17.

Slope of Rib.—Lines *xx* and *yy* are drawn parallel to the mid-line and at distances from it respectively of one-quarter and three-quarters the length of C*d*. Points x_1 and y_1 are located on *xx* and *yy* where these lines cut the mid-line of the eighth rib. The line β, drawn through y_1 perpendicular to *xx* and *yy*, cuts *xx* at a point below x_1, and at a distance from x designated as α. The slope of the rib is taken as the average value of α/β as measured on the right and left sides.

Meaning of Indices.—The ratio of height to width may depend on (1) the general skeletal proportions and (2) the mean position of the chest and diaphragm during respiration. Increase in the chest volume by elevation of the ribs will increase both height and width by elevating the sternum. Increase by lowering the diaphragm will increase the height alone without altering the width appreciably. The ratio of height to width will consequently increase under these conditions. The slope of the rib will be unaffected by a diaphragmatic alteration in chest capacity, but will decrease if such alteration is brought about by elevation of the ribs.

Results.—In comparing the height with ratio and the slope of the eighth rib in members of the expedition, it is clear that the individual variations in the measurements are so large that no significance can be attached to such differences as occur in the films made at sea-level and at various times after reaching the high altitude.

Comparing the Anglo-Saxon group with the native Peruvian group, it is clear enough that, on the whole, the former present a larger height-width ratio and a greater rib-slope. There is, however, a considerable overlapping of the two groups. The distinctness of the grouping becomes clear when the two factors are plotted simultaneously, as in a correlation table. It then appears that the areas occupied by the two groups of subjects do not overlap. The meaning appears to be that the chest volume of the Peruvian is attained by an elevation of the ribs, which lowers the slope, whereas relatively the Anglo-Saxon has a more elongated chest, in which the volume is attained with less elevation of the ribs, and either a relatively greater depression of the diaphragm or by a relatively elongated spinal column. The problem is one requiring statistical treatment, and for this the number of observations is insufficient. They suffice, however, to point out a very interesting problem in physiological anthropology.

The measurements of the Anglo-Saxon miners seem too scanty to warrant much consideration, particularly as we were unable to get the heights of two of them.

TABLE XI.

Name, place and date.	Height.	Width.	$\frac{\text{Height}}{\text{Width}}$.	α.		β.	$\frac{\text{Slope}}{(\text{Mean } \alpha/\beta)}$.
				Right.	Left.		
Redfield, Boston, Mass., Mar. 24, 1922	18·0	27·2	0·64	3·2	2·2	6·7	0·395
	17·9	26·4	0·67	3·5	1·9	6·6	0·409
	17·9	27·0	0·66	3·4	2·0	6·8	0·397
		Mean	0·66				0·400
Cerro de Pasco, Dec. 30, 1921 .	17·9	26·8	0·67	3·25	2·25	6·7	0·410
	17·7	27·0	0·66	3·4	2·3	6·8	0·420
		Mean	0·66				0·415
Meakins, Oroya, Dec. 23, 1921 .	20·1	27·8	0·725	3·4	2·2	6·96	0·403
	20·7	27·2	0·762	2·9	1·6	6·8	0·330
	19·7	27·3	0·723	2·8	1·8	6·8	0·338
		Mean	0·733				0·357
Cerro de Pasco, Jan. 10, 1922. .	20·7	26·4	0·793	3·25	1·6	6·6	0·362
	20·6	26·0	0·793	3·0	1·5	6·5	0·346
	20·8	27·2	0·766	3·3	1·6	6·8	0·360
		Mean	0·784				0·356
Edinburgh, April 7, 1922 . . .	20·0	28·2	0·71	2·5	1·8	7·0	0·308
	19·7	28·3	0·698	2·3	2·1	7·0	0·304
		Mean	0·704				0·306

TABLE XI—*continued.*

Name, place and date.	Height.	Width.	$\frac{\text{Height}}{\text{Width}}$.	α.		β.	$\frac{\text{Slope}}{(\text{Mean } \alpha/\beta)}$.
				Right.	Left.		
Forbes, Boston, Mass., Mar. 24, 1922	19·4	27·0	0·72	2·05	1·8	6·8	0·284
	19·7	26·4	0·75	1·9	1·6	6·6	0·265
	21·0	26·5	0·794	1·75	1·6	6·6	0·254
		Mean	0·75				0·268
Oroya, Dec. 21, 1921	19·9	25·6	0·78	1·7	1·9	6·4	0·281
	19·3	25·0	0·77	1·6	2·0	6·4	0·281
	19·7	25·9	0·76	1·9	1·8	6·5	0·285
		Mean	0·77				0·282
Bock, Boston, Mass., Mar. 24, 1922	15·7	29·0	0·54	2·75	0·7	7·2	0·517
	17·0	26·8	0·635	3·5	3·9	6·7	0·552
	16·1	26·9	0·600	2·9	3·9	6·7	0·507
		Mean	0·592				0·525
Oroya	17·5	27·9	0·63	1·5	4·5	7·0	0·428
	16·3	27·2	0·60	2·75	4·2	6·8	0·511
	17·2	27·5	0·626	3·2	4·3	6·9	0·543
		Mean	0·618				0·470
Barcroft, Oroya, Dec. 23, 1921 .	18·8	25·2	0·746	3·8	2·2	6·3	0·477
	19·2	26·0	0·740	3·4	2·2	6·5	0·431
		Mean	0·743				0·454
Cerro de Pasco, Jan. 10, 1922 .	19·0	24·0	0·793	3·3	1·3	6·0	0·383

TABLE XII.

Name, place and date.	Height.	Width.	$\frac{\text{Height}}{\text{Width}}$.	α.		β.	$\frac{\text{Slope}}{(\text{Mean } \alpha/\beta)}$.
				Right.	Left.		
McLaughlan, Cerro de Pasco, Jan. 2, 1922	19·2	26·4	0·73	1·2	0·8	6·6	0·15
	19·1	26·4	0·72	1·3	0·4	6·6	0·13
	19·3	26·4	0·73	1·3	0·5	6·6	0·14
		Mean	0·73				0·14
Cuthbertson, Cerro de Pasco . .	14·9	28·8	—	2·2	2·8	7·2	0·35
McQueen, Cerro de Pasco . . .	14·3	28·6	—	0·8	0·0	7·2	0·55

TABLE XIII.

Name.	Height.	Width.	$\frac{\text{Height}}{\text{Width}}$.	α.		β.	$\frac{\text{Slope}}{(\text{Mean } \alpha/\beta)}$.
				Right.	Left.		
Verastigo	19·6	28·7	0·684	1·4	2·0	7·2	0·236
	20·1	28·6	0·700	1·5	1·9	7·2	0·236
		Mean	0·69				0·236
Villareal	18·4	26·0	0·71	1·1	1·1	6·5	0·171
Marino	13·5	24·0	0·564	2·6	2·5	6·0	0·421
Zalada	16·2	26·6	0·61	1·4	1·2	6·6	0·197
Baracoyle	18·2	27·0	0·675	1·2	2·2	6·7	0·203
Brava	14·9	26·0	0·574	1·6	2·2	6·5	0·293
Leandro	16·9	29·2	0·580	1·1	0·6	7·3	0·117

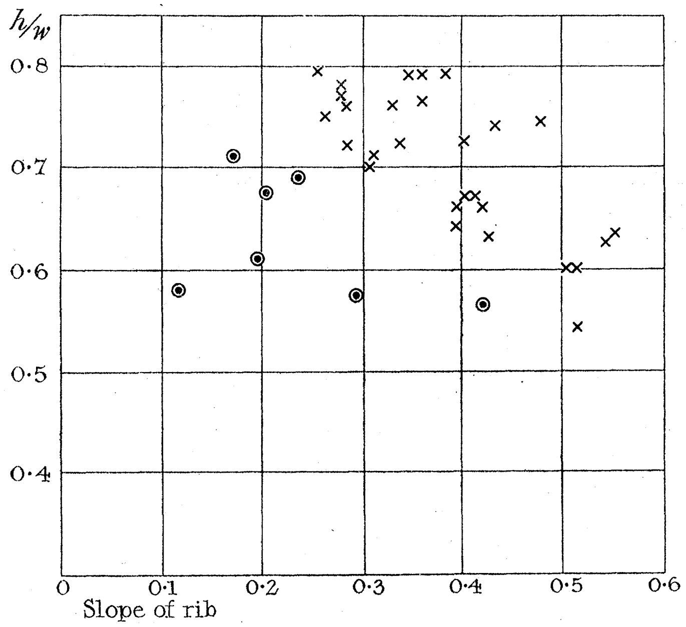

FIG. 18.—Correlation between height-width ratio and slope of the eighth rib in five Anglo-Saxons (×) and seven Peruvians, natives of high altitudes ⊙.

Measurements of the external dimensions of the chest tell much the same story. A calculation was made from Prof. DREYER'S data, which are based on measurements of Anglo-Saxons, showing that men of the average trunk-length of the native residents might be expected to have a chest circumference of 79·2 cm. Instead of this being the case, the average chest circumference of the persons concerned was 87·3 cm., a difference of about 10 per cent.

When it is remembered that the sectional area of the chest varies more or less as the square of the circumference, it would appear that these mountain dwellers had an area of trunk 20 per cent. larger than that of average Europeans of similar trunk measurement. The above-mentioned natives were not in any way selected or calculated from their occupations to be of exceptional development. They were such persons as clerks, waiters, etc.

Another group of eight persons was measured, who either worked in mines or the machine shops, or in other ways earned their livelihood by considerable physical work. Their chests were naturally even larger, though their statures were much the same; according to Prof. DREYER'S Tables, their chests would have measured 79·2 cm., while in reality they measured 92·3 cm.—a difference of over 16 per cent. in the circumference, which would correspond to a difference of between 30 and 60 per cent. in the sectional area. A good deal of care was taken to ascertain whether the chest in this case of the native resident was more barrel-shaped than that of the European. Certainly the impression which these people gave was that of peculiar depth of chest, and, as compared with the American and British residents at Cerro, it is clear that the front-to-back diameter was relatively much greater in the case of the residents, the average ratio of $\frac{\text{anterior posterior diam.}}{\text{transverse diam.}}$ in the case of the Anglo-Saxons being 72·9, and that of the natives of the neighbourhood of Cerro being 82·5.

We were much surprised, however, when we came to compare our own party with the natives in this respect to find that, in spite of appearances, there was very little difference. It may be that some of us have chests that are both shallow and narrow; that the Anglo-Saxon residents have chests that are signally broad, but not signally deep; whilst the natives of long-standing ancestry have chests which are both signally broad and signally deep, for their heights. Without laying too much stress on the shape, the above information may be summed up roughly by saying that the native of 5 feet 3 inches has the chest of a man of 6 feet. The details of the physical measurements are given in detail in the enclosed Tables.

We are indebted to Sir ARTHUR KEITH for a fuller analysis of our data, which will be found in Appendix IV.

A recognisable, though not great, degree of "clubbing" of the fingers is not uncommon among the natives. Fig. 3 (Plate 19) shows a type of hand which is not infrequent. The interesting point is that there were no pulmonary or cardiac lesions associated with the clubbed fingers in the cases which we examined.

E. AND F. DETERMINATIONS OF VITAL CAPACITY AND RESIDUAL ALVEOLAR AIR.

Measurements were made, in connection with the above work, of the vital capacity, middle capacity, and alveolar residual air of members of the expedition at sea-level and after a week or more of residence at Cerro de Pasco. The calibrated recording spirometer used for the diffusion constant experiments was employed, with the ordinary technique (29). The determinations indicated clearly, as shown in the accompanying Tables, that in this space of time, at least, no remarkable alteration had taken place in any of these measurements, calculated of course, unreduced, at the actual volume of gas existing in the lungs at the time of measurement.

TABLE XIV.—Lung Measurements. Vital Capacity Determinations.

	Dec. 16–18, Lima.	Jan. 8–10, Cerro.
Forbes	4690 c.c.	4740 c.c.
Redfield	5160	4475
Harrop	4840	4750
Binger	5290	5055
Bock	3990	3850
Meakins	—	4875
Philpotts	—	4510
MacQueen	—	4220
Rogers	—	4950

TABLE XV.—Alveolar Residual Air Determinations.

	Dec. 7–10, Lima.	Jan. 8–10, Cerro.
Forbes	1770 c.c.	1780 c.c.
Bock	1275	1310
Binger	1090	1080
Redfield	1990	1980
Harrop	1410	1380
Barcroft	—	1350
Meakins	—	1250
Doggart	—	1260
Philpotts	—	1130
Cuthbertson	—	1480
Colley	—	1080
McLaughlan	—	1110
Rogers	—	1960

G. DETERMINATIONS OF DIFFUSION COEFFICIENT BY THE CARBON MONOXIDE METHOD.

Determinations were made of the diffusion coefficient by the carbon monoxide method according to the technique of Dr. MARIE KROGH (30). Use was made of a spirometer and other apparatus from Prof. KROGH's laboratory.* The spirometer and time records were calibrated at Copenhagen. The calibrations were checked after the

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* It is desired to make grateful acknowledgment of Prof. Krogh's kindness in placing this apparatus at our disposal, and of his interest and many valuable suggestions as to the technique of carrying out the determinations.

instruments were set up at Lima and found to be essentially unchanged. For the gas analyses use was made of a portable model of the gas apparatus used in the laboratory at Copenhagen, which was designed by Dr. EINER LILJESTRAND, and purchased and calibrated through the kindness of Prof. A. V. SAHLSTED of Stockholm. It is provided with a burette with a capacity of 10 c.c. and with a U-shaped manometer filled with very dilute taurocholic acid solution for the purpose of adjusting the volume between the analysing and compensating burettes.

There seems to be a slight tendency on the part of the majority of diffusion coefficients to rise. This, however, does not take place in every case and would not seem to be an important element in acclimatisation. A number of diffusion coefficients were measured on residents. It is clear that, on the whole, they are higher than those of the party. It must be borne in mind that they should be regarded as selected individuals. The possible relation of the diffusion coefficients to "soroche" is considered later (see p. 449).

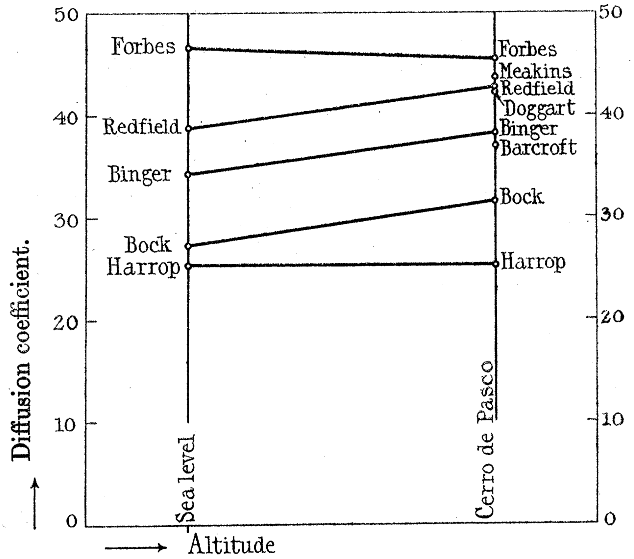

FIG. 19.—Diffusion coefficient = O_2 absorbed per c.c. mean difference of pressure.

TABLE XVI.—Diffusion Coefficient Determinations. CO Method.

	Diffusion Coefficient for CO.	Diffusion Coefficient for O_2.
Montserrate, December 12–16.		
Harrop (Copenhagen, May 27)	20·5	25·3
Bock	22·1	27·1
Barcroft	—	—
Binger	27·8	34·2
Doggart	—	—
Redfield	31·6	38·8
Forbes	38·1	46·8
Meakins	—	—

TABLE XVI—*continued.*

	Diffusion Coefficient for CO.	Diffusion Coefficient for O_2.
Cerro, December 27 to January 10.		
Harrop	20·6	25·4
Bock	25·9	31·8
Barcroft	29·2	36·0
Binger	31·3	38·3
Doggart	34·7	42·6
Redfield	34·9	42·9
Meakins	35·5	43·8
Forbes	37·0	45·6
Cerro, December 30 to January 10.		
Philpotts	35·2	43·4
McLaughlan	36·5	44·9
Cuthbertson	36·4	44·7
Colley	33·7	41·5
Rogers	53·1	65·3

H. INCREASE IN RED BLOOD CORPUSCLES AND HÆMOGLOBIN.

All recent observers (31) have noted that residence extending over some days or weeks at altitudes of over 12,000 feet is attended by an increased red blood count.

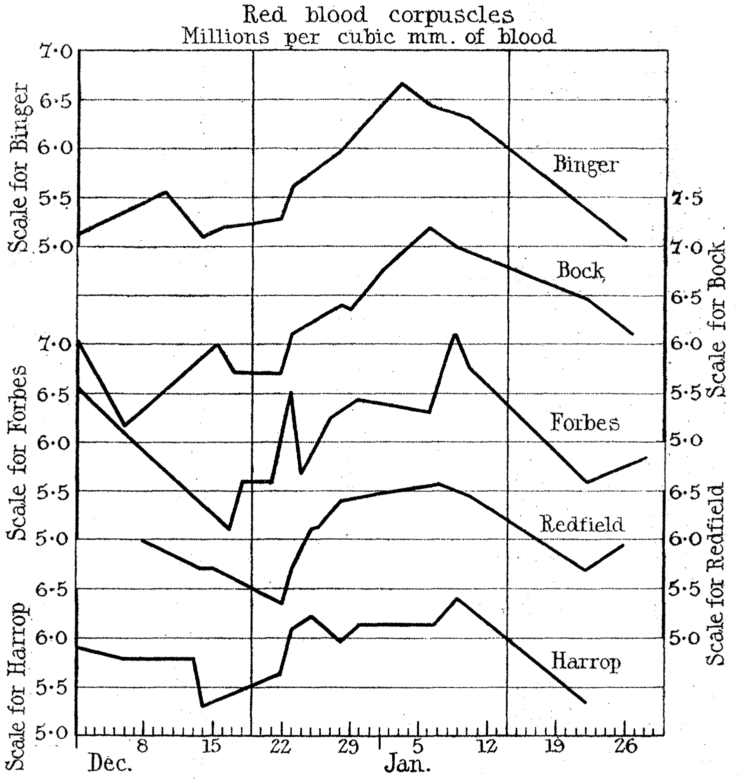

FIG 20.—The vertical lines represent the dates on which this party left and returned to Lima.

The question was very thoroughly gone into by the Pike's Peak Expedition of 1911, and we have little to add to their findings so far as the members of the party were concerned. Our corpuscle counts—and our hæmoglobins—rose very shortly after ascending the mountain. The counts which we made on the Anglo-Saxon residents were also quite similar to those made on the staff of the Pike's Peak Laboratory. In addition we made a large number of observations on the native population, who also had high red blood counts and hæmoglobin values.

The following Tables show the results obtained :—

TABLE XVII.—Hæmoglobin and Red Cell Counts.

Name.	Date.	Altitude.	Hb per cent.	R.B.C. millions.	R.B.C. per cent.	Colour index.
PARTY.						
Binger . . .	1/12/21	Sea-level		5·1	101	
	10/12/21	„		5·6	110	
	14/12/21	„		5·0	101	
	16/12/21	„		5·2	104	
	22/12/21	12,000 feet		5·3	106	
	23/12/21	12,000 „		5·6	111	
	25/12/21	14,000 „		6·0	120	
	26/12/21	14,000 „		5·7	113	
	28/12/21	14,000 „	106	6·0	121	0·9
	1/ 1/22	14,000 „	112			
	3/ 1/22	14,000 „	—	6·7	135	0·85
	6/ 1/22	14,000 „	112	6·5	129	0·85
	9/ 1/22	14,000 „	112	6·3	126	0·9
	22/ 1/22	Sea-level	—	5·0		
Bock . . .	1/12/21	„	—	6·0	120	
	6/12/21	„	—	5·1	102	
	15/12/21	„	—	6·1	121	
	17/12/21	„	—	5·7	114	
	22/12/21	12,000 feet	—	5·7	113	
	23/12/21	12,000 „	—	6·1	122	
	28/12/21	14,000 „	112	6·4	128	0·9
	29/12/21	14,000 „	112	6·4	127	0·9
	30/12/21	14,000 „				
	1/ 1/22	14,000 „	116	6·8	136	0·85
	2/ 1/22	14,000 „	—	6·9	138	0·9
	6/ 1/22	14,000 „	128	7·2	144	
	9/ 1/22	14,000 „	120	7·0	140	0·85
	22/ 1/22	Sea-level	—	6·6		
	26/ 1/22	„	—	6·0		
	2/ 2/22	Boston	—	6·0		
	18/ 5/22	„				
Forbes . . .	1/12/21	Sea-level	—	6·6	132	
	16/12/21	„	—	5·1	102	
	17/12/21	„	—	5·6	112	
	22/12/21	12,000 feet	—	6·0	120	
	23/12/21	12,000 „	—	6·6	131 (exer.)	
	25/12/21	14,200 „	—	5·7	113	
	26/12/21	14,200 „	—	6·3	125	

TABLE XVII—*continued.*

Name.	Date.	Altitude.	Hb per cent.	R.B.C. millions.	R.B.C. per cent.	Colour index.
PARTY (*contd.*)						
Forbes (*contd.*)	27/12/21	14,200 feet	108	—	—	0·85
	29/12/21	14,200 ,,	108	—	—	0·85
	30/12/21	14,200 ,,	—	6·4	129	
	6/ 1/22	14,200 ,,	124	6·3	126	1·0
	9/ 1/22	14,200 ,,	118	7·1	142	0·85
	10/ 1/22	14,200 ,,	112	6·8	136	0·8
	22/ 1/22	Sea-level	—	5·7		
	26/ 1/22	,,	—	6·0		
	8/ 5/22	,,	—	5·8		
	10/ 5/22	,,	—	5·1		
	11/ 5/22	,,	—	4·9		
	15/ 5/22	,,	—	5·6		
	16/ 5/22	,,	—	5·2		
Harrop.	1/12/21	,,	—	5·9	117	
	6/12/21	,,	—	5·8	116	
	13/12/21	,,	—	5·8	116	
	14/12/21	,,	—	5·4	107	
	22/12/21	12,000 feet	—	5·5	111	
	23/12/21	12,000 ,,	—	6·1	121	
	25/12/21	14,200 ,,	—	6·2	124	
	26/12/21	14,200 ,,	—	6·2	124	
	28/12/21	14,200 ,,	102	5·9	119	
	30/12/21	14,200 ,,	104	6·1	121	0·85
	4/ 1/22	14,200 ,,	—	6·1	121	0·85
	6/ 1/22	14,200 ,,	118	6·1	122	0·95
	9/ 1/22	14,200 ,,	120	6·4	128	0·95
	22/ 1/22	Sea-level	—	5·3		
Redfield	1/12/21	,,	—	4·9	98 (diarrhœa)	
	8/12/21	,,	—	6·0	119	
	13/12/21	,,				
	14/12/21	,,	—	5·7	114	
	15/12/21	,,	—	5·7	114	
	22/12/21	12,000 feet	—	5·3	106	
	23/12/21	12,000 ,,	—	5·7	114	
	25/12/21	14,000 ,,	—	6·1	122	
	26/12/21	14,000 ,,	—	6·1	122	
	28/12/21	14,000 ,,	—	6·4	127	
	1/ 1/22	14,000 ,,	116	6·5	129	0·9
	7/ 1/22	14,000 ,,	124	6·6	131	0·95
	10/ 1/22	14,000 ,,	120	6·5	130	0·95
	22/ 1/22	Sea-level	—	6·0		
	26/ 1/22	,,	—	6·0		
	11/ 5/22	,,	—	5·8		
	12/ 6/22	,,	—	5·3		
Meakins	11/12/21	,,	92			
	28/11/21	,,	95			
	29/11/21	,,	98			
	4/12/21	,,	96			
	14/12/21	,,	95			
	16/12/21	,,	94			
	20/12/21	3,000 feet	95			
	22/12/21	7,900 ,,	97			

TABLE XVII—*continued.*

Name.	Date.	Altitude.	Hb per cent.	R.B.C. millions.	R.B.C. per cent.	Colour index.
PARTY (*contd.*)						
Meakins (*contd.*)	23/12/21	7,900 feet	102			
	25/12/21	14,200 „	—	5·9	118	0·90
	26/12/21	14,200 „	106			
	30/12/21	14,200 „	106	6·3	127	0·85
	8/ 1/22	14,200 „	124	6·4	128	0·90
	9/ 1/22	14,200 „	122	6·2	123	1·0
	22/ 1/22	Sea-level	—	5·0		
	26/ 1/22	„	—	5·5		
Doggart . .	3/11/21	„	105			
	22/12/21	7,900 feet	95			
	23/12/21	7,900 „	103			
	30/12/21	14,200 „	112	5·6	112	1·0
	10/ 1/22	14,200 „	132	6·6	131	1·0
	26/ 1/22	Sea-level	—	5·5		
Barcroft . .	30/11/21	„	100			
	6/12/21	„	95			
	8/12/21	„	90			
	9/12/21	„	92			
	15/12/21	„	98			
	22/12/21	7,900 feet	96			
	23/12/21	7,900 „	101			
	28/12/21	14,200 „	108	6·6	132	0·8
	29/12/21	14,200 „	108	6·5	130	0·85
	7/ 1/22	14,200 „	116			
	8/ 1/22	14,200 „	—	7·0	140	0·85
	10/ 1/22	14,200 „	130	6·5	131	1·00
	22/ 1/22	Sea-level	—	5·0		
	22/ 1/22	„	—	4·9		
	26/ 1/22	„	—	5·3		

Name.	Date.	Altitude.	Hb per cent.	R.B.C. millions.	R.B.C. per cent.	Colour index.	Retic. cells of R.B.C. per cent.
WHITE RESIDENTS.		feet					
Hanna	28/12/21	14,200	—	6·7	125		
	8/ 1/22	14,200	128	6·9	128	0·95	
Philpotts	31/12/21	14,200	110	6·3	125	0·88	1·3
McLaughlan	1/ 1/22	14,200	120	6·6	132	0·90	1·5
	3/ 1/22	14,200	120				
McQueen	28/12/21	14,200	110	5·9	117	0·94	1·5
	31/12/21	14,200	118	6·4	128	0·95	
Cuthbertson	8/ 1/22	14,200	124	6·3	126	0·99	1·5
NATIVE RESIDENTS.							
G. Lavado	26/12/21	14,200	—	7·1	142		
E. Jaco	26/12/21	14,200	—	6·8	135		
B. Leandro	27/12/21	14,200	—	6·2	124		
A. Ochoa	2/ 1/22	14,200	—	7·3	146	—	1·3
	10/ 1/22	14,200	136	7·9	157		

TABLE XVII—*continued.*

Name.	Date.	Altitude.	Hb per cent.	R.B.C. millions.	R.B.C. per cent.	Colour index.	Retic. cells of R.B.C. per cent.
NATIVE RESIDENTS (*contd.*)		feet.					
Zalada	3/ 1/22	14,200	146	7·3	145		
Baracoyle	4/ 1/22	14,200	134	7·3	146	0·90	
Marino	4/ 1/22	14,200	122	6·4	127	0·95	
Villareal	4/ 1/22	14,200	148	7·1	141	1·05	1·2
Guzman	6/ 1/22	14,200	126	6·3	126	1·00	
Villar	2/ 1/22	14,230	122	6·9	138	0·90	1·7
	7/ 1/22	14,200	122				
Ventura	10/ 1/22	14,200	138	6·5	129	1·05	
Azabache	2/ 1/22	14,200	—	7·7	154		
Bravo	2/ 1/22	14,230	142	7·3	146	0·95	2·0
Malpastida	2/ 1/22	14,200	138	7·2	144	0·95	1·3
Portal	2/ 1/22	14,200	—	8·5	169	0·90	1·3
	6/ 1/22	14,200	150	8·4	168		

Colour Index.

The colour index showed no constant change in the party. The blood of the white residents and of the native residents had a normal colour index.

By an interesting paradox, the increase in hæmoglobin is so great that, in spite of the decreased saturation of the blood, and in spite of the fact that the "subjects are suffering more or less from oxygen want," there is actually more oxygen in each cubic centimetre of blood at Cerro than at the sea-level in most cases.

TABLE XVIII.

Subject.	Hæmoglobinometer reading.		Saturation.	Oxygen content per 100 c.c. blood.	Altitude.
Normal . . .	100 =	18·5 c.c.	O_2 × 96 p.c. =	17·7 c.c.	
Meakins . . .	99	18·3	95	17·4	Sea-level.
,, . .	100	18·5	95	17·5	,,
,, . . .	123	22·9	83	19·0	14,200 feet.
,, . . .	122	22·4	91	20·4	,,
Redfield . . .	99	18·4	97	17·9	Sea-level.
,, . . .	129	24·0	87·5	21·0	14,200 feet.
Binger	115	20·8	84	17·4	,,
Bock	100	18·5	95	17·5	Sea-level.
,, ...	128	23·8	82	19·6	14,200 feet.
McQueen . . .	110	20·4	86	17·5	,,
Philpotts . . .	110	20·4	91	18·5	,,
McLaughlan . .	120	22·2	86	19·2	,,
Cuthbertson . .	124	22·6	87	20·0	,,
Zalada	146	27·1	86	22·8	,,
Villareal . . .	148	27·4	82·5	22·8	,,
Baracoyle . . .	134	24·8	83·5	20·8 .	,,

The Reticulated Cell Counts.

The number of reticulated red cells in the blood of the various members of the party showed consistent changes. The normal figures obtained before the ascent were between 1—1·5 per cent. These figures are higher than the usually accepted ones. In counting the reticulated cells much depends upon the excellence of the film, exact focussing and a certain personal equation on the part of the counter enters; thus if two men A and B count the reticulated cells in the same film, A will always give an estimate which is consistently higher or consistently lower than B. In the present series all the counts have been made by one person, FORBES.

In five cases the data are pretty complete; in each the percentage of reticulated cells was much increased at Cerro; the maximal count was usually after about one week's residence. The count remained above the normal throughout the whole period of residence in every case, though in one, that of FORBES, it had dropped nearly to the normal before we left. The count on January 10 being 1·8 per cent. of the red corpuscles, that before the ascent being 1·5 per cent.

A remarkable feature of the series was the low counts which were obtained after we came down. The percentages in the second week after the descent being for the most part about 0·5—0·6 per cent.

The study of the *percentage* which the reticulated cells form of the total red cell count gives but a partial idea of their increase; the number of reticulated cells per cubic millimetre of blood is at least as instructive. The following figure shows it in the cases of which we have the most numerous counts.

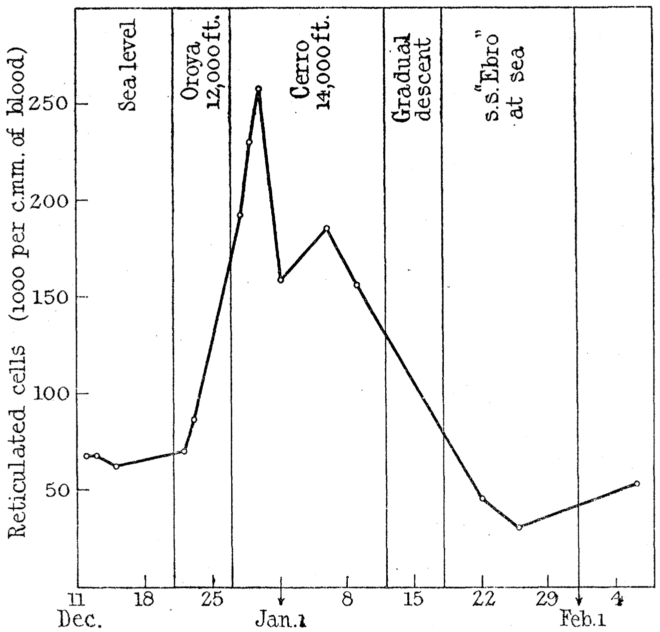

FIG. 21.—Reticulated cells in Bock's blood at different altitudes.

TABLE XIX.

Name.	Date.	Place and altitude.	Red corp. per cubic mm., millions.	Per cent. retic. cells.	Retic. cells per cubic mm., thousands.
Redfield	December 1	Lima	4·9		
	,, 8	500 feet	6·0		
	,, 13	—	—	1·3	74
	,, 14	—	5·7		
	,, 15	—	5·7		
	,, 22	Oroya	5·3	1·8	96
	,, 23	12,000 feet	5·7	2·2	125
	,, 25	Cerro	6·1	2·9	178
	,, 26	14,000 feet	6·1		
	,, 28	—	6·4	3·0	193
	January 1	—	6·5	2·6	169
	,, 7	—	5·6	2·1	118
	,, 10	—	6·5	1·9	123
	,, 22	S.S. Ebro	5·7	0·9	51
	,, 26	Sea-level	6·0	0·6	36
	May 11	Boston	5·8	1·2	69
	,, 18	,,	5·3	1·3	69
Forbes	December 1	Lima	6·9		
	,, 16	500 feet	5·1	1·5	76
	,, 17	—	5·8		
	,, 22	Oroya	6·0	1·5	90
	,, 23	12,000 feet	6·6		
	,, 25	Cerro	5·7	2·4	137
	,, 26	14,000 feet	6·3		
	,, 29	—	—	3·0	193
	,, 30	—	6·4	3·5	222
	January 1	—	—	2·7	173
	,, 2	—	—	2·0	128
	,, 6	—	6·3		
	,, 9	—	7·1		
	,, 10	—	6·8	1·8	122
	,, 22	S.S. Ebro	5·7	0·7	40
	,, 26	Sea-level	6·0	0·5	30
	May 8	Boston, A.M.	5·8	1·6	92
	,, 8	Boston, P.M.	—	1·6	92
	,, 10	,, ,,	5·1	1·6	82
	,, 11	,, ,,	4·9	1·2	86
	,, 15	,, ,,	1·6	1·5	84
	,, 16	,, ,,	5·2	1·3	68
Binger	December 1	Lima	5·1		
	,, 10	500 feet	5·6		
	,, 14	—	5·0	1·3	65
	,, 16	—	5·2		
	,, 22	Oroya	5·3	2·0	106
	,, 23	12,000 feet	5·6	2·6	146
	,, 25	Cerro	6·0	4·9	293
	,, 26	14,000 feet	5·7	4·9	280
	,, 28	—	6·0		
	January 3	—	6·7	3·7	248
	,, 6	—	6·5	3·3	214
	,, 9	—	6·3	2·0	126
	,, 22	S.S. Ebro	5·0	0·5	25
		Sea-level			

Table XIX—*continued.*

Name.	Date.	Place and altitude.	Red corp. per cubic mm., millions.	Per cent. retic. cells.	Retic. cells per cubic mm., thousands.
Harrop	December 1	Lima	5·9		
	„ 6	500 feet	5·8		
	„ 13	—	5·8		
	„ 14	—	5·2	1·3	68
	„ 22	Oroya	5·6	1·2	67
	„ 23	12,000 feet	6·1	1·4	85
	„ 25	Cerro	6·2	2·9	180
	„ 26	14,000 feet	6·2		
	„ 28	—	5·9		
	„ 30	—	6·1	4·1	250
	January 4	—	6·1		
	„ 6	—	6·1		
	„ 9	—	6·4	1·8	115
	„ 22	S.S. Ebro	5·3	0·5	26
		Sea-level			
Bock	December 1	Lima	6·0		
	„ 6	500 feet	5·1		
	„ 13	—	—	1·2	73
	„ 15	—	6·1		
	„ 17	—	5·7		
	„ 22	Oroya	5·7	1·2	68
	„ 23	12,000 feet	6·1	1·4	85
	„ 28	Cerro	6·4	3·0	192
	„ 30	14,000 feet	6·4	3·6	228
	January 1	—	6·8	3·9	265
	„ 2	—	6·9	2·3	156
	„ 6	—	7·2	2·6	186
	„ 9	—	7·0		
	„ 10	—	—	2·2	154
	„ 22	S.S. Ebro	6·6	0·7	46
	„ 26	Sea-level	6·0	0·5	30
	February 2	Boston	—	0·9	54
	„ 3	Sea-level (approx.)	6·0		
	May 18	—	—	1·5	
	„ 22	—	5·9	1·5	88
White Residents.					
Philpotts.	31/12/21	Cerro (14,200 feet)	6·3	1·3	82
McLaughlan . . .	1/ 1/22	„ „	6·6	1·5	100
McQueen	31/12/21	„ „	6·4	1·5	96
Cuthbertson . . .	8/ 1/22	„ „	6·3	1·5	95
Native Residents.					
Villareal	4/ 1/22	„ „	7·1	1·2	85
Ochova	2/ 1/22	„ „	7·3	1·3	95
Villar.	2/ 1/22	„ „	6·9	1·7	117
Bravo	2/ 1/22	„ „	7·3	2·0	146
Malpastida	2/ 1/22	„ „	7·2	1·3	97
Portal	2/ 1/22	„ „	8·5	1·3	110

The question naturally arises—would our reticulated cell counts have dropped to the normal level had we spent longer time on "at Cerro"? The only answer which we can give is that furnished by a study of the natives and of the Anglo-Saxon population. The following is a synopsis of the range of reticulated counts in these as compared with our sea-level counts and the last taken before our departure from Cerro:—

	Sea-level.	Last estimation at Cerro.	Anglo-Saxons at Cerro.	Natives at Cerro.
Per cent. of reticulated cells	1–1·5	2·2–1·8	1·3–1·5	1·2–2·0
Thousands of reticulated cells per cubic mm. blood .	58–77	115–154	82–100	85–146

The percentage of reticulated cells in the residents at Cerro was scarcely above the sea-level value of our party, and was markedly below that of our party when we left Cerro. It seems reasonable to suppose therefore that our reticulated cells, reckoned on a percentage of the total number of red blood corpuscles, would have fallen to or almost to its sea-level value. In other words, the increase in number of reticulated cells in a count (and this is very marked) goes hand in hand with the increase in the total number of red cells, just as the increase in the number of children, say of two years old, follows that of the general population. The most reasonable construction to put upon the above facts seems to be the following:—On reaching a high altitude there is a considerable growth both in the degree of activity and the actual amount of red marrow. As time goes on, and as an equilibrium is reached, the heightened activity passes off, but an increased quantity of marrow, proportional to the increased number of blood corpuscles in the body, remains. This marrow is normal in character, it is merely hypertrophied. If then we may regard the marrow as an organ, we have an instance of the hypertrophy of an organ in man brought about by a climatic change, namely, exposure to low barometric pressure. In animals it has been observed by Zuntz and his colleagues (10) on Monte Rosa, and by Dallwig, Kolls and Loevenhart in chamber experiments (32).*

Nucleated Red Cells.

None were found in films of blood either from ourselves or the natives.

I. The Pulse.

There is considerable divergence of opinion with regard to the effect of altitude on the pulse (31). The observations which have been made by us on the subject have not been many, and in some cases have been incidental; nevertheless, they seem to point to certain conclusions on the subject which may at least be helpful to future workers.

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* We should like to record our thanks to Dr. Cecil K. Drinker for his kindness in helping us to interpret the above results.

The first comparison which we would make, and as it seems to us the proper starting point, is that between the pulse under basal conditions at sea-level and at Cerro de Pasco. In making this comparison, we would draw attention to the fact that the values obtained at Cerro were in every case after several days of residence there. The figures given are averages usually of about four counts, which agree within a few beats.

The following Table will suffice :—

TABLE XX.—Pulse under Basal Conditions.

Name.	Place.	Pulse.	Pulse at Cerro.
Meakins	S.S. Victoria	63	60–63
	,,	63	
Barcroft	,,	60	58
	,,	64	
Bock	Lima	60	61
Binger	,,	60	60
Redfield	,,	57	65
			59
Harrop	,,	58	62

It is clear from the above that there is no difference between the basal pulse of one resident at Cerro de Pasco and the same person resident at sea-level. Whether this is true of altitudes higher than Cerro de Pasco we do not know, nor do we know whether it would be true at Cerro of persons with weaker hearts than our own. Within the period covered by the first few days of residence at Cerro, the pulse in bed in the morning was higher in most cases than the figure given above. In the case of Redfield, for instance, whose pulse at Lima was 57, on successive days after arrival at Oroya it was 64, 70, 70, 64, 62, 60; the last was at Cerro. Hence two reasons have revealed themselves for the divergence of opinion which exists: firstly, the lack of precise statement as to the conditions; and, secondly, as to the number of days after arrival.

Granting then that we take the basal condition as our starting point, what is the effect of exertion ? This matter we tested, though less completely than we could have wished, by the now well-known method of response to graduated exercises. The precise details of the test were used by Dr. G. H. Hunt of Guy's Hospital. This method is as follows: The subject carries out a series of exercises, each more severe than the last. Each exercise consists in getting on and off a stool a given number of times in 3 minutes. The severity of the exercise is regulated by the number of ascents on to the stool in that time. The stool is one-third of a metre in height. If time had allowed us to go into this matter in greater detail it would have been well worth while to obtain complete records, such as those published by Meakins and

Gunson (49) from the Hampstead Military Hospital. The pulse is taken at rest before each exercise, and for the 2 minutes immediately succeeding each exercise. The post-exercise pulse rate is divided by the resting pulse rate, and an index is obtained. For example :—

TABLE XXI.

Exercise.	No. of steps in 3 minutes.	Kilogram metres.	Resting pulse 2 minutes.	Post exercise pulse.		Index.
				1st min.	2nd min.	
I	36	—	146	84	78	1·11
II	54	—	140	89	78	1·19
III	72	—	138	108	83	1·38
IV	90	—	140	130	105	1·67

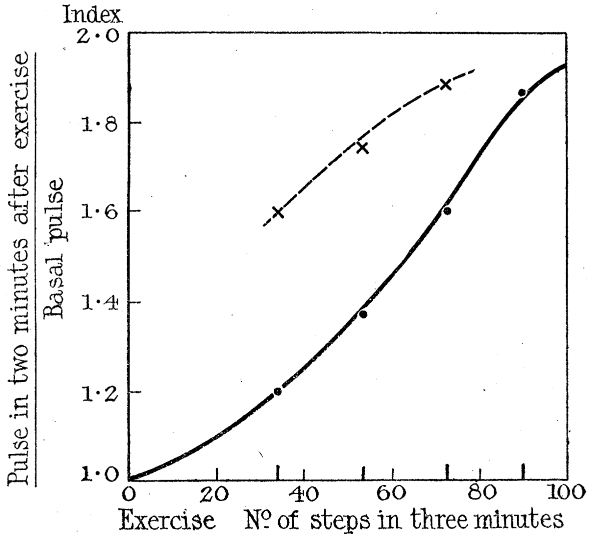

FIG. 22.

A graph is then constructed in which the index is the ordinate, and the severity of the exercise (either expressed in steps or kilogram metres) is the abscissa. In this way the amount of work which can be done before a certain index is reached can be ascertained.

In the present case we varied the method to this extent that, instead of using the resting pulse as obtained in the sitting posture, we used the basal as the denominator of the index. In the construction of the above graph, therefore, 62 is used as the basal pulse at the sea-level and 58 at Cerro de Pasco. The response of the pulse to the exercise stated is shown at sea-level by the black dots which represent observations made on the S.S. Victoria. At Chosica (2,700 feet) the response clearly does not differ (circle) from that at the sea-level. At Cerro de Pasco, however, the response to exercise is quite different, a much smaller degree of exercise being necessary to produce a given response. Quite similar results were obtained with regard to Meakins' pulse.

Fig. 22 suggests that the maximal response possible is no greater at Cerro than at sea-level. That response is obtained with a less degree of exercise.

Had the above figure been drawn from indices obtained by taking the resting pulse as the divisor instead of the basal pulse, little difference would have been seen between the curves at Cerro and at sea-level, the resting pulses being accelerated in about the same proportions as the exercise pulses.

One set of observations which appeared to be anomalous is of interest, as it brought out a special feature of the pulse. Whether the appearance of this feature was accidental, or whether it would always appear if the subject went to the same altitude from sea-level, could only be determined by a course of experiments. Barcroft, in the second minute after exercise, experienced a marked bradycardia, at Matucana, 7,700 feet, the following were the figures obtained from successive exercises. Similar *effects*, instances of bradycardia, were observed by Barcroft, Hunt, and Dufton in their investigations of gassed patients.

Table XXII.

Exercise	I	II	III
Steps in 3 minutes	36	54	72
Pulse at rest	67, 66	66, 67	65, 66
Pulse after exercise—			
First minute	75	80	90
Second minute	*62*	*67*	*74*
S.S. Victoria.			
Pulse at rest	64, 64	64, 65	68, 68
Pulse after exercise—			
First minute	79	98	
Second minute	*69*	*79*	

A number of estimations of the basal metabolism at Cerro and at the sea-level were made. These came out within normal limits at each place. It is not possible, therefore, to refer any quickening of the pulse which takes place to anything like hyperthyroidism. We conclude then that the basal pulse at Cerro was normal, that the exercise response was excessive, and that there is an exercise element in the usual pulse which makes it more rapid than at sea-level under the ordinary circumstances of life.

The cardiac response to exercise at these altitudes is very similar to that found in cases of so-called "irritable heart." In both instances there is an excessive cardiac rate on exercise, the increase being out of proportion to the amount of work done.

Furthermore, the rate continues to be excessive after the exertion has ceased and usually requires a much longer period of rest before returning to the free exercise rate. Another resemblance will be noted when the size of the heart is discussed. In the normal fit person the cardiac shadow, whether determined by instantaneous X-ray photographs or by the orthodiagraph, becomes distinctly smaller during exercise. This diminution in size is most apparent in systole, suggesting that there is a more complete systolic contraction (50). The evidence would indicate that the cardiac shadow during diastole followed the change during systole or nearly so in the majority of normal people. In cases of "irritable heart," however, there is no diminution in the cardiac shadow during exercise, or only in those cases where the symptoms are comparatively mild and of a temporary character. It will be noted in section K that there was a distinct diminution in the cardiac shadow in certain of the members of the Expedition at high altitudes, and that this was most definite in those who showed the least symptoms of "soroche."

TABLE XXIII.—Caloric Metabolism. Basal Conditions.

		R.Q.	Cals. per H.		Mean cals. per H.	Cals. per H. per sq. m.
			O_2 L.	CO_2 L.		
Meakins . .	Victoria . .	0·87	65·1	66·1	65·6	
	Victoria . .	0·91	66·3	66·4	66·3	35·0
	Cerro . . .	0·72	77·9	77·6	77·7	43·1
Barcroft . .	Victoria . .	0·79	59·8	58·2	59·0	
	Victoria . .	0·90	54·2	56·1	55·1	
	Cerro . . .	0·74	48·8	48·3	48·5	
Bock . . .	Lima . . .	0·82	68·0	67·8	67·9	
	Cerro . . .	0·87	60·7	60·7	60·7	
Binger . .	Lima . . .	0·92	63·8	63·9	63·8	
	Cerro . . .	0·93	61·3	61·1	61·2	
Redfield . .	Lima . . .	0·90	62·9	62·4	62·6	
	Cerro . . .	0·77	70·6	70·5	70·6	
Harrop . .	Lima . . .	0·98	60·9	60·9	60·9	33·4
	Cerro . . .	0·80	66·8	67·1	67·0	37·6

TABLE XXIV.—Basal Conditions.

Name.	Date.	Place.	Pulse.	Syst. pressure.	Resp.	Total ventilation L/L at 0 and 760.	CO_2 per cent.	O_2 per cent.	O_2 taken out.	R.Q.	O_2/m.	CO_2/m.
Meakins .	Dec. 5	Victoria	63	112	—	329	3·60	17·97	4·06	0·87	222	196
	„ 12	„	63	109	7	353	3·57	17·17	3·81	0·91	224	204
	Jan. 3	Cerro	60–63	150/90	12	256	4·69	15·64	6·46	0·72	276	198
Barcroft .	Dec. 4	Victoria	60	115	10	339	3·22	17·06	4·05	0·79	208	160
	„ 10	„	64	119/82	10–11	380	3·10	17·69	3·29	0·90	184	171
	„ 29	Cerro	58	130–90	14	211	3·60	15·72	4·87	0·74	172	126
Bock . .	„ 16	Lima	60	118/85	13	306	3·79	16·49	4·60	0·82	235	192
	„ 28	Cerro	66	118/75	14	220	4·94	15·52	5·63	0·87	207	180
Binger. .	„ 31	„	60	115/78	12	221	5·42	15·20	5·85	0·92	215	198
	„ 14	Lima	60	108/74	8	271	4·25	16·87	4·58	0·93	206	191
	Jan. 21	Ebro	60									
Redfield .	Dec. 13	Lima	57	112/78	17·18	321	3·59	17·02	3·96	0·90	213	190
	„ 26	Cerro	66	—	17	299	3·84	16·22	4·94	0·77	207	190
	Jan. 10	Ebro	59	120–95								
Harrop .	Dec. 12	Lima	58	125–85	14–18	323	3·73	17·16	3·77	0·98	202	198
	Jan. 1	Cerro	62	132–82	17	273	4·10	15·84	5·10	0·80	232	186

J. THE "MINUTE-VOLUME" OF BLOOD DRIVEN ROUND THE BODY.

Several methods have been described for the measurement of the number of litres of blood which pass from the right to the left side of the heart per minute. Those based on the absorption of nitrous oxide appeared to be unsuitable for our purpose as they need all the resources of a well-equipped laboratory. We were thrown back on some of the many methods for the application of FICK's principle, namely, that the amount of oxygen absorbed by the body per minute (or CO_2 exhaled) divided by the oxygen (or CO_2) difference between the arterial and venous blood (in cubic centimetre per litre of blood) gives the minute-volume in litres. Three modifications of the method have been used by us: that described (1) by BARCROFT, ROUGHTON and SHOJI (51); (2) MEAKINS and DAVIES (52); (3) a method to be alluded to as that of "Triple extrapolation." These methods are designated on Table XXV as B, M and T respectively. In method B the basis of the method is oxygen. The method, which is in principle, very similar to one previously described by FREDERICIA, gives satisfactory results during rest and on most persons; its principal drawback lies in the fact that during exercise the subject is likely to have his power of carrying out the details of the experimental procedure impaired. While the test appears to give a correct answer, and while all the corrections have been carefully worked out, there yet seems to be some doubt as to whether the equilibrium set up in the lung is not a somewhat artificial one.

The method of MEAKINS and DAVIES is based on the CO_2 estimations. It has the advantage of demanding little on the part of the subject and he never suffers from

TABLE XXV.

Name.	Date.	Method.	Place.	Altitude in feet.	Venous CO_2 pressure (mm.)	Venous CO_2 content vol. (p.c.).	Arterial CO_2 pressure (mm.).	Arterial CO_2 content vol. (p.c.).	Venous O_2 pressure (mm.).	Venous O_2 p.c. saturation.	Arterial O_2 p.c. saturation.
Meakins	11/12/21	B. & M.	Sea	0	46·3	53·9	37·7	49·8	36·8	69·5	95
,,	14/12/21	,,	,,	0	45·7	53·7	37·7	49·8	36·4	69·0	95
,,	16/12/21	,,	,,	0	44·1	53·0	37·0	49·4	36·8	69·5	95
,,	22/12/21	M.	Matuc.	7,880	42·4	52·2	36·4	49·0	—	60·0 ?	92 ?
,,	30/12/21	T.	Cerro	14,200	32·3	36·0	25·5	33·0	17·5	32·0	83
,,	9/ 1/22	T.	,,	14,200	29·0	35·0	25·9	33·0	28·0	60·0	91
,,	9/ 1/22	T.	,,	14,200	30·0	35·5	23·4	31·5	19·0	38·0	78·6
,,	27/ 1/22	T.	S.S. Ebro	0	43·8	32·8	37·0	49·2	37·0	65·0	95
Redfield	20/ 6/21	T.	Cambridge	50	45·0	53·4	36·3	50·5	36·0	68?	95
,,	26/12/21	T.	Cerro	14,200	32·0	37·0	24·2	32·3	32·0	62·0	87 ?
,,	7/ 1/22	T.	,,	14,200	29·3	34·8	22·8	31·0	30·5	58·0	87
,,	7/ 1/22	T.	,,	14,200	31·9	37·0	24·0	32·5	27·0	48·0	90
,,	28/ 1/22	T.	S.S. Ebro	0	40·3	51·0	30·0	47·0	39·0	73·0	95
Barcroft	6/12/21	B. & M.	S.S. Victoria	0	43·5	52·7	39·1	50·2	38·4	73·5	95
,,	8/12/21	B.	,,	0	—	—	—	—	38·5	73·5	95
,,	9/12/21	B. & M.	,,	0	45·1	53·5	38·8	50·1			
,,	15/12/21	,,	,,	0	43·4	52·7	37·2	49·5	39·6	75·0	95
,,	22/12/21	M.	Matuc.	7,880	44·1	52·9	38·9	50·4			
Harrop	20/12/21	M.	Chosica	3,000	46·0	46·0	38·3	43·0			

TABLE XXV—*continued.*

Name.	Date.	Method.	Place.	Altitude in feet.	CO_2 difference vols. (p.c.).*	O_2 difference vols. (p.c.).	CO_2 given up (c.c.).	O_2 taken up (c.c.).	Blood flow by CO_2 litres.	Blood flow by O_2 litres.	Pulse rate.
Meakins	11/12/21	B. & M.	Sea	0	6·0	5·00	249	273	4·15	5·36	69.
,,	14/12/21	,,	,,	0	5·88	5·46	216	254	3·68	4·68	66.
,,	16/12/21	,,	,,	0	5·5	5·36	270	311	4·91	5·86	72.
,,	22/12/21	M.	Matuc.	7,880	5·1	5·72 ?	286	325	5·6	5·68 ?	72 O_2 fig. assumed.
,,	30/12/21	T.	Cerro	14,200	5·5	9·8	304	399	5·53	4·1	86 Venous O_2 too low.
,,	9/ 1/22	T.	,,	14,200	3·5	6·99	201	252	5·75	3·2	75 at rest.
,,	9/ 1/22	T.	,,	14,200	6·0	9·0	815	877	13·6	9·8	— at work.
,,	27/ 1/22	T.	S.S. Ebro	0	5·4	5·9	293	316	5·42	5·36	66.
Redfield	20/ 6/21	T.	Cambridge	50	4·5	5·13	187	215	4·17	4·19	— Barcroft's O_2 curve.
,,	26/12/21	T.	Cerro	14,200	6·0	5·5	190	247	3·17	4·5 ?	66 (base).
,,	7/ 1/22	T.	,,	14,200	5·2	6·6	241	259	4·64	3·90	78 rest.
,,	7/ 1/22	T.	,,	14,200	5·6	9·6	849	958	15·2	10·0	— work.
,,	28/ 1/22	T.	S.S. Ebro	0	5·2	4·7	236	314	4·35	6·66	60.
Barcroft	6/12/21	B. & M.	S.S. Victoria	0	3·9	3·75	218	278	5·58	7·46	67.
,,	8/12/21	B.	,,	0	—	3·56	—	208	—	6·40	
,,	9/12/21	B. & M.	,,	0	4·7	—	252	—	5·36	—	80.
,,	15/12/21	,,	,,	0	4·5	3·64	222	242	5·0	6·60	66.
,,	22/12/21	M.	Matuc.	7,880	3·8	—	187	—	4·87	—	64.
Harrop	20/12/21	M.	Chosica	3,000	4·2	—	178	—	4·24	—	60.

* Volume percentage added on account of reduction of blood.

oxygen want during the test. It assumes, however, the validity of the CO_2 dissociation curves, which are of course much less stable than oxygen dissociation curves; the margin also between the CO_2 pressures in the arterial blood as indicated by the alveolar air and that obtained for the venous blood by analysis of the air samples is very small, being only a few millimetres; therefore an error of 1 mm. will make a great alteration in the apparent blood flow. Thirdly, there is a good deal of doubt as to what relation may exist between the CO_2 pressure in the bag and the CO_2 pressure that would have existed in the venous blood had no measurements been taking place. The last difficulty, though clearly set forth in Haldane's writings, seems to be but little understood and can best be grasped from an example.

Let us suppose (1) the amount of CO_2 given out to be 200 c.c. per minute, (2) that the CO_2 dissociation curves for oxidised and reduced blood are those given in the paper of DOUGLAS, CHRISTIANSEN and HALDANE, (3) that the pressures of gas in normal alveolar air and in the sample analysed after respiration from bag are as follows:—

	Alveolar air.	Henderson bag.
O_2	100 mm.	60 mm.
CO_2	40 mm.	45 mm.

If no corrections are made and the CO_2 contents are read off the CO_2 dissociation curve for oxidised blood, the CO_2 contents corresponding to the arterial and venous bloods would then be—

Blood.	Arterial.	Venous.	
Pressure . . .	CO_2 = 40 mm.	45 mm.	
Content . . .	CO_2 52 vols. p.c.	54 vols. p.c.	difference 2 vols. p.c.
Point on fig. 24	A.	B.	

According to this calculation the CO_2 difference would be 20 c.c. per litre of blood and the "minute-volume" 200 per cent. = 10 litres. Neither the arterial blood nor the venous blood are, however, completely oxidised. The arterial blood may be taken as 95 per cent. oxidised at sea-level, therefore the CO_2 will be

$$52+\left(\frac{5}{100}\times 57-52\right) = 52{\cdot}25, \quad \text{Fig. 24, point C}$$

(57 per cent. being the CO_2 content of reduced blood at 40 mm. pressure). The venous blood presents a more difficult problem. The gas in the expired sample contained 60 mm. oxygen. With this the blood was assumed to have been in equilibrium at the end of the last expiration and may be taken as 82 per cent. saturated with oxygen. On this basis the CO_2 content of the venous blood is

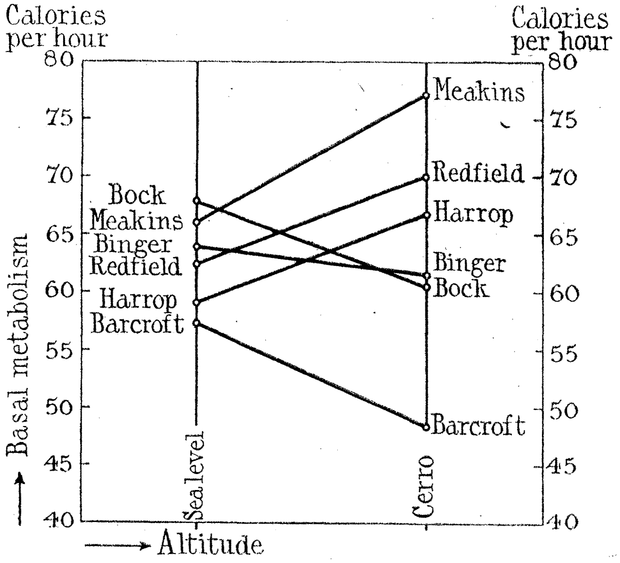

FIG. 23.

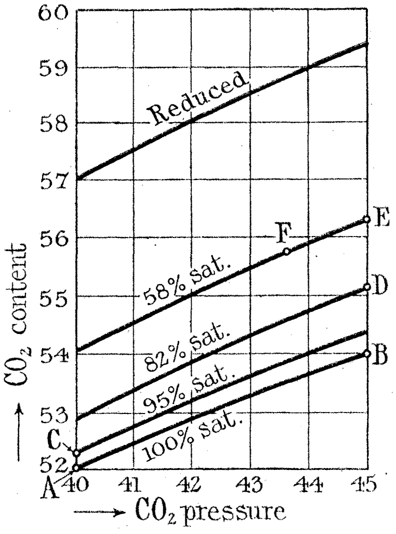

FIG. 24.

$$54+\left(\frac{108-82}{100}\times 59{\cdot}5-54\right) = 54{\cdot}99 \quad \text{(Fig. 24, D)}$$

(59·5 being the CO_2 content of reduced blood at 45 mm.). The minute-volume then would work out

$$200/10\,(54{\cdot}99-52{\cdot}25) = \frac{200}{27{\cdot}4} = 7{\cdot}3 \text{ litres.}$$

It is certain that even if such an equilibrium is reached, it is quite artificial.

The venous blood normally reaches the lung with a partial pressure of oxygen which in most persons is between 30 and 40 mm. The reason why it is 60 mm. in the bag is because venous blood cannot reduce the mixture of alveolar air, bag air and dead space air, which is drawn into the alveoli at the commencement of the respiration, below 60 mm. in the prescribed time. There is a temptation then to argue as follows :—Assuming the correct oxygen pressure to be about 35 mm., the correct oxygen saturation for the venous blood would be about 58 per cent., which would suggest the following content :—

$$54+\left(\frac{100-58}{100}\right)\times 5{\cdot}95-54 = 56{\cdot}31 \quad \text{(Fig. 23, E).}$$

The minute-volume would be

$$200/10\,(56{\cdot}31-52{\cdot}25) = 5 \text{ litres.}$$

But if the blood in the alveolar capillaries was in equilibrium with alveolar air at an oxygen pressure of 60 mm. and a CO_2 pressure of 45 mm., and if the oxygen pressure were reduced to 35 so that you could work on the 58 per cent. saturated curve, the CO_2 pressure would automatically alter, becoming less because there is less oxygen pressure to turn the CO_2 out of the blood; therefore, if the calculated figure is too high for oxygen it is automatically too high for CO_2 also; and if you apply the observed excessive figure for CO_2 pressure to the CO_2 dissociation curve for the correct oxygen saturation you will get too high a CO_2 content, too high a CO_2 difference between the arterial and venous blood, and too low a blood volume.

The correct point F which corresponds to a lower pressure of CO_2 will be situated at an indeterminate point lower down the curve.

In the observations marked T in Table XXV we have corrected up the figures on the basis of the points C and E, and the minute-volumes may be regarded as minimal. We also give in Table XXVI the CO_2 data treated as described in MEAKINS and DAVIES' paper (53); *i.e.* worked out on the basis of points A and B in the figure. To avoid these sources of error the method of "Triple extrapolation" was adopted. In it three successive tests are made as follows :—Each of three bags is filled with a mixture of nitrogen, oxygen and CO_2. This mixture is drawn into the lung in a deep inspiration, about one half is expired and a sample of alveolar air taken. After about 7 more seconds the rest is expired and another sample of alveolar air taken. It is not assumed that any of these samples have been in equilibrium with the mixed venous blood, merely that the second is more nearly in equilibrium than the first. If composition of the first and second samples plotted on graph, in which the oxygen is the abscissa and the CO_2 the ordinate, and a line be drawn from the first to the second and produced it will approach the true equilibrium point for both oxygen and CO_2. If the initial percentages of O_2 and CO_2 in the bags vary considerably from one another three such lines may be drawn which may meet in a point. If they do, the point

TABLE XXVI.—Blood Flow.

CO_2 Method. Calculated on " A and C " Points.

Date.	Place.	Conditions.	Altitude.	Venous CO_2 press. (mm. Hg).	Venous CO_2 vol. (p.c.).	Arterial CO_2 press. (mm. Hg.).	Arterial CO_2 vol. (p.c.).	Diff. vol. (p.c.).	CO_2 given up (c.c.).	Blood flow per min. (litres).	Pulse rate per min.	Volume per beat (c.c.).
					Meakins.							
27/10/21	Edinburgh	Rest chair . .	0	44·4	53·1	38·5	50·3	2·8	217	7·75	64	121
28/10/21	,,	Work 252 kgm. per M.	0	55·9	58·1	41·4	51·7	6·4	1104	17·25	141	122
11/12/21	At sea	Rest chair . .	0	45·3	53·5	37·7	49·8	3·7	249·5	6·74	69	98
14/12/21	,,	,, ,, . .	0	45·5	53·6	37·7	49·8	3·8	215·5	5·67	66	86
16/12/21	,,	,, ,, . .	0	44·4	53·0	37·0	49·4	3·6	270·5	7·50	74	102
22/12/21	Matucana	,, ,, . .	7,880	42·4	52·2	36·4	49·0	3·2	269·0	8·40	72	117
30/12/21	Cerro	,, ,, . .	14,200	32·3	36·0	25·5	33·0	3·0	304·0	10·10	86	116
9/ 1/22	,,	,, ,, . .	14,200	29·8	35·0	25·3	32·8	2·2	201·0	9·14	75	122
9/ 1/22	,,	Work 230 kgm. per M.	14,200	30·0	35·5	23·4	31·5	4·0	815·0	20·40	170–180	120–114
27/ 1/22	At sea	Rest chair . .	0	44·1	52·9	37·0	49·4	3·6	293·0	8·14	66	123
9/ 5/22	Edinburgh	,, ,, . .	0	44·8	53·6	39·0	50·4	3·2	250·0	7·81	65	120
					Redfield.							
20/ 6/21	Cambridge	Rest chair . .	50	45·0	53·4	36·3	49·2	4·2	187	4·45	?	?
26/12/21	Cerro	Basal	14,200	31·6	36·6	24·2	32·3	4·3	190	4·42	66	67
7/ 1/22	,,	Rest chair . .	14,200	29·3	34·8	22·8	31·0	3·8	241	6·34	80	79
7/ 1/22	,,	Work 193 kgm. per M.	14,200	31·9	37·0	24·6	32·7	4·3	849	19·74	125 ?	?
28/ 1/22	At sea	Rest chair . .	0	41·1	51·5	32·8	47·0	4·5	236	5·25	60	87

has been accepted as giving the true partial pressures of oxygen in the mixed venous blood and from it both oxygen and CO_2 contents may be obtained. The method is given in detail in Appendix V. Reverting to the methods of correcting the HENDERSON method, it is probable that any of them would give a fairly correct picture of the relative quantities of blood passing through the chest per minute at a given barometric pressure.

The differences between them become reduced at high altitudes, as owing to the low oxygen pressure in the inspired air, the discrepancy between the oxygen pressure in the bag and that in the mixed venous blood is reduced. At high altitudes no assumption can be made as to the composition of the arterial blood. It is necessary to obtain the blood by arterial puncture, and determine the oxygen and CO_2 contents by direct analysis.

We have treated our results in the following way :—(*a*) The minute-volume has been worked out on FICK'S principle both on the oxygen basis and the CO_2 basis, on the basis of points C and E; the two have then been averaged. We also give the results as calculated by MEAKINS and DAVIES, *i.e.* on the basis of the A and B points (fig. 24). These naturally give a greater minute-volume throughout and show a trifling rise in the minute-volume at Cerro, but they agree in the main with other methods in the following respects. Rough as the methods are, one or two facts emerge. A very trifling amount of exercise on the bicycle ergometer raises the blood flow between 100 to 300 per cent. No change of this order takes place as the result of residence at high altitudes, if one seeks for a change approaching one-tenth of this order, namely 20–30 per cent., one just reaches the point at which the discrepancies as between one method and another loom very large. It is not possible to be certain of a change of 20 per cent. in either direction, and at present one must consider that neither a rise nor a fall in the minute-volume of 20 per cent. was established at Cerro, whilst a change of a larger order was disproved. Since the pulse quickens, the systolic output may appear to be reduced, or approximately unchanged according to the method of estimation employed (see figs. 25 and 26). The above statements apply only to the two persons on which experiments were performed—Redfield and Meakins.

The following Tables give the data and the general summary of the variations which take place in pulse minute-volume and systolic output.

The effect of anoxæmia on the minute-volume had been tested by DOI on cats under urethane in the Cambridge (Eng.) Physiological Laboratory. Rather to our surprise, he found that, although there was an increase in the pulse rate, there was a fall in the minute-volume of blood which the heart discharged. We were inclined to attribute the result to the use of an anæsthetic by DOI. The above results, however, show that DOI'S observations on cats gave a true picture of what takes place in man (35), and confirm the Chamber experiments of HASSELBALCH and LINDHARD (20).

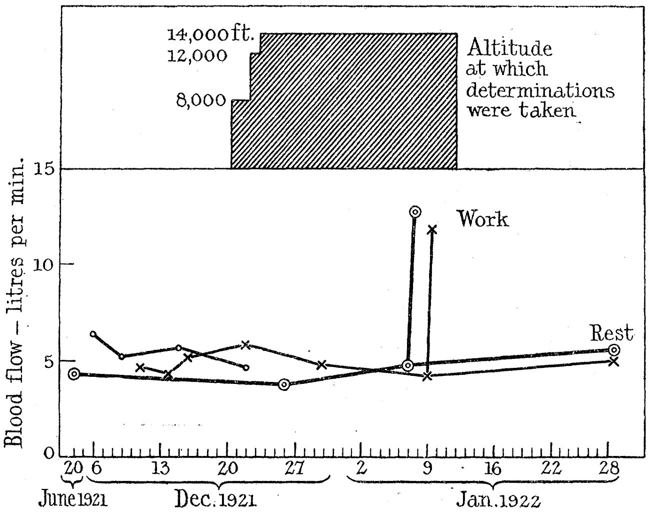

FIG. 25.

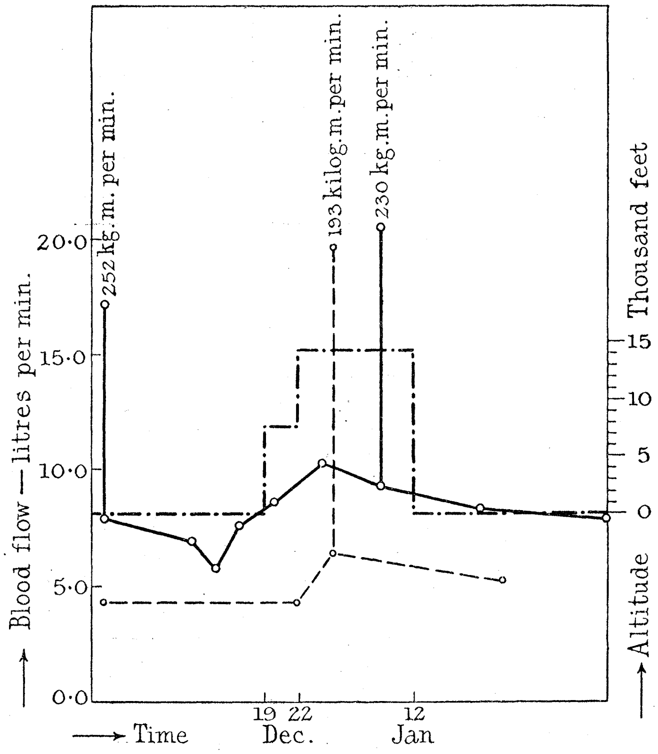

FIG. 26.

TABLE XXVII.

Redfield. Sea-level (rest).			Meakins and Davies' method.
Date.	By CO_2.	By O_2.	
20/ 6/21	4·17	4·19	
28/ 1/22	4·53	6·6	5·25
Mean . . .	4·35	5·8	
	5·1 litres per min.		

TABLE XXVII—*continued.*

Cerro (rest).

Date.	By CO_2.	By O_2.	Meakins and Davies' method.
26/12/21	3·17	4·5 ?	
7/ 1/22	4·64	3·9	6·4
	3·9	4·2	
	4·1 litres per min.		

Cerro. Exercise (193 kgm. per min.).

Date.	By CO_2.	By O_2.	Meakins and Davies' method.
7/ 1/22	15·2	10·0	9·7
	12·6		

Meakins. Sea-level.

Date.	By CO_2. Max.	By CO_2. Min.	By O_2.	Meakins and Davies' method.
11/12/21	5·2	4·15	5·31	7·8
14/12/21	5·03	3·68	4·68	7·8
16/12/21	7·00	4·91	5·86	
27/ 1/22	5·42	5·42	5·36	
Mean	5·1		5·3	7·8
Mean	5·2 litres per min.			

Matucana.

	By CO_2.	By O_2.	Meakins and Davies' method.
	—	—	8·4

Cerro.

Date.	By CO_2.	By O_2.	Meakins and Davies' method.
30/12/21	5·53	4·1	10·1
2/ 1/22	5·75	3·2	9·1
Mean	5·6	3·8	9·6
Mean	4·7 litres per min.		

Cerro. Exercise (231 kgm. per min.).

Date.	By CO_2.	By O_2.	Meakins and Davies' method.
9/ 1/22	13·6	9·8	
	11·9 litres per min.		

Edinburgh. Exercise (25·3 kgm. per min.)

	By CO_2.	By O_2.	Meakins and Davies' method.
The following are the data as calculated by the Meakins and Davies' method:			20·4
	—	—	17·3

The Blood Flow through the Hand.

The minute-volume of blood through the hand was determined by STEWART'S method in the case of Redfield. The general lines were similar to those in which SCHNEIDER and SISCO (36) worked on Pike's Peak (36), where they found an appreciable rise in the heat given out by the hand.

The same type of calorimeter and the method described by G. N. STEWART (37) was used. The actual calorimeter was kindly lent by Prof. MACLEOD, of Toronto. It was modelled after STEWART'S, but an electrical stirring device was added, consisting of a small propeller blade fixed to the lower end of a celluloid rod, whose bearing was above the calorimeter top, and was turned by a small motor driven by three dry cells. After each test a determination of the rate of cooling of the calorimeter was made, the wrist hole being plugged by a felt pad and the stirrer continued as during the test.

All tests were made under basal conditions in bed the first thing in the morning. The subject sat up in bed, his shoulders and right arm covered by a thick blanket. The left hand alone was used for the tests. STEWART'S equation was used for calculating the blood flow, the principle being that the amount of heat lost by the blood passing through the hand is equal to the amount of heat gained by the calorimeter and its contents.

For the equation, the following data are determined directly or are derived from known equivalents: the temperature of arterial and venous blood at the wrist; the specific heat of blood; the volume of water in the calorimeter; the rise in temperature of this water and rate of heat lost by the calorimeter during the test; the water equivalent of the hand and of the calorimeter itself. From these, the number of grammes of blood per minute passing through the hand may be calculated by the following equation:—

$$(\text{Vol. } H_2O + \text{water equivalent of cal.} + (\text{vol. hand} \times (\text{specific heat of hand})\ 0{\cdot}8)$$
$$\times\ (\text{cooling} + \text{rise in T. of cal.})$$
$$\text{Min. of test} \times (\text{art. temp.} - \text{ven. temp.}) \times 0{\cdot}9\ (\text{specific heat of blood}).$$

Art. temp. (radial) = rectal T. − 0·5°.
Ven. temp. (wrist) = av. temp. of H_2O in calorimeter.
Water equivalent of this calorimeter = 100.

TABLE XXVIII.—Blood Flow in Hand, Stewart's Method. Subject, A. C. Redfield.

Date.	Place.	Time. (A.M.).	Pulse.	Temperature.			Vol. hand c.c. left.	° C. Heat loss by cal. during expt.	° C. Observed rise in cals. T. during expt.	Blood flow in 100 c.c. of hand grms. per minute.
				Rectal.	Room.					
					Wet.	Dry bulb.				
Dec. 26	Cerro	7.30	66	36·9	10·0	12·2	350	0·28	0·68	14·5
,, 26	,,	7.30	66	36·9	10·0	12·2	350	0·28	0·50	13·2
,, 30	,,	7.20	62	36·4	10·5	14·0	405	0·27	0·40	9·4
,, 31	,,	7.15	60	36·5	11·1	13·3	410	0·28	0·55	11·5
Jan. 3	,,	7·25	68	36·7	11·1	14·4	420	0·24	0·53	10·0
,, 3	,,	7.25	68	36·7	11·1	14·4	420	0·24	0·47	10·2
,, 8	,,	7.55	66	36·95	12·2	17·0	390	0·20	1·20	17·8
,, 10	,,	8.35	60	36·7	11·1	14·4	460	0·23	0·53	9·2
										Average = 11·9
March 7	Boston	7.30	56	36·4	10·8	13·3	440	0·24	0·20	5·6
,, 8	,,	7.10	56	36·4	11·1	14·2	420	0·25	0·44	9·5
,, 9	,,	7.10	55	36·3	9·1	13·3	430	0·25	0·40	8·8
,, 21	,,	7.25	52	36·1	10·5	14·0	430	0·18	0·46	9·1
,, 22	,,	7.10	54	36·3	11·5	14·6	440	0·21	0·38	7·4
,, 30	,,	7.15	52	36·4	11·1	15·2	465	0·20	0·85	13·8
April 15	,,	7.25	60	36·55	11·7	14·8	430	0·20	1·15	17·8
										Average = 10·3

$$\left.\begin{array}{lcl} \text{Vol. of } H_2O \text{ in calorimeter} & = & 2500 \text{ c.c.} \\ \text{Water equivalent of cal.} & = & 100 \\ \text{Specific heat of hand} & = & 0{\cdot}8 \\ \text{,, \quad ,, \quad blood} & = & 0{\cdot}9 \end{array}\right\} \text{calculated.}$$

The figures show a wide variation in a given individual under nearly identical basal conditions, both at sea-level and at 14,000 feet. In one place, determinations made on different days may vary as much as 200 per cent. Between Cerro de Pasco and Boston, however, the variation between averaged figures was only about 16 per cent. The blood flow through the hand at 14,000 feet altitude appears to be the same as at sea-level, under resting conditions. These figures show no evidence to the contrary at least.

The chief factor, causing a change in peripheral blood flow, appears to be the temperature of the whole skin surface. The thickness of blankets, as well as the room temperature, seemed to be very important. It is probable that the blankets in Peru were warmer than those in Boston, for they certainly were thicker. Also, Redfield, at Cerro, put on a very heavy woollen shirt over his pyjamas. At Boston he did not have this. On April 15, at Boston, an extra blanket was added. On this day his blood flow reached the highest figure obtained, exactly equalling the maximum at Cerro. On each of those days he remarked that he "felt warmer" than previously. The room temperatures at Boston were somewhat lower than those at Cerro, but scarcely enough difference to be noteworthy.

TABLE XXIX.

	Cerro.		Boston.	
	Wet bulb.	Dry.	Wet bulb.	Dry.
Room temperature average . .	11·0°	14·2°	10·8°	14·1°

The pulse was higher at Cerro (sitting up in bed). The rectal temperature was somewhat higher at Cerro.

K. SYSTOLIC OUTPUT AND RADIOGRAMS SHOWING HEART SIZE.

From the minute-volume and the pulse rate, the mean systolic output may be calculated as follows :—

TABLE XXX.

	Meakins.		Redfield.	
	Sea-level.	Cerro.	Sea-level.	Cerro.
I. Minute-volume, litres (rest) . .	5·2	4·7	5·1	4·1
Mean pulse, rest	68	80	60	72
Systolic output, c.c	76	59	85	57
II. Minute-volume, litres (work) . .	—	11·9	—	12·6
Pulse rate	—	125 ?		
Systolic output	—	95		

The method of Meakins and Davies gives the following estimate :—

TABLE XXXI.

	Meakins.		Redfield.	
	Edinburgh.	Cerro.	Sea-level.	Cerro.
I. Minute-volume (rest)	7·8	9·6	5·3	6·4
Pulse (rest)	65	81	60	73
Systolic output, c.c.	120	119	88	87
II. Minute-volume (work)	17·3	20·4	—	19·7
Pulse (work)	141	170–180	—	125
Systolic output	122	120–114	—	158

During the resting periods the systolic output is reduced (Table XXX), or at least an increase is "not proven" (Table XXXI), a fact which may throw some light on the X-ray measurement of the heart, which will now be discussed.

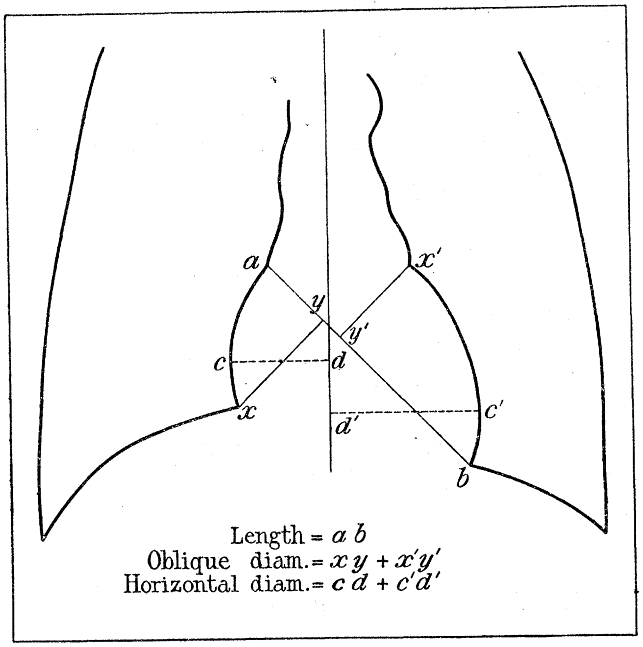

FIG. 27.

One to three exposures were made at each station. The subject was sitting upright with film holder held vertically against chest. The target was behind the subject at a distance of 7 feet from the film. The elbows were elevated to the level of the shoulder to draw the scapulæ outward; normal breathing was continued during the exposure, which consisted of three doses of 10 seconds' duration, separated by intervals of 5 seconds. The Coolidge portable X-ray outfit, which was kindly loaned to us by the General Electric Company, gave excellent service.

Measurement.—The indices used to express the heart size are the following :—The shadow is that of the heart during diastasis.

Oblique Diameter.—The distance from the junction point, A, of the right auricle with the right margin of the aortic shadow to the junction point, B, of the margin of the left ventricle with the shadow of the diaphragm (line *ab*, fig. 27).

Width.—A line is drawn from x, the junction of the shadow of the right margin of the heart with the diaphragm perpendicular to ab. A second line is drawn perpendicular to ab from x, the junction of the left auricle and ventricle. The intersection of these lines with ab are designated y and y' respectively in fig. 27. The width is the sum of the lengths of xy and $x'y'$.

Horizontal Diameter.—A line is drawn through the mid-line of the vertebral column. Through c and c', the extreme lateral points on the left and right margins of the heart shadow, lines are drawn perpendicular to the mid-line intersecting it at points designated d and d' respectively. The sum of the lengths of cd and $c'd'$ is the horizontal diameter.

The following measurements made on the heart of H. S. Forbes at sea-level indicate the consistency with which these indices can be measured :—

TABLE XXXII.

	Oblique Diameter.	Width.	Horizontal diameter.
	14·2 cm.	9·3 cm.	12·1 cm.
	15·3	10·4	12·1
	15·0	10·8	12·4
	14·6	10·7	12·1
	15·3	10·2	11·9
	15·1	10·3	12·4
	14·8	10·0	12·2
	15·1	10·7	12·4
Mean . .	14·9	10·3	12·2

The least disperse measurements are of the horizontal diameter. The greatest deviation from the mean is 0·3 cm. Next in uniformity are the measurements of the oblique diameter. The greatest deviation from the mean is 0·7 cm., the next greatest 0·4 cm. The least satisfactory measurements are of the width which shows a maximal deviation from the mean of 1·0 cm. These deviations are to be attributed to the difficulty in locating the index points on the film rather than to alterations in the dimensions of the heart.

Heart measurements were made on five members of the Expedition at sea-level, either before or a month after the sojourn at a high altitude ; at Oroya (12,178 feet) within two hours after arrival ; and at Cerro de Pasco (14,208 feet) after two and three weeks' residence on the sierra.

The results may be considered in three groups, characterised by definite conditions with regard to anoxæmia and the severity of the "soroche" experienced by the subject.

In these two individuals (Table XXXIII) it is clear that there is no significant change in the size of the heart, even at the time of their arrival at Oroya, when both were extremely ill with soroche, being confined to their beds, in one case for several days thereafter. That some alteration in the heart of one of them occurred, which is not evident from the measurements, is indicated by the fact that on the morning after his arrival at Oroya a bruit could be distinctly heard which was not present when he was at sea-level.

The measurements of Table XXXIII show that the heart of the subject was essentially of the same size on arrival at Oroya as it was at Edinburgh several months after his return from the Andes. After eleven or eighteen days of acclimatisation at Cerro de Pasco it had become distinctly smaller (see fig. 28). A difference is also clearly suggested between the two days of observation at the latter place. The differences in the measurements are obviously greater than can be accounted for by the inaccuracy of the method of observation.

On arrival at Oroya this subject was suffering from a severe headache and shortness of breath, but was not otherwise inconvenienced by soroche.

TABLE XXXIII.

	Oblique diameter. cm.	Width. cm.	Horizontal diameter. cm.
J. Barcroft. Heart.			
Sea-level	14·3	10·3	12·1
Boston, U.S.A.	14·1	10·1	11·9
February 20, 1922	14·3	10·0	12·1
Mean	14·2	10·1	12·0
Oroya	14·5	10·3	12·3
December 23, 1921	14·1	10·0	12·3
Mean	14·2	10·1	12·2
Cerro de Pasco	14·5	9·5	12·5
January 3, 1922	14·3	9·7	11·8
Mean	14·4	9·6	12·1
Cerro de Pasco	14·1	10·3	11·6
January 10, 1922	14·2	9·9	12·0
Mean	14·1	10·1	11·8
A. V. Bock. Heart.			
Sea-level	14·7	9·7	13·6
Boston	14·5	9·6	14·0
March 24, 1922	14·7	10·0	13·9
Mean	14·6	9·8	13·8

TABLE XXXIII—*continued.*

	Oblique diameter. cm.	Width. cm.	Horizontal diameter. cm.
A. V. Bock. Heart—*continued.*			
Oroya	13·8	9·2	12·7
December 21, 1921 .	14·8	9·0	13·5
Mean	14·5	9·2	13·3
Cerro de Pasco . . .	14·9	9·6	14·0
December 30, 1921 .	14·5	9·9	13·7
	14·9	10·3	13·8
Mean	14·8	9·9	13·9
Cerro de Pasco . . .	—	—	—
January 10, 1922 . .	—	—	—
Mean	14·4	9·5	13·6

In the subjects in Table XXXIV it is perhaps doubtful whether the differences in the heart measurements at sea-level and on the sierra are significant. The figures suggest strongly, however, that their hearts were slightly smaller at the high altitude than at sea-level. Neither suffered more than the slightest discomfort from soroche.

TABLE XXXIV.

	Oblique diameter. cm.	Width. cm.	Horizontal diameter. cm.
J. C. Meakins. Heart.			
Oroya	15·1	11·2	13·4
December 23, 1921 .	15·0	11·4	12·9
	14·5	*10·6*	*12·8*
Mean	14·8	11·1	13·0
Cerro de Pasco . . .	13·9	10·5	12·5
January 3, 1922 . .	13·9	10·7	12·3
Mean	14·0	10·4	12·4
Cerro de Pasco . . .	13·5	10·8	11·2
January 10, 1922 . .	13·8	10·9	11·6
	14·0	10·8	11·5
Mean	13·8	10·8	11·4
Edinburgh	14·8	11·2	13·0
April 7, 1922 . . .	14·6	11·0	12·9
Mean	14·7	11·1	12·9

The shadow of Meakins' heart undoubtedly became smaller at Cerro after some days (B, fig. 28). In the absence of any certain knowledge that the systolic output is changed considerably, this decrease must be regarded as a diminution in the size of the heart as a whole. This statement, if the systolic output is undiminished, or nearly so (Table XXXI), involves the implication that Meakins' normal heart by no means clears itself of blood at systole, and the same would be true of Forbes and Redfield, which responded to the high altitude at once. The number of cases studied are much too few to justify such an important generalisation; and, indeed, another construction might possibly be put upon the curves, namely, that the quickening of the pulse which takes place mainly at the expense of the diastole causes the average size of the heart, and so the shadow, to be smaller. If this were so, the hearts whose shadows grow smaller may have changed but little in diastolic volume and those whose shadows remain constant would have dilated. Our results point, however, to the possibility of a most instructive research being carried out along the lines we have indicated.

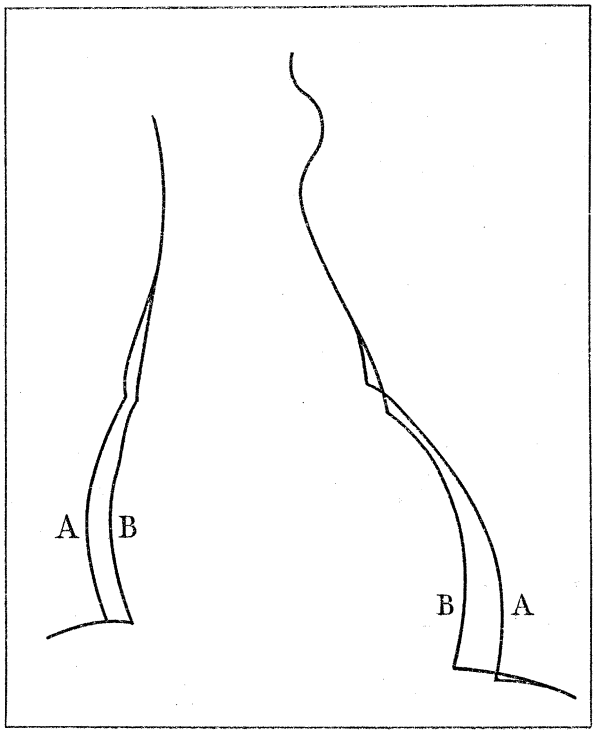

Fig. 28.

TABLE XXXV.

	Oblique diameter. cm.	Width. cm.	Horizontal diameter. cm.
H. Forbes. Heart.			
Boston	14·2	9·3	12·1
October 31, 1921 . .	—	—	—
November 9, 1921 . .	15·3	10·4	12·1
	15·0	10·8	12·4
	14·6	10·7	12·1
	15·3	10·2	11·9
March 22, 1922 . . .	15·1	10·3	12·4
	14·8	10·0	12·2
	15·1	10·7	12·4
Mean	14·9	10·3	12·2
Oroya	14·3	10·4	11·4
December 21, 1921 . .	14·0	9·9	11·7
	14·2	*10·3*	*11·4*
Mean	14·2	10·2	11·5
Cerro de Pasco . . .	14·5	10·5	11·5
January 8, 1922 . .	14·4	10·3	11·3
Mean	14·4	10·4	11·4
A. C. Redfield. Heart.			
Boston	14·6	10·2	12·7
October, 1921 . . .	14·2	—	12·7
March 24, 1922 . . .	14·7	10·3	13·6
	14·0	10·0	13·1
	14·3	10·0	13·0
Mean	14·4	10·1	13·0
Cerro de Pasco . . .	14·1	9·8	12·0
December 30, 1921 . .	13·8	9·2	12·5
Mean	13·9	9·5	12·2

L. THE VOLUME OF BLOOD IN THE BODY.

It had been our intention to carry our researches on the circulatory system to the point of ascertaining the proportion which existed between the amount of blood driven round the body per minute, and the whole quantity of blood in the body. This comparison involved measurements of the blood volume at the sea-level and at Cerro de Pasco.

Our object was frustrated by the fact that we obtained no constant proportion between the minute-volume and the blood volume at the sea-level—a fact which, to our surprise, was chiefly due to inconstancy in the mass of blood. As the changes in the sea-level blood volume appear to be of considerable interest in themselves, we give them in spite of the fact that their relation to altitude is uncertain. The most that can be said is that they throw doubt on whether the effects attributed by other authors to altitude are really due to that cause alone.

The method used was, in principle, that described by Haldane—a known quantity of carbon monoxide is taken into the circulation by inhalation; when sufficient time has elapsed for it to have distributed itself over the hæmoglobin of the blood, a few drops of blood are withdrawn from the finger. The volume carbon monoxide per cubic centimetre of blood is estimated. The details of the method are those described by Douglas, except in one particular—instead of using the carmine titration method for the final estimation of CO we used the Hartridge (38) reversed spectroscope.

The method gave very regular results before leaving England. In spite of considerable variations in the amount of CO taken in (201—325 c.c.), and in the time over which the inhalation lasted (8—16 minutes), the following figures were obtained:—

Barcroft Blood Volume in Cambridge.

Date: November.	5.	6.	9.	11.
Blood volume litres	4·32	4·42	4·39	4·34

Again, Meakins' blood volume was measured under two similar circumstances in two successive days at sea, giving 4·56 and 4·46 litres respectively. These figures suggest an error in either direction of about 2 per cent. as being the approximate experimental error of the method. So far there was a fair degree of uniformity, as between the figures themselves, and moreover the blood volume appeared to be reasonable in amount, being 1/16 of the body weight in Barcroft's case and about the same in those of Meakins and Doggart. As we made routine observations on board the S.S. "Victoria," the apparent blood volume commenced to change after we had been about a fortnight at sea. In every case it increased. A similar tendency was noticed in the case of Douglas' blood volume on the way to Teneriffe (14). There, however, the increase showed itself much sooner.

From the commencement of December till about December 14 in each case, the blood volume rose and from that date it fell rapidly. The change in volume was about 1—1½ litres. It can be followed on the charts (fig. 29).

Of the possible sources of experimental error, the following statement may be made. There was no appreciable error in the measurement of the volume of CO inhaled. The tightness of the oxylith bag was tested, the CO was always analysed, it was put in out of a vessel of known volume and the residual gas in the bag was measured and analysed. Usually it contained about 0·1 per cent. CO, which would be in fair agreement with the value calculated to be in equilibrium with the blood.

Our suspicion rested on the Hartridge technique. It seemed possible that it might fail us in one of two ways, either some change might take place in the eye which would alter the calibration of the instrument or the instrument itself might have been effected by the temperature of the tropics. The instrument, of course, depends upon

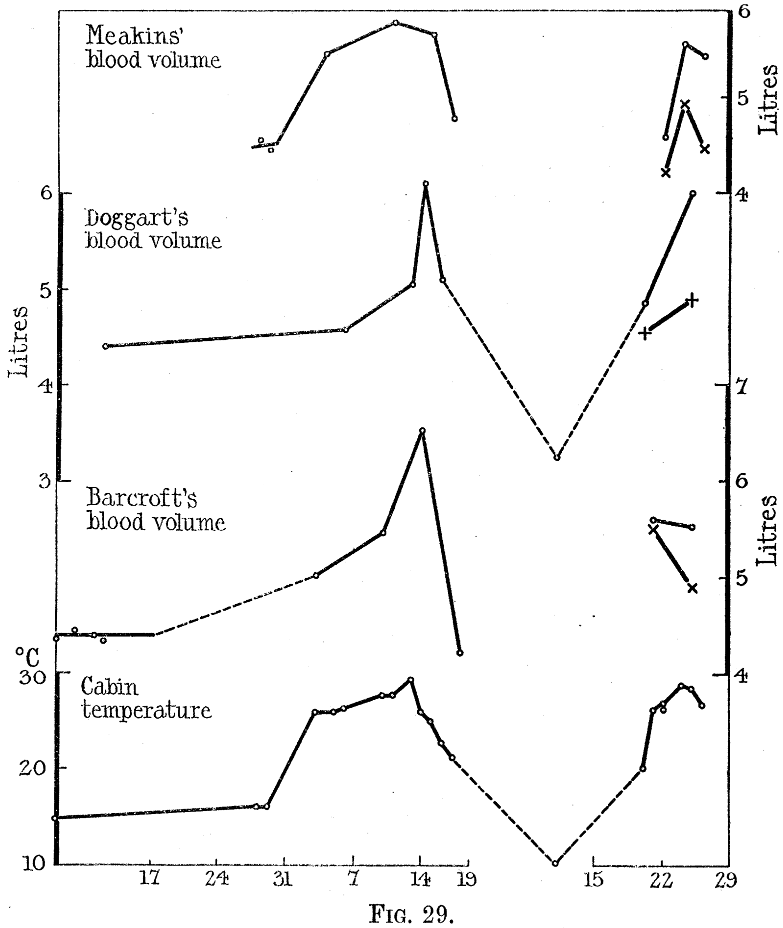

FIG. 29.

the following principle:—Two spectra of hæmoglobin are seen, one above the other; in the upper one the red end of the spectrum is at the right-hand side of the field, in the lower one it is at the left. One of these spectra is adjustable, so that the α-band of oxyhæmoglobin in one spectrum may be brought to a position just above that in the other. The position of the band is read off on the scale of the instrument. What this precise position is depends, so far as our experience goes, upon the eye of the observer and the strength of the hæmoglobin solution.

The instrument requires recalibrating for the eye of every person who uses it. We trusted it no further than to assume that if with a certain strength of oxyhæmoglobin solution it gave a certain reading and that another solution containing, say, 30 per cent. of CO-hæmoglobin, gave a reading 12 divisions away from the oxyhæmoglobin reading, then a 30 per cent. COHb solution would always give a reading 12 divisions removed from the oxyhæmoglobin solution, and so for other strengths. Yet when we found an apparently great change in our blood volumes we began to wonder whether we could trust the instrument so far.

It is fair to the Hartridge technique to say that since returning from Peru we have taken the instrument to bits at least three times, and in addition, by minor manipulations, have shifted the zero (oxyhæmoglobin) reading to different parts of the scale, but we have always found our original assumption justified. Three calibration curves are given in fig. 30. The fact that the framework of the instrument was made of wood made us additionally suspicious at the time. It seemed possible that in the tropics the frame might warm.

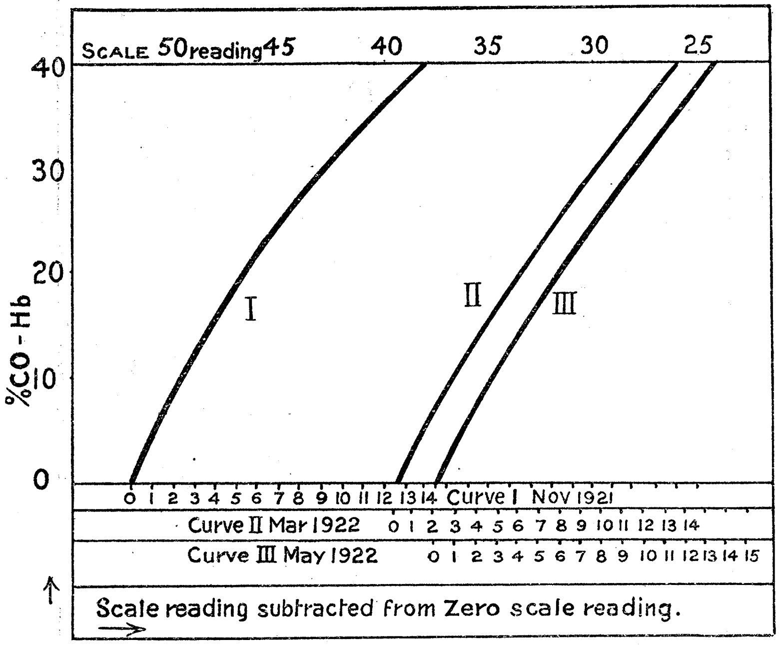

FIG. 30.

It is impossible, we think, to study fig. 29, in which the estimations of the blood volumes of three members of the expedition are plotted above the cabin temperature, without being convinced that there is some connection between the two.

TABLE XXXVI.—Blood Volume.

Date.	Position.	CO N.T.D. c.c.	P.c. CO Hb.	P.c. Hb.	O_2 capacity.	Hartridge method.	Van S. method.	Carmine method.	Temperature °C.
				Doggart.					
12/11/21*	Cambridge	258	28	110	956	4·45			
5/12/21	27.4 N., 73.12 W.	263	29·5	105	893	4·60	—	—	26
13/12/21	5.45 N., 80.16 W.	282	29·1	104	969	5·05	—	—	29
14/12/21	1.14 N., 81.9 W.	276	23·8	103	1160	6·10			
16/12/21	7.34 S., 81.19 W.	257	26·6	102	964	5·10	—	—	22·5
10/ 1/22	Cerro de Pasco	177	23·5	130	757	(3·20)			10
20/ 1/22	—	288	27·0	119	1066	4·85	4·53	—	25
24/ 1/22	—	269·3	21·5	112	1274	6·00	4·98	—	29
				Barcroft.					
5/11/21	Cambridge	268	32·5	102	825	4·32			
6/11/21	,,	308	37	100	836	4·42			
9/11/21	,,	201	24·2	102	835	4·39			
11/11/21	,,	325	39	102	828	4·34			
3/12/21	31.2 N., 63.26 W.	289	30·7	101	941	5·02	—	—	26
10/12/21	16.21 N., 81.59 W.	280	26·8	105	1044	5·42	—	—	28
14/12/21	1.14 N., 81.9 W.	290	23·8	100	1204	6·50	—	—	26·5
17/12/21	Callao	297	35·6	108	838	4·19	—	—	21·0
21/ 1/22	—	283	25·0	110	1112	5·57	5·5	—	26
25/ 1/22	—	288	25·0	108	1152	5·76	4·8	—	28·5
				(116)		(5·35)			
15/ 3/22	Edinburgh	260	28·0	105	929	4·76	—	4·26	16·5
21/ 3/22	,,	230	26·5	98	869	4·85	4·4	4·8	16
23/ 3/22	,,	225	28	95	804	4·5	4·9	4·1	18
				Meakins.					
28/11/21	38.28 N., 36.54 W.	214	26·8	95	800	4·56	—	—	16
29/11/21	36.13 N., 43.53 W.	257	31·5	98	814	4·46	—	—	24·2
5/12/21	27.4 N., 73.12 W.	247	26·1	94	947	5·45	—	—	26
11/12/21	12.1 N., 80.21 W.	217	21·3	95	1017	5·78	—	—	28
15/12/21	3.2 S., 81.19 W.	286	28·1	98	1020	5·67	—	—	25
17/12/21	Callao	240	28·0	98	858	4·77	—	—	21
22/ 1/22	—	243	27·7	104	900	4·55	4·2	—	27
24/ 1/22	—	251	22	108	1181	5·55	5·0	—	29
26/ 1/22	—	271	25	107	1084	5·47	4·46	—	26·5
17/ 3/22	Edinburgh	237	28	90	847	5·1	5·3	5·2	17
20/ 3/22	,,	223	—	88	—	—	4·75	5·3	14

* Various corrections—see attached sheet.

It will be observed that the blood volume rises and falls with the temperature—but with a lag. It seems impossible that the effects should be due to mere coincidence, and that chance errors in blood volume estimation should have distributed themselves in measurements made on three separate persons in just this way. There remain, then, two possibilities :—(1) that the change in temperature changes the blood volume ; (2) that the change in temperature affects the methods of measurement. We determined to eliminate the latter possibility. This we have done in more than one way : (1) by elaborating a method depending on quite other principles than the Hartridge technique; (2) by carrying out parallel experiments in a heated chamber in one or more laboratories in which the subject was exposed to the altered temperature, but the researchers and their instruments were not. The results of the latter plan are given in Appendix I. The results of the former, so far as they could be put into operation on the way back from Peru, may now be given.

The technique (39), which had much in common with that of Salveson (39), consisted in extracting the gases from 2 c.c. of blood, obtained by venous puncture, in a Van Slyke pump, transferring it to a Haldane gas analysis apparatus and measuring the CO by combustion. We did not on the S.S. "Ebro"—as we did later—make a preliminary estimation for CO before each experiment. We tested this method by saturating drawn blood with CO and ascertaining that we could extract an amount of that gas which corresponded to the calculated CO capacity. The CO capacity was ascertained by a Haldane's hæmoglobinometer.

The journey home, however, offered a far less favourable opportunity for the research than the journey out to Peru—going out, we started from England in what may be regarded as a stable condition; immediately prior to coming home we had, of course, been in all sorts of temperatures and at all sorts of altitudes. The combustion method gave constantly lower results than the Hartridge method.

The following figures show the results, on Barcroft and Meakins respectively, of observations made in the Tropics and subsequently in Edinburgh:—

Table XXXVII.—Barcroft's Blood Volume (litres).

Tropics.		Edinburgh.	
Hartridge method.	Combustion.	Hartridge method.	Combustion.
5·57	5·50	4·76	4·40
5·76	4·80	4·86	4·90
		4·50	—
5·67	5·15	4·56	4·65
5·4		4·6	

Meakins' Blood.

Tropics.		Edinburgh.	
Hartridge method.	Combustion.	Hartridge method.	Combustion.
4·55*	4·2	5·3	5·2
5·55	5·0	4·75	5·3
5·47	4·46	5·02	5·25
5·19	4·55	5·1	
4·9			

---

* Possibly it would be fairer to omit this determination, as although the cabin temperature was 27° we had only just emerged from the cool Humboldt current.

The evidence, then (with the exception of one item), both going out and coming home, points to an unduly high blood volume when we went through the Carribean Sea and the Panama Canal. The only set of observations which are out of line with that deduction are those on Meakins in Edinburgh in March last. It appears, therefore, as though the external temperature were a factor, though not the only factor, in the regulation of the blood volume.

The probable physiological significance of the connection between temperature at blood volume is not far to seek. Recently, both Meakins and Davies, and Barcroft and Nagahashi, have shown that if the arm be exposed to the hottest water which can comfortably be borne, about fifty times as much blood runs through it as when it is exposed to cold. Clearly, then, if the whole skin is flushed with blood, the internal organs might fare badly unless some increase took place in the volume of circulating fluid. In other words, if the volume of the vascular bed is increased over intervals of time measured by days, the volume of blood increases as well. How long the increase is maintained we do not know.

The moral, so far as high-altitude research goes, seems to be that the blood volumes at different altitudes can only be regarded as comparable if the temperature conditions are the same at both. The rise in Douglas' blood volume between leaving England in March, 1910, and arriving at Teneriffe has already been mentioned. The transition was from a cold to a hot climate. It is interesting also to note that, while the blood volumes of the Pike's Peak party rose during their residence at Pike's Peak (the rise being attributed to altitude), they did not attain a value which was higher than that found at New Haven subsequently :—

Maximal Reading of Blood Volume (litres).

	At Pike's Peak.	At New Haven.
Henderson	5·2	5·1
Haldane	5·5	5·8
Douglas	4·9	5·0
Mean	5·2	5·3

M. The Relative Importance of some of the Observed Factors in Acclimatisation.

There seems to be no alternative but to use the diffusion coefficient as a tool with which to shape some sort of comparison between the importance of such factors as the increased total ventilation, the alteration in the oxygen dissociation curve, the concentration of the red blood corpuscles, etc., in assisting the organism to compete with the handicap at which it is placed by the respiration of an atmosphere poor in oxygen.

Our diffidence in the use of the coefficient (40) rises not from any doubt that remains in our minds about the possibility of secretion; it is due to the fact that the conditions of respiration make the accurate application of the coefficient difficult and, indeed, impossible. Yet, granting the impossibility of obtaining sufficiently accurate data for the estimation of the diffusion coefficient by BOHRS' method, we may still derive some useful information by the application of this theory to a set of conditions such as may be assumed from our observations to occur at various altitudes, and if various degrees of compensation have been accomplished. The sources of our misgiving should be stated at the outset.

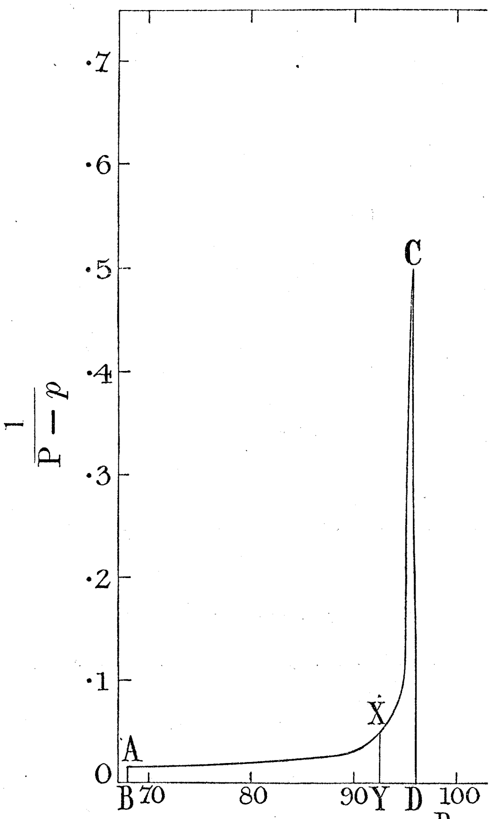

FIG. 31A.

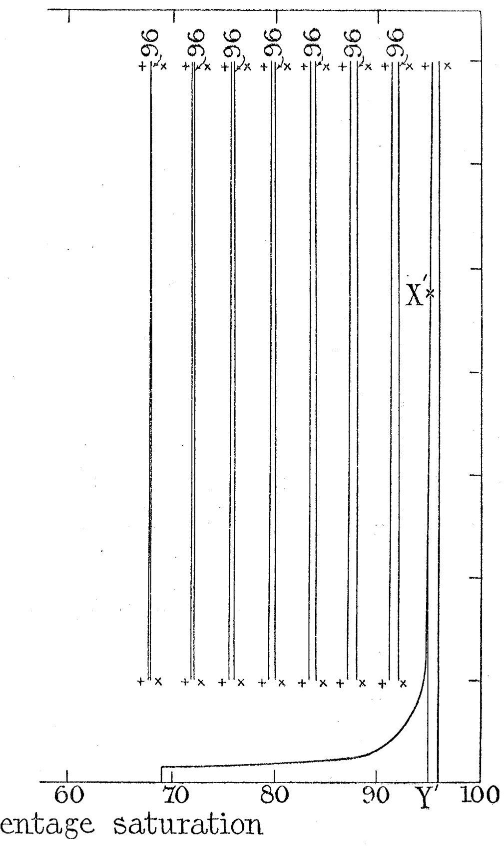

FIG. 31B.

(1) The diffusion coefficient is by definition: the quotient of a fraction in which the average difference of pressure between the oxygen contained in the alveolar air and the oxygen contained in the living capillaries (the average oxygen pressure) is the divisor, and the oxygen consumption per minute the dividend. The "average oxygen pressure" is obtained by BOHRS' (41) method of graphic integration, *i.e.* a diagram is drawn such that the percentage saturation of the blood in the capillary is the abscissa, and the reciprocal of the difference in oxygen pressure between the alveolar air and the capillary blood, $1/P - p$, is the ordinate. The average is found by dividing the area (*e.g.* fig. 31A) into two equal parts by such a line as

XY. The area AXYB = XCDY. XY is the reciprocal of the average difference of pressure to be alluded to in the following paragraphs as $1/P - p_1$. In this particular figure it is assumed that the venous blood is 68 per cent. saturated and the arterial 96 per cent., that the difference of oxygen pressure between the alveolar air and the arterial blood is 2 mm., and that, as the blood traverses the capillary, the pressure at each percentage saturation is that shown on the intracapillary dissociation curve. (The particular data are derived from Meakins' blood.) Now the point of uncertainty is the value of $1/P - p$ in the case of the blood leaving the lung. In the diagram we have assumed $P - p$ to be 2 mm., but so far as our experimental methods can tell us for blood at sea-level it may equally be 0·2 mm., for our methods are not accurate to less than 2 mm. The maximum value of $P - p$ is not likely to be more than 2 mm., but it may be much less. If now we were to assume it to be 0·2 mm., the limiting value of $1/P - p$ becomes not 0·5, but 5·0; the diagram acquires a high and acute spike, which can only be fitted on to the paper by cutting it into pieces and laying them side by side. The area of the extreme right of the figure is so exaggerated that the mean shifts to X′Y′, and instead of the value of $1/P - p_1$ being 0·037, as in fig. 31A, it becomes 0·47, as in fig. 31B; $P - p_1$ becomes not 27 mm. but 2·1. If the quantity of oxygen used up be 250 c.c. per minute, the diffusion coefficient becomes not 9 but 120.

(2) The second difficulty about the use of the diffusion coefficient is that the oxygen pressure in the alveolar air is not constant; and therefore it is probable that the exaggerated pinnacle on the curve which plays so prominent a part in settling the value of $1/P - p$ is something that waxes and wanes with each respiration. We may point out one property of these curves which seems to be of great importance. If Q be the quantity of oxygen used, and D the diffusion coefficient, and by definition $D = Q/P - p_1$, then if Q be doubled, and D remain constant, $P - p_1$ must also be doubled, and $1/P - p_1$ must be halved. The effect of halving $1/P - p_1$ on its position in figs. 31A and 31B, respectively, is very different. In fig. 31B, if it (*i.e.* X′Y′) were halved, its position would scarcely alter, whereas in fig. 31A, if XY were halved, it would have to move from a position which cut the abscissa at 92·5 per cent. saturation to one which cuts it at 76 per cent. saturation. Suppose that the blood flow is also doubled, the region of utilisation will remain 28 per cent. of the whole oxygen capacity; but it must move with XY, for, by definition, XY must bisect the area then enclosed between the vertical lines which form through the upper and lower limits of the region of utilisation.

Put into words, the above argument amounts to this, that in the case represented by fig. 31B the capillaries are permeable enough, and long enough, for equilibrium to be practically established during rest, while as yet the corpuscle has only traversed a small length of the capillary. In fig. 31A the equilibrium is only approached as the corpuscle leaves the capillary. In fig. 31B, therefore, there is a reserve length of capillary, in case more oxygen must be taken in; in fig. 31A that is not the case, the equilibrium therefore, in exercise, is never approached at all closely when the oxygen consumption is great and the arterial blood becomes dark in colour.

Instances could be cited in actual life, both in which the arterial blood does, and in which it does not, darken on exercise. Normally, there is little or no change in the colour of the arterial blood when the oxygen consumption increases, a fact which looks as though fig. 31B was the one which most correctly represents the normal condition, for in it the value of $1/P - p_1$ could decrease to one-fifth of that shown in the picture without any appreciable shift in the position of the line; and even if its length were reduced 1/16 of that shown, X'Y' would only revert to the position of 90 per cent. saturation, and the saturation of the arterial blood would be above 95 per cent. instead of 96 per cent. On the other hand, in rabbits poisoned with pulmonary irritant, in which the diffusion coefficient must be very low, for a great part of the lung is out of action altogether and the rest much impaired, the properties of the animal are such as would be suggested by fig. 31A. If the legs are thrown into contraction the arterial blood at once darkens, and presumably because, as Q increases, $1/P - p$ must decrease, and this can only be obtained by the whole region of utilisation, including even its upper limit, being forced away from the position of approximate equilibrium with the alveolar air (see Appendix VI).

Let us then, for purposes of the present investigation, frankly assume that the diffusion coefficient in Meakins' case was 44 (though admitting that this figure may be of a very rough character), that the oxygen consumption during rest was 254 c.c. per min., and that the mean value of $P-p$ (*i.e.* $P-p_1$) was 5·7 mm., $1/P-p_1$ would then be 0·175. Further, we may assume that the arterial blood was 96 per cent. saturated (approximately) and that the venous blood was 68 per cent. saturated—the difference being 28 per cent. Following the nomenclature of KROGH (42), we may use the term "degree of utilisation" to indicate the percentage of oxygen taken out of the blood (*i.e.* the quantity of oxygen expressed as a percentage of the total oxygen capacity), and the "position of utilisation" to indicate the points on the ordinate of the oxygen dissociation curve between which the utilisation lies.

CASE I. *Normal.*—The following would then be complete data for the normal blood of Meakins:—

Difference in O_2 pressure between alveolar air and blood in pulmonary vein	1 mm. about.
Ditto between alveolar air and blood in pulmonary artery	60 mm.
Mean difference in pressure in capillary ($P-p_1$)	5·7 mm.
Degree of utilisation	28 p.c.
Position of utilisation	96–68 p.c.

CASE II. *Lowered Oxygen Pressure in the Alveolar Air.*—Let us suppose that no other alteration takes place but that of a reduction in the oxygen pressure of the alveolar air. The oxygen consumption will be assumed to be the same, the blood-flow the same, the degree of utilisation will be the same, what is the position of utilisation? The alveolar oxygen will be taken as 38 mm., the figure at which it would have stood had no change in the total ventilation taken place. The problem resolves itself into making a graph for $1/38-p$ and determining the percentage saturation which corresponds to 1·75 for the value of $1/(38-p)$, and then finding a region of utilisation 28 per cent. in degree and so disposed that equal areas on the graph are mapped out between the 1·7 line and limiting lines. The following data are obtained in this way:—

	Case II.	Case III.
Diffusion coefficient	44	25
Alveolar pressure	38 mm.	38 mm.
$P-p_1$	5·7 mm.	10 mm.
$1/P-p_1$	0·17	0·1
Difference between O_2 pressure in alveolar air and blood in pulmonary vein	2·0 mm.	6 mm.
Ditto and blood in pulmonary artery	12·5 mm.	20 mm.
Degree of utilisation	28 p.c.	28 p.c.
Position of utilisation	59–31 p.c.	48–20 p.c.
Saturation on oxygen dissociation curve corresponding to an equilibrium with 38 mm. O_2	63 p.c.	63 p.c.

CASE III. *Lower Diffusion Coefficient at High Altitude.*—The question may now be considered: how would the above figures be affected if the diffusion coefficient had been assumed to be 25, about that of the lowest in our party, instead of 44? The data would have been those given in the above Table under the heading Case III.

If the saturation of the arterial blood only fell to a figure which would be in equilibrium with the alveolar air the position would be serious enough. It would then be about 63 per cent. saturated, but it is important to notice that the margin by which the arterial blood falls short of equilibrium widens out as the alveolar pressure falls. Inappreciable at an alveolar pressure of 100, it is now a matter of about 6 per cent. saturation if the alveolar air exerted 38 mm. pressure of oxygen and the diffusion constant 44, while it would be 12 per cent. saturation if the diffusion constant were only 25. We shall presently discuss the whole subject of cyanosis, but it is clear that the depression of the region of utilisation caused by failure of the arterial blood to approach equilibrium with the alveolar air may be an important factor.

CASE IV. *Increase in Total Ventilation.*—At Cerro the alveolar oxygen went up to about 50 mm. Let us, therefore, revert to the diffusion constant of 44, and assuming the alveolar pressure to be 50 mm., ascertain the position of the region of utilisation. The data would be as follows:—

Diffusion coefficient	44
Alveolar pressure O_2	50

$P - p_1$	5·7 mm.
$1/P - p_1$	0·17
Difference between O_2 pressure in alveolar air and blood in pulmonary vein	2 mm.
Ditto and pulmonary artery	18 mm.
Degree of utilisation	28 p.c.
Limits of position of utilisation	78–50 p.c.
Middle of position of utilisation	64 p.c.
Saturation of oxygen dissociation curve corresponding to equilibrium with 50 mm. O_2	80 p.c.

CASE V. *Concentration of Red Cells.*—Starting from the same position as that from which we started for the consideration of Case IV, namely, the standard conditions and an alveolar oxygen of 38 mm., let us see what benefit would have accrued if no other change had taken place than an increase of the hæmoglobin from 100 to 140. We are not, of course, dealing with the secondary effect on the dissociation curve, but only the direct influence.

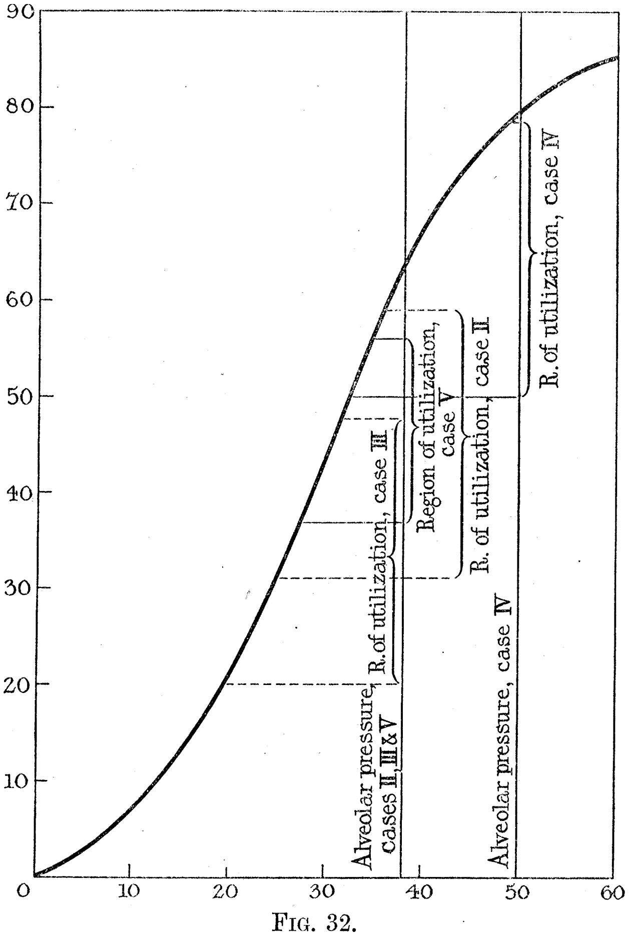

FIG. 32.

Fig. 32 showing regions of utilisation on oxygen dissociation curves in Cases II, III, IV, V, and fig. 33 in VI and VII.

In the tabulated data in Case II, which must be used as a basis of calculation, the only one which needs modification is the degree of saturation. If the hæmoglobin value is 140, the degree of utilisation will become $28 \times 100/140 = 20$ per cent. Where then will be the region of utilisation?

Case V.

Diffusion coefficient	44
Alveolar air	38
$P-p_1$	5·7 mm.
$1/P-p_1$	0·17 mm.
Difference between oxygen pressure in alveolar air and in pulmonary vein	2·8 mm.
Ditto in pulmonary artery	10 mm.
Degree of utilisation	20 p.c.
Region of utilisation	36–56 p.c. (sat.)
Saturation in equilibrium with alveolar air	63 p.c. (sat.)

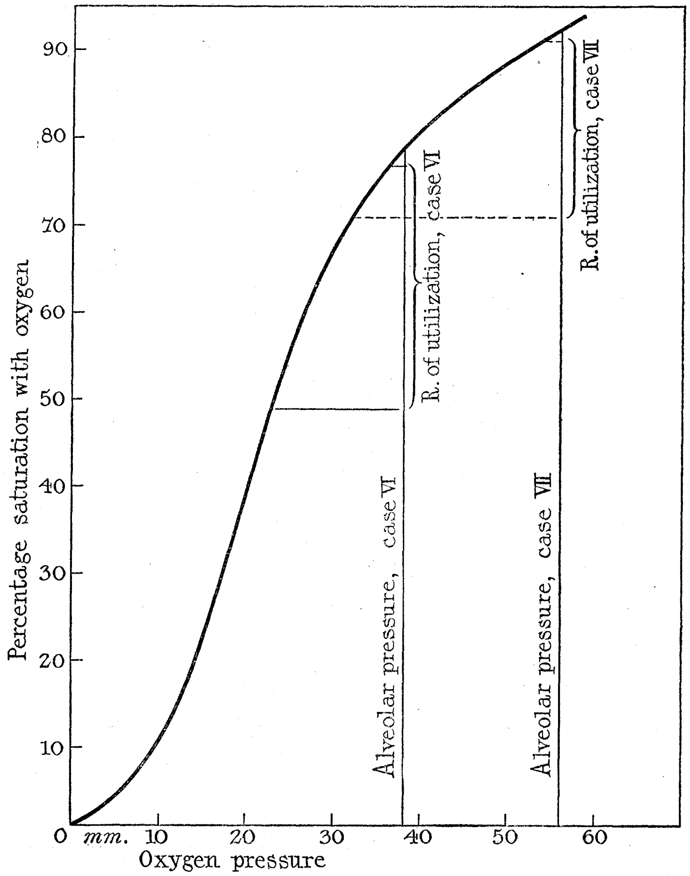

FIG. 33.

FIG. 32 showing regions of utilisation on oxygen dissociation curves in Cases II, III, IV, V, and fig. 33 in VI and VII.

Case VI. *Altered Dissociation Curve.*—Reverting once more to Case II as the basis, let us consider the position of utilisation if no other change were to take place than that which is observed in the oxygen dissociation curve. The data would then be :—

Diffusion coefficient	44
Alveolar pressure	38 mm.
$P-p_1$	5·7 mm.
$1/P-p_1$	0·17 mm.
Difference between O_2 pressure in alveolar air and in blood in pulmonary vein	1·5 mm.
Ditto in pulmonary artery	15 mm.
Degree of utilisation	28 p.c. (sat.)
Position of utilisation	49–77 p.c. (sat.)
Saturation on oxygen dissociation curve corresponding to equilibrium with 38 mm.	79 p.c.

Of the three factors in acclimatisation—change in the alveolar air, change in the concentration of red corpuscles and change in the dissociation curve—the following Table shows the positions of utilisation as compared with the normal.

	Region of utilisation.		
	Upper limit.	Middle.	Lower limit.
Case I.—Normal	96 p.c.	82 p.c.	68 p.c. (sat.)
Case II.—Base from which acclimatisation takes place	59	45	31 ,,
Case IV.—Alveolar O_2 raised	78	64	50 p.c.
Case V.—Hæmoglobin raised	56	46	36
Case VI.—Dissociation curve raised	77	63	49
Combination of IV, V, and VI	91	81	71

It will be seen that so far as the rise in "position of utilisation" is concerned, there is little difference whether it be wrought by the observed rise in the alveolar oxygen or the observed rise in the dissociation curve. The former rise, however, though it secures blood as much oxygen as the latter, secures it at a higher oxygen pressure—a very important matter.

Case VII. Let us now combine Cases IV, V and VI in order to get a picture from the theoretical point of view of what the blood actually would be like with all three modes of acclimatisation; we can thus compare it to what the blood actually was. The alveolar pressure will be taken not as 50 mm. as in Case III but at 56, which was observed in Meakins on the occasion with which we wish to deal.

Diffusion coefficient	44
Alveolar CO_2	56 mm.
$P-p_1$	5·7

$1/P-p$	0·17
Difference between O_2 pressure in alveolar and in pulmonary vein	1·4 mm.
Ditto in pulmonary artery	25 mm.
Degree of utilisation	20 p.c.
Region of utilisation calculated	91–71 p.c.
Region of utilisation observed	90–69 p.c.
Saturation on oxygen dissociation curve corresponding to equilibrium with alveolar air	92·2 p.c.
Observed region of utilisation in Meakins' blood	90–69 p.c.

It will be seen that the calculated and observed results agree very closely.

The graph corresponding to Case VII (fig. 34) is of interest. It will be seen that the point at which $1/P-p$ cuts the curve is just where the curve bends sharply. It

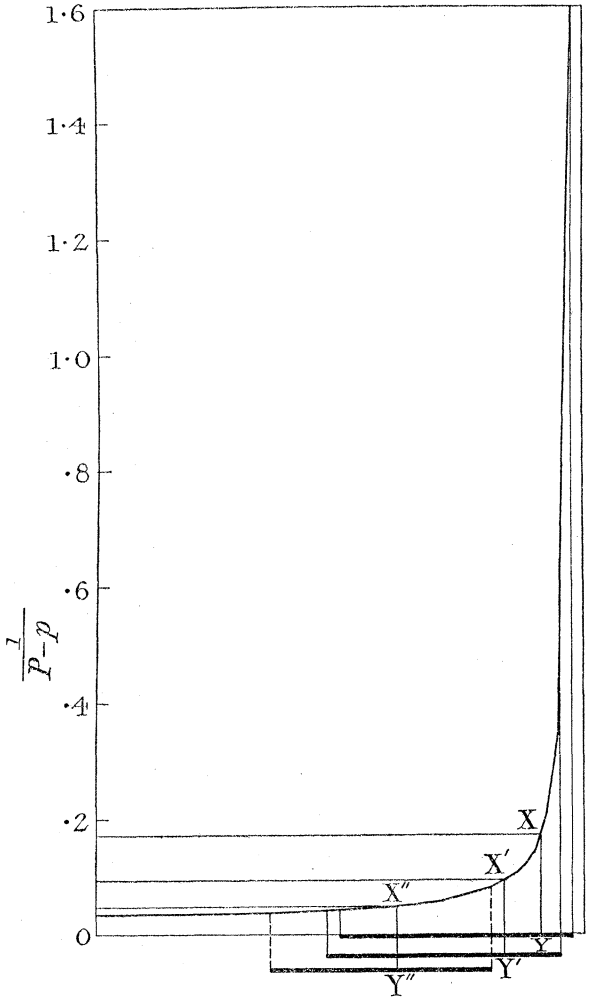

FIG. 34.—Graph of Case VII showing movement of region of utilisation with diminution in value of $1/P-p$.

follows from this that if $1/\text{P}-p$ were much smaller than it is the point would move rapidly to the left, while if it were to get larger the point would scarcely move to the right. If the length of the line XY in Case VII were halved it would move to $\text{X}'\text{Y}'$, whilst if it were reduced to one-quarter the length, *i.e.*, 0·044 instead of 0·175, it would move to $\text{X}''\text{Y}''$. Halving the value of $1/\text{P}-p$ would only produce a trifling change in the region of utilisation, namely, from 91–71 per cent. to 90–70 per cent., but reducing it to one-quarter would produce a considerable change, namely, to 85–65 per cent. Such a movement would take place if the quantity of oxygen consumed and the quantity flowing in next time both doubled so that the degree of utilisation remained the same. At high altitudes therefore a phenomenon is observed which does not take place to an appreciable extent normally at sea-level, namely, the position of utilisation recedes from the position of saturation.

A good example of this was afforded by Prof. MEAKINS when taking exercise. He became deeply cyanosed, in part no doubt because the position of utilisation broadened, but in part also because the arterial blood as well as the venous blood became more unsaturated ; this is illustrated in fig. 35.

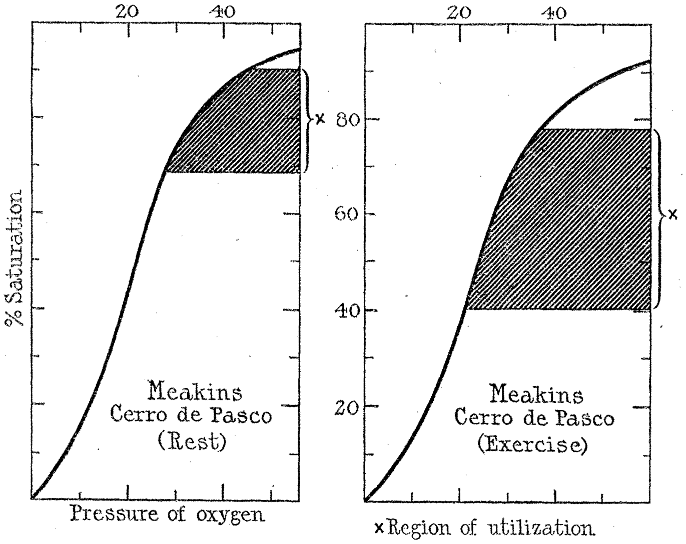

FIG. 35.—Meakins' curves showing descent of position of utilisation in oxygen dissociation curve when muscular work was undertaken by Meakins at 14,200 feet.

	Rest.	Exercise.
Meakins—		
Diffusion coefficient	44	44
Oxygen used	254	815 c.c. per min.
Position of saturation—		
Upper limit	91 p.c.	78 p.c. (observed)
Middle	80 p.c.	
Per cent. corresponding to $\text{P}-p$.	88·3 p.c.	63 (observed, graph assumed)
Lower limit	69 p.c.	41 (observed)
Degree of utilisation	28 p.c.	37 p.c. (observed)

II.—CYANOSIS.

Cyanosis plays so prominent a part in the phenomena observable at high altitudes that it is desirable to attempt some further analysis of it than what is to be found in the literature.

A judgment formed of the colour of the lips, or the flesh beneath the finger nails, is really one of the average colour of the capillary blood, a point recently emphasised by LUNSGAARD (43). This average is not the same as a mixture in equal parts of arterial and venous bloods would be. To realise this it is only necessary to look back at what has already been said about the nature of the blood in the pulmonary circulation. There the main transference of oxygen from the alveolus to the blood takes place at the very commencement of the capillary. The blood rapidly gets almost into equilibrium with its surroundings, and over a great proportion of the capillary it is practically arterial blood. If this capillary be divided into equal lengths, presumably each length will make the same contribution as its neighbour to the visual judgment of colour. Therefore the integrated colour effect will be an approximation to that of arterial blood.

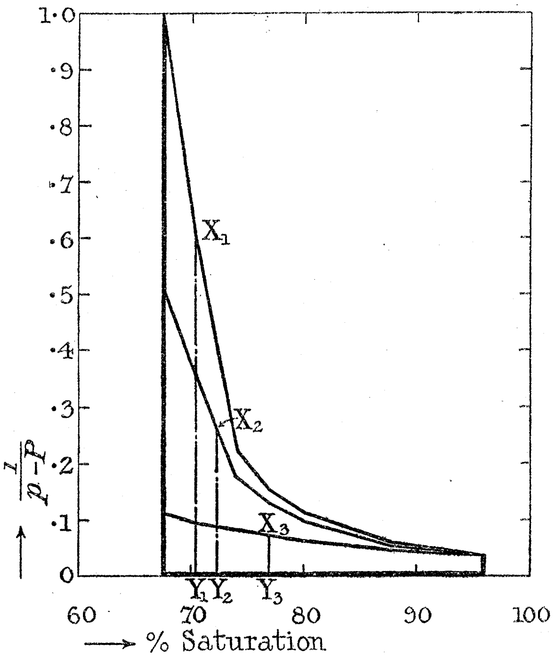

FIG. 36.

In the tissues, on the other hand, the colour of the capillary blood, as judged by the eye, is an approximation to the colour of the venous blood which flows from the area in question. Sometimes, however, the approximation will be closer than at others. The more nearly the venous blood gets into equilibrium with the tissues, the more nearly will the capillary blood approximate to the venous blood in colour. The data are, however, more difficult to review on account of our comparative ignorance of the pressure in the tissues. Fig. 36 indicates the percentage saturation which corresponds to the average capillary pressure under three conditions. In each the "degree of utilisation" is assumed to be 28 per cent. of the oxygen capacity as heretofore, and the position 96–68 per cent.; the oxygen consumption and blood flow are the same in each case, but, owing to differences in the diffusion coefficient, the pressure in the tissue P is 1, 2, and 10 mm. respectively, lower than p_V the oxygen pressure in the venous blood. X_1Y_1 corresponds to $p_V - P = 1$ mm., and its position is 70·5 per cent. saturation, the venous blood being 68 per cent. Where $p_V - P = 2$ mm. $X_2 - Y_2$ is placed at 72 per cent. saturation, and where $p_V - P = 10$ mm. $X_3 - Y_3$ is at 77 per cent. saturation. As a first approximation, therefore, the question of cyanosis resolves itself in the following. What causes contribute to a darkening of the colour of the venous blood in the subcutaneous area?

1. *Increase in the Degree of Utilisation of Oxygen from each Cubic Centimetre of Blood.*

Slowing of the Blood Flow.—It has been shown by more than one observer that the venous blood coming from the arm may be as much as 93 per cent., or as little as 7 per cent., saturated with oxygen, according to the temperature to which the skin of the arm is exposed. Cold, therefore, is a common source of blueness, simply because it broadens the region of utilisation, and in so doing depresses its lower limit.

Cold is a very common contributory cause of cyanosis at high altitudes. In our ascent to Oroya, however, it was not so, as we went up the railway in a heated car.

Increase of oxygen consumption without corresponding increase in the blood flow will produce cyanosis in the organ in question, but not general cyanosis.

2. *Lowering of the Area of Utilisation.*

The most obvious way in which the area of utilisation may be lowered, is by lowering the oxygen pressure in the air breathed whilst keeping the consumption of oxygen constant.

Thus at high altitudes the cyanosis at first is very marked and later is less so, presumably because, at first, the alveolar air feeds blood with a normal dissociation curve, and later it feeds blood with a raised dissociation curve. The venous conditions reflect the arterial conditions. The blueness which takes place with exercise, both at high altitudes and at the sea-level, in pulmonary complaints in which the diffusion coefficient is lowered (*e.g.* gas poisoning with pulmonary irritants, see Appendix VI), presents an interesting problem. The lip does not use more oxygen because the leg or the arm is taking exercise—nevertheless, the lip becomes blue—but why? As has already been indicated, the arterial blood becomes darkened for the following reason:—If the diffusion coefficient is low, the position of XY will be to the left of the critical part of the curve in such a graph as fig. 31A. In that position an increase of oxygen consumption must depress the whole "region of utilisation." The observations made on Meakins, during exercise on the bicycle ergometer, are a good example of this type of cyanosis. On the occasion in question the cyanosis was most marked. Now it is true that, considering his body as a whole, more oxygen was being taken from each cubic centimetre of blood during exercise than during rest. This, however, is beside the mark, for the extra consumption was to be referred to muscles and not to the lips. The cyanosis in the lips was due to the depression in saturation of the arterial blood to a point considerably below its former level. This depressed saturation was reflected in the venous blood for his face, the colour of which was, as a first approximation, the governing factor in cyanosis

III.—Mental Tests Used.

The following tests were employed to judge of mental impairment :—

1. *Duplicate Letter Test.*—One duplicate capital letter is added to a complete alphabet of capital letters, arranged irregularly but compactly, on a flat surface. Each result represents the amount of time used by the subject in identifying the only letter which occurs twice. The subject was asked not to take each consecutive letter in the alphabet individually and move his eye over the others to see if it was repeated. This method would have been cumbersome, and would also have made it necessary to make some correction for the order occupied by the particular letter in the alphabet. On the other hand, no correction could have been applied with any constancy, because a letter near the end of the alphabet would probably have been casually determined before its turn to be considered separately had arrived. Therefore, it was suggested that the subject should adopt the method of running his eye over the letters with the utmost attention in order to remember each letter encountered. Sometimes the duplicate letter would be unnoticed in the first round of the search. On December 8, 1921, and subsequently, a small cross marks the results when the letter was unrecognised until the eye had looked over at least part of the collection more than once. The test was repeated ten times at a sitting, except once with Meakins when he began to feel a headache after doing it five times immediately after reaching a height of about 14,000 feet. Often confusion was caused in the mind of the subject by failure to identify the duplicate letter in the first glance round. Thus an unusually long time might pass before its discovery. One or two of these large results can raise the calculated mean of a series to such an extent that it hardly gives a fair representation of the performance. For this reason the median is also recorded. The median is taken in this connection to be the middle result when the series is arranged in order of magnitude, or when there is an even number of results in the series, the mean of the middle two results.

2. *Clock Test.*—A clock-face was employed with its figures arranged in a reversed way so that it had the same appearance as an ordinary clock reflected in a mirror. The hands were moved into various positions, and the subject asked to distinguish as quickly as possible what time was represented by each position. The results are

expressed in the number of seconds necessary to produce a correct answer. Readings were also taken from an ordinary watch-face.

The median and mean of each are calculated.

3. *Handwriting Test.*—A short passage is dictated as rapidly as can be permitted by the pace of the writer, who has previously been instructed to alter the usual style of his small e's and r's, *i.e.* ϵ instead of *e*, *r* instead of 𝓇, or *vice versâ*. The number of times he omitted to make the necessary change is counted afterwards, and the time occupied in writing is taken. Mistakes must not be altered.

4. *Memorising Test.*—Practice was given in memorising numbers of five and more digits exposed to view for 10 seconds. Each number was written down by the subject immediately after the end of the exposure time. It was found that they were capable of memorising a proportion of the ten-digit numbers, and so after the first practice only ten-digit numbers were used. No allowance was made for numbers which were partially memorised.

5. *Multiplication Test.*—A five-digit number is multiplied by another five-digit number. The number of mistakes and the time taken for doing the sum are both recorded. The same digits (3, 4, 5, 6, 7) are always used, but are arranged differently each time.

Test 1 does not seem to demonstrate anything definitely as the results stand. At an altitude of 8000 feet, Barcroft gave results which were up to his usual standard, although he felt less alert mentally than he usually did at sea-level. At 14,000 feet altitude his median was better than ever previously, and his mean there improved on all his earlier results except one. Meakins also felt less efficient at 8000 feet above sea-level, but his results in the duplicate letter test were not abnormal. 14,000 feet up he felt an approaching headache while doing the test, and therefore only did it five times instead of ten. The median for these five results was 15, which compares evenly with his three medians most recent to this—14, 15, 16.* Redfield performed the test more easily at 14,000 feet altitude than he did at sea-level on a hot, relaxing day near Panama.

In Test 2, Barcroft's median and mean are higher at each of the two increases in altitude, in the reversed clock-face readings. His ordinary watch-face readings are diminished, so that the differences between the ordinary and reversed face reading show an even more marked increase. At sea-level, only five readings were taken. If we compare the medians of the first five results, both at Matucana and at Cerro de Pasco, with these five, we shall find an even larger change.

	Reversed face, median.	Ordinary face, median.	Difference.
Sea-level	5″	2·6″	2·4″
Matucana (1st five results) . .	8″	2″	6″
Cerro de Pasco (1st five results)	10″	1·6″	8·4″

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* *i.e.* the medians of the first five results in the three previous sittings.

Meakins' results at 8000 feet do not show any similar change. The median of his first five results at Matucana is the same as at sea-level.

The results of Tests 3 and 4 do not seem to justify any conclusions. In the multiplication test, Test 5, Barcroft's performances at Cerro de Pasco and at sea-level are of almost equal value, but Doggart shows uniformly better results at sea-level. Meakins also shows marked improvement at sea-level, so that this test would seem to indicate a deterioration of efficiency at high altitudes, so far as as multiplication is concerned.

At Matucana, Barcroft and Meakins felt abnormally sleepy, and thought they used up much more time than at sea-level in doing the calculations involved in their work. During the first evening Meakins had a feeling akin to what he thought would be produced in him by excess of alcohol. They two and Doggart were all sleepy and heavy-limbed on the journey between Matucana and Oroya.

The members of the party all seemed to agree that their minds became fatigued at Cerro de Pasco after less work than would have been necessary to make them feel tired (31) (43) in ordinary circumstances, and some thought that their powers of calculation had become less speedy and accurate. On the other hand, it must be remembered that they were working at high pressure all the while, in order to achieve as much as possible in the short time at their disposal. Thus a great deal of the mathematical work was done in the evening after dinner, when the whole day up to dinner-time had been spent in laboratory work. But then, again, the engineers and clerical staff, with varying numbers of years' experience of work at that altitude, seemed to be unanimous in holding that up there they were definitely incapable of doing their own sea-level standard of work, whether mental or physical. It might have been possible approximately to discover the amount by which efficiency was diminished, had much longer tests been employed, and had it been possible to experiment for several hours a day with five or six subjects who had undergone several hours' practice every day for at least six weeks. As it is, the tests give no clear message as to the manner and extent in which mental capacity is affected by altitude. But since subjective observations agree in attributing to high altitude an effect like the one above remarked, we may conclude that probably the tests were too easy or too short.

Doggart was an exception in the party, in that he had no fixed programme of work to occupy every available moment, and so, unlike the others, had no possibility of experiencing a very considerable degree of fatigue to complicate the effect of altitude. He was not conscious of any feeling that his text-books, at which on most days he was working for several hours, seemed more difficult to follow, or that his pace in reading them was at all lessened. Thus it may be, though we have no exact data by which to prove it, that the effect of altitude on mental work, except in the first day or two of acclimatisation, is more likely to occur towards the end of a number of consecutive hours' effort—in other words, is more likely to alter the quantity than the quality, unless work is prolonged past the inclination to stop.

Duplicate Letter Test. (Barcroft.)

	Sea-level.					Matucana, 8000 ft.	Cerro de Pasco, 14,000 ft.
	21/11/21	24/11/21	5/12/21	8/12/21	13/12/21	21/12/21	27/12/21
	2′ 37″	19″	25″	64″	26″	37″	14″
	1 42	16	19	19	29	65	41
	38	7	8	45	11	6	28
	1 35	14	44	67	90	50	25
	35	5	24	3	31	71	12
	26	21	3	64	22	15	12
	16	20	36	30	2	35	23
	25	29	13	43	40	32	14
	15	7	67	13	43	7	8
	13	28	42	5	15	15	13
Mean . . .	53·2″	16·6″	28·1″	35·3″	30·9″	36·8″	19″
Median . .	30·5″	17·5″	24·5″	36·5″	27·5″	36″	14″

(Meakins.)

							Matucana
	21/11/21	24/11/21	5/12/21	8/12/21	5/12/21	8/12/21	21/12/21
	32″	5″	9″	9″	9″	9″	16″
	13	8	13	15	13	15	16
	18	10	20	17	20	17	9
	50	34	36	5	36	5	19
	40	27	14	15	14	15	15
	15	75	7	31	7	31	13
	12	46	18	6	18	6	20
	21	6	40	12	40	12	30
	15	13	19	22	19	22	26
	6	14	13	12	13	12	13
Median . .	22·2″	23·8″	22·2″	23·8″	18·8″	14·4″	17·7″
Mean . .	16·5″	13·5″	16·5″	13·5″	16″	13·5″	16″

24/12/21 (Between Oroya and Cerro de Pasco, 14,000 ft. up)

15″ (Only half the usual number was given, because Meakins began to feel a headache.)
12
19
15
17

Mean 15·6″
Median 15″

Duplicate Letter Test. (Redfield.)

	24/12/21 (as above)	19/1/22 (Ebro)
	6″	11″
	51	26
	21	10
	6	2
	6	23
	13	45
	14	12
	13	9
	1	30
	20	31
Mean	15·1″	19·9″
Median	13″	17·5″

N.B.—Heat made him feel relaxed.

Clock Test. (Barcroft.)

	21/11/21 (" Victoria ") Reversed face.	21/11/21 (" Victoria ") Ordinary face.	21/12/21 (Matucana) Reversed face.	
	4″	2″	8·5″	
	3	2·8	12	(wrong answer at 7″)
	7	2·6	6	
	6	4	3	
	5	2·4	8	
			7	
			7	
			5	
			8	(wrong answer at 7″)
			5	
Mean	5″	2·7″	6·9″	
Median	5″	2·6″	7″	

Clock Test. (Barcroft)—*contd.*

	21/12/21 (Matucana) Ordinary face.	27/12/21 (Cerro de Pasco) Reversed face.	27/12/21 (Cerro de Pasco) Ordinary face.
	2″	21″ (wrong answers at 7″ and 12″)	1″
	2	10	1·8
	1·2	10	1·6
	2	9	1
	3	9	1·6
	2·2	6	1
	1	5	1·2
	1·6	4·5	2·2
	2	6·5	1·4
	2·2	7	1·6
Mean . . .	1·9″	8·8″	1·4″
Median . .	2″	8″	1·5″

(Meakins.)

	21/11/21 Reversed face.	21/11/21 Ordinary face.	21/12/21 (Matucana) Reversed face.	21/12/21 (Matucana) Ordinary face.
	3·2″	2″	1·2″	2″
	6	2	2·6	1·8
	3·4	2·2	10	1·8
	2	1·6	4·6	1·4
	3	2	3·2	2·6
			3·8	1·6
			2	1·6
			2·4	1·6
			2·4	1·6
			3·8	1·6
Mean . .	3·5″	2″	3·6″	1·8″
Median .	3·2″	2″	2·9″	1·6″

Handwriting Test. (Barcroft.)

21/11/21		6 e's wrong	Time	2′	21″
8/12/21		6 e's ,,	,,	2	14
		2 r's ,,			
13/12/21	(1)	4 e's ,,	,,	2	15
		1 r ,,			
	(2)	5 e's ,,	,,	2	5
		1 r ,,			
21/12/21		5 e's ,,	,,	1	55
		1 r ,,			
27/12/21	(1)	2 e's ,,	,,	2	19
		1 r ,,			
	(2)	7 e's ,,	,,	1	49
		2 r's ,,			

(Meakins.)

21/11/21	1 e wrong			
	1 r ,,	Time	2′	21″
8/12/21	4 e's ,,			
	1 r ,,	,,	2	21
21/12/21	1 e ,,			
	1 r ,,	,,	2	15

(Doggart.)

28/12/21	(1)	1 e wrong	Time	2′	8″
	(2)	No mistakes	,,	1	48
	(3)	,, ,,	,,	1	40
27/1/22 (Ebro)		,, ,,	,,	1	41

Memorising Test. (Barcroft.)

21/11/21	Two each 4-, 5-, 6-, 7- and 8-digit numbers correctly remembered. The two 9-digit numbers were wrongly and imperfectly remembered. One out of four 10-digit numbers correct.
24/11/21	Four out of ten ,, ,, ,,
5/12/21	Three out of five ,, ,, ,,
8/12/21	Four ,, ,, ,, ,,
13/12/21	Three ,, ,, ,, ,,
21/12/21	Four ,, ,, ,, ,,
27/12/21	Four ,, ,, ,, ,,

Memorising Test. (Meakins.)

21/11/21	No mistake until the 9-digit numbers, both of which were incorrect. All four 10-digit numbers wrong.			
24/11/21	Five out of ten 10-digit numbers correct.			
5/12/21	None out of five	"	"	"
8/12/21	Two "	"	"	"
21/12/21	One "	"	"	"

Multiplication Test. (Meakins.)

24/12/21 (between Oroya and Cerro de Pasco, 14,000 ft. up)	Time	1′	16″	2 mistakes.
30/1/22 ("Ebro")	"	1	3	No "
30/1/22	"		54	" "

(Doggart.)

24/12/21 (as above)	Time	60″	1 mistake.
25/12/21 (Cerro de Pasco)	"	61	No mistakes.
28/12/21 "	"	59	" "
26/1/22 ("Ebro")	"	53	" "
27/1/22 "	"	54	" "
28/1/22 "	"	51	" "

(Barcroft.)

27/12/21 (Cerro)	Time	1′	32″	1 mistake.
28/12/21 "	"	1	35	No mistakes.
26/1/22 ("Ebro")	"	1	23	2 "

IV.—"SOROCHE" OR MOUNTAIN SICKNESS, AND THE EXTENT TO WHICH IT MAY BE PREDICTED.

The untoward symptoms which the members of the party experienced at Oroya (12,000 feet) and Cerro de Pasco (14,000 feet) may best be considered under two heads: first, those acute symptoms which came on the first or second day after arrival, and, secondly, those symptoms which persisted in perhaps lessening degree throughout the sojourn at high altitudes. To the first group of symptoms the name of "soroche" is generally applied. These are sufficiently outspoken, though variable in their manifestation, to constitute what might be called a "clinical entity." Of the eight members of the party four had "soroche" in sufficiently severe degree to force them to go to bed from one to four days. Rest in bed was as imperative to their feeling of well-being as it would be to a patient in the first few days of an acute infection. The remaining four all had symptoms, but not severe enough to disable them. After the acute "soroche" subsided all members of the group were able to put in a good day's work of nine to ten hours' duration in the laboratory, followed frequently by an hour or two on calculating in the evening. The Table of Symptoms (pp. 447–8) refers to those felt at any time during the period of exposure to low atmospheric pressures.

A few excerpts taken from diaries of members of the party will describe the onset and course of symptoms perhaps better than any attempt at a more general description of the illness.

I. Example of a mild case :—

Dec. 19. Railroad. Tamborague, 9,826 feet. Pulse 64.

San Matteo, 10,534 feet. Pulse 74. Respirations more marked. Thoracic in type. Loosened my waistcoat and belt. Felt distinctly inclined to sit still.

Rio Blanco, 11,430 feet. Pulse 78. Felt a bit light-headed and cold in my feet.

Casapalca, 13,606 feet. I began to feel really bad with a good vigorous headache and a slight feeling of nausea. Feet and hands cold—chilly sensations.

Summit, 15,860 feet.

Yauli, 13,420 feet. Headache practically gone.

Oroya, 12,178 feet. Pretty winded in lifting baggage out of car window.

Dec. 20. I feel exactly as one does on the first day out after a week of tonsillitis or grippe. Unsteady on my pins. Walked about very very slowly perhaps $\frac{1}{8}$ of a mile—my legs ached as if I had walked 30 miles.

Dec. 23. Spent A.M. straightening up car and walked back to house. Climbed up a hill 100 feet without undue blowing. Ran part of the way from house to hospital without getting winded.

II. Example of a more severe case of short duration :—

Dec. 23–24. Arrived Cerro de Pasco (14,200 feet) about 10 P.M. Felt very well, probably rather euphoric. During night severe headache behind the eyes and in occipital region. In A.M. rather deaf and vision was very dim. I had photophobia and felt very irritable. No appetite. Could not sleep. Muscular pain in back and thighs. Rectal temperature 100°.

Dec. 26. Attack cleared up and I felt in normal condition again.

III. Symptoms lasting over 5 days.

Dec. 21 Casapalca (13,606 feet).
3.10 P.M. Drowsiness, headache, malaise, slight cyanosis.
3.20 Slightly deaf and can't see very well.
4.00 Ticlio (15,600 feet). Severe frontal and parietal headache. Feel rotten—lying down. Cyanosed—dim vision—nausea. Difficult to reply to questions.
4.20 Vomited.
4.30 Vomited again—grey cyanosis.
Oroya (12,178 feet). Lying back with eyes closed.
5.30 Able to walk back from train to auto. Very dizzy—splitting headache. Taken directly to hospital—put to bed.
Dec. 21–24. In bed with severe headache, which prevented sleep. No nausea or vomiting after first night. Weakness. Felt as if I had been hit with a brick.
Dec. 25. Out of bed. Short of breath. No headache.

IV. Very transient symptoms.

Dec. 19. After headache. Shortness of breath and sense of lassitude of gradually increasing severity—the following notes:—

R. R. Ticlio. I had only one desire, and that was to be horizontal in a warm bed.

Oroya (12,178). It was about all I could do to handle my big bag. I was winded; splitting headache; teeth chattered. Slightest motion caused my head to ache violently. My face was flushed and lips a dull lavender. Finger nails cyanotic about the base and white at the tips. Hands and feet cold. Went to bed about midnight. While undressing had a pretty severe chill. Head ached furiously—retrobulbar and occipital. Felt alternately hot and cold. Temporal arteries throbbing. Heart palpitated and felt short of breath. Respirations 24. Pulse 92. Temperature by rectum 102·6° F. Felt as if in the prodromal stage of an acute infectious disease.

Dec. 20 A.M. Physical examination negative, except for cyanosis, fever, and rapid pulse. Lungs clear.
Dec. 21. Temperature normal; general improvement; headache persists the less.
Dec. 22. Out of bed; feel weak; headache still present. Even slow walking produces dyspnœa.
Dec. 23. Cerro de Pasco (14,300 feet). No ill effect from added altitude.
Dec. 24. Awoke with very severe headache. Stayed in bed till noon. Danced two dances at Xmas eve party with slight puffing. No further acute symptoms.

These notes give a fairly representative description of "soroche" as experienced by members of the Expedition. More severe types of longer duration, and indeed sudden death, are described by some, but we have confined our account to what we ourselves have observed.

After the acute symptoms of "soroche" had subsided, the effects of the high altitude were manifest in a variety of ways in different individuals. Cyanosis was constantly present in all the members of the party to a greater or less extent. The degree by casual observation was not necessarily indicative of the degree of arterial oxygen saturation. Those individuals who normally had a more or less florid complexion appeared more cyanosed than did those whose appearance was paler. The contrast between the natives and Europeans in this regard was most striking. Practically all the healthy natives were of a "plum colour" in those anatomical areas where arterial blood lends colour to the skin. This was particularly evident in the children. In those native adults where this was not conspicuous it was evident that they were probably suffering from some organic disease, such as miner's phthisis, tuberculosis, etc., or were chronic *habitués* of cocaine. We were fortunate to have the opportunity of observing the effect of the altitude upon one of the Anglo-Saxon engineers, who has been resident in Cerro de Pasco for some years. He was a man of very powerful physique, who was in no manner troubled by the altitude. His cyanosis was of an extreme type, but it was also noted that his skin capillaries were particularly prominent and presented the appearance of being extremely well filled. His blood examination showed the red cells to number 6,800,000 and the hæmoglobin to be 128 per cent. He accompanied us to sea-level, where the alteration in his appearance was most remarkable. Instead of being of a deep "plum colour," his complexion was a brilliant red, as if he had recently become intensely sunburnt. The change in his appearance was duplicated by certain of our party, but he afforded an example which all could observe without prejudice.

The general well-being of the party differed considerably in degree as time passed. It seemed to bear no relation to the severity of the initial symptoms. This probably was to be expected, as those who had suffered from acute "soroche" had had their lesson, and deported themselves in combined work and play more circumspectly than did those who had escaped. The latter, as time passed, showed a distinct slackening of their energy. The desire was unimpaired, but the capacity was distinctly lessened. This was particularly evident in so far as prolonged physical exertion was concerned. Not that their capacity was diminished below their fellows, but they were comparatively less capable of exertion as time progressed, and in consequence they required more rest, and were approaching the more sensible attitude of their associates who had been early less fortunate.

In all members of the Expedition the effect on the mental processes were insidious, but eventually quite apparent. Although short and precise exercises did not exhibit any pronounced change in the nervous and reflex capacity of the members of the party, prolonged concentration gave evidence of lowered control. Whereas at sea-level certain members of the party would use a Haldane gas-analysis apparatus or other similar technique for days on end without a mistake, rarely a day passed at Cerro de Pasco without once or oftener having to take apparatus apart and cleaning it through some stupid mistake of manipulation.

In the matter of arithmetic similar mistakes were evident. It was not so much that gross errors were made, as that frequently simple sums had to be gone over repeatedly before the worker was satisfied as to the accuracy. Like conditions were observed when the slide-rule and logarithms were used.

Although the party worked for long hours on end in the laboratory—it being the custom for certain members to have their lunch and tea there daily—the amount of work accomplished in a day was sometimes disappointing. This was undoubtedly due to the conspicuous mental and physical fatigue which gradually developed as the day wore on, with the inevitable slowness and clumsiness which ensued. This effect of prolonged and steady work was not confined only to the members of the party. Men who had lived at Cerro de Pasco for years without any symptoms of acute "soroche," informed us that the best work in the end was obtained by short periods of work with long rests between. This was particularly the case in those whose occupation was mental—accountants, draftsmen, etc.

It has been stated that life at high altitudes is conducive to irascibility of temper. As far as the present party was concerned this was not evident. On no occasion was any petulance or unreasonableness exhibited by members of the party one to another. On the other hand, impatience at one's own mistakes was commonly manifest, and usually produced a considerable amount of amusement amongst the rest of the party.

The other symptoms which developed during our stay at Cerro de Pasco were confined to our physical well-being. The appetite was often capricious and irregular. At times it was almost voracious, and at others the mere mention of food was distasteful. Sleep was almost uniformly disturbed and not of long duration. Those who were accustomed to 8 to 10 hours' sleep would usually find it impossible to sleep more than 6–8 hours. At intervals, however, certain members of the party, who usually sleep the least, would sleep for 12 to 14 hours on end. One of the most notable features, due to the residence at high altitudes, was loss of weight. This occurred in all members of the party, but more in some than in others. The greatest loss of weight was a decline from 155 to 131 lbs. in twenty-seven days. This amount was quickly regained when the individual returned to sea-level. We were informed by those who had lived at high altitudes for some years that an initial loss of weight was almost universal, but that a certain amount was subsequently regained, although the former sea-level weight was seldom reached.

The following Table gives a detailed statement of the symptoms suffered by each member of the party :—

TABLE XXXVIII.

	Central nervous symptoms.	Cardiac symptoms.	Peripheral circulatory symptoms.	Respiratory symptoms.	Gastro-intestinal symptoms.
Barcroft. . . .	Headache + Vertigo 0 Impaired vision 0 Impaired hearing 0 Lassitude + Increased fatigue + + Sleeplessness Restlessness 0 Depression 0	Precordial pain + Palpitation 0 Arrhythmia 0	Chills 0 Chilly sensations 0 Cold extremities + + Flushing 0 Feeling of heat 0 Sweating 0 Fever 0 Cyanosis + + Epistaxis 0 Arterial throbbing 0	Shortness of breath + Periodic breathing 0 Sighing 0	Nausea + Vomiting + Diarrhœa 0 Constipation 0 Abdominal pain 0 Anorexia +
Meakins . . .	Headache 0 Vertigo 0 Impaired vision 0 Impaired hearing 0 Lassitude 0 Increased fatigue + Sleeplessness 0 Restlessness + Depression 0	Precordial pain + Palpitation + Arrhythmia 0	Chills 0 Chilly sensations 0 Cold extremities 0 Flushing 0 Feeling of heat 0 Sweating 0 Fever 0 Cyanosis + + Epistaxis 0 Arterial throbbing	Shortness of breath + Periodic breathing + Sighing +	Nausea 0 Vomiting 0 Diarrhœa 0 Constipation 0 Abdominal pain 0 Anorexia 0
Doggart . . .	Headache 0 Vertigo 0 Impaired vision 0 Impaired hearing 0 Lassitude 0 Increased fatigue + Sleeplessness Restlessness 0 Depression 0	Precordial pain 0 Palpitation 0 Arrhythmia 0	Chills 0 Chilly sensations 0 Cold extremities 0 Flushing 0 Feeling of heat 0 Sweating 0 Fever 0 Cyanosis + Epistaxis 0 Arterial throbbing 0	Shortness of breath + Periodic breathing + Sighing +	Nausea 0 Vomiting 0 Diarrhœa 0 Constipation 0 Abdominal pain 0 Anorexia 0

TABLE XXXVIII—(*contd.*).

	Central nervous symptoms.	Cardiac symptoms.	Peripheral circulatory symptoms.	Respiratory symptoms.	Gastro-intestinal symptoms.
Binger	Headache + + Vertigo 0 Impaired vision 0 Impaired hearing 0 Lassitude + Increased fatigue + + Sleeplessness Restlessness 0 Depression	Precordial pain + Palpitation + Arrhythmia 0	Chills + + Chilly sensations + Cold extremities + Flushing 0 Feeling of heat + Sweating 0 Fever + Cyanosis + Epistaxis 0 Arterial throbbing +	Shortness of breath + Periodic breathing + Sighing +	Nausea + Vomiting 0 Diarrhœa 0 Abdominal pain 0 Constipation 0 Anorexia +
Bock	Headache + + + Vertigo 0 Impaired vision + Impaired hearing + Lassitude + + Increased fatigue + + Sleeplessness + Restlessness 0 Depression + +	Precordial pain 0 Palpitation 0 Arrhythmia 0	Chills 0 Chilly sensations 0 Cold extremities Flushing + Feeling of heat + Sweating + Fever 0 Cyanosis + + Arterial throbbing + Epistaxis +	Shortness of breath + Periodic breathing + Sighing + +	Nausea + Vomiting + + Diarrhœa 0 Constipation 0 Abdominal pain + Anorexia +
Forbes	Headache + Vertigo + Impaired vision + Impaired hearing 0 Lassitude 0 Increased fatigue + Sleeplessness + Restlessness 0 Depression 0	Precordial pain + Palpitation + Arrhythmia 0	Chills 0 Chilly sensations + Cold extremities + Flushing 0 Feeling of heat 0 Sweating 0 Fever 0 Cyanosis 0 Arterial throbbing 0 Epistaxis 0	Shortness of breath + Periodic breathing + Sighing +	Nausea + Vomiting 0 Diarrhœa 0 Constipation 0 Abdominal pain 0 Anorexia 0

Determinations of the diffusion constant of the lung on all the members of the party were made at Cerro de Pasco, as well as upon five American residents. It was not found possible in the limited time available to train native subjects sufficiently to obtain satisfactory data, but it was quite obvious that, under favourable conditions, such results would not be difficult to obtain. Control determinations upon the members of the party were also made at sea-level (Lima, New York, Copenhagen), and a striking agreement was in general obtained, both in the values for the specific permeability and for the diffusion constants as well. We regard it not only as good evidence that there was essentially no change in the values as measured at rest, but that changes in the circulation rate at rest through the lungs, if they exist at high altitudes, are certainly not large.

At the outset of this investigation it was thought likely, in case the assumptions regarding the significance of the diffusion coefficient are approximately correct, that one would be justified in expecting, under conditions of low barometric pressure, that the physiological effects of oxygen want, the symptoms of mountain sickness or "soroche," would be most severe in those whose diffusion coefficients were lowest, or, in other words, through whose lung epithelium oxygen diffuses with the greatest difficulty. Under normal atmospheric pressures such differences need not be evident; the amounts of oxygen diffusing through the lungs will ordinarily be more than sufficient to satisfy physiological requirements. But when the margin of safety is removed, and oxygen want begins to be felt, it is to be expected that individual variations in the value of the coefficient will become of significance. A comparison of the relative severity of the clinical symptoms of mountain sickness shown by the eight members of the party, with the values obtained for their diffusion coefficients, shows that for this group, at least, our expectation has been substantially realised. A detailed account of the symptoms suffered by the party has been given already. Arranged in the order of the values obtained for the coefficient (as has been done in the Table), it was found that the four persons having the highest coefficients suffered not at all, or at least had comparatively trivial symptoms, while all of the four men who had the lowest values suffered to a more or less severe degree. And of these four, Harrop and Bock, who had the lowest values of all, certainly had the most severe symptoms.

A further indication that the diffusion coefficient gives a rather accurate estimate of what may be expected to be the reaction of the individual exposed to life at high altitudes may be found in the results of the determinations upon five American mining engineers who had lived at Cerro de Pasco for two years or more. All of these men were in good health and able to carry on their work efficiently, and they were free from the usual chronic manifestations of difficulty in withstanding the stress and strain of living at low oxygen pressures—loss of weight, sleeplessness, digestive disturbances, excessive breathlessness with or without physical exertion, excessive irritability, feelings of more or less indefinite lack of well-being, etc. None had ever suffered from "soroche," and all had diffusion coefficients for oxygen 40. One of them, indeed, Mr. Rogers, formerly a trained college athlete and long-distance runner, was found to have the highest coefficient yet recorded for a man at rest—65·3.

While discussing these studies upon completely acclimatised individuals, it is desirable to draw attention to the fact that the values for the specific permeability, calculated at the mean capacity, are in all of these persons rather high, and in the cases of two of them (Messrs. Cuthbertson and Rogers) very high indeed. On the other hand, their lung measurements are by no means remarkably different from the usual ones found in men of similar general physique at sea-level. The interesting question arises as to what influence, if any, life at high altitudes may have in increasing the specific permeability of the lungs. As above stated, measurements upon natives, with the limitations imposed by lack of time for the training necessary to secure proper co-operation by unintelligent subjects, were not found to be practicable, but they would be highly desirable in order to clear up this question. There is reason to believe that age and certain peculiarities of the alveolar structure produced by disease may cause decided changes in the permeability, and it is not improbable that very high values may be found as a rule in natives acclimatised for generations to high altitudes.

V.—SUMMARY AND CONCLUSIONS.

Of the factors which might be held to assist in acclimatisation some at least appear to have little value at the altitudes at which we have worked (14,200 feet). Such are oxygen secretion, alterations in the vital capacity, residual tidal air, diffusion coefficient, and increased quantity of blood driven round the body per minute.

The pulse, under basal conditions, beats at the same rate at 14,000 feet as it does at sea-level. It gives a greater response to exercise, however, the increase being most marked with light exercise; and, indeed, the ordinary conditions of life, as compared to basal conditions, constitute a degree of exercise which renders the normal pulse more rapid at Cerro than at sea-level. Inasmuch as the minute volume of blood is little altered, the increased pulse rate must be regarded, in the words of SCHNEIDER, as a signal of distress and not a form of acclimatisation. In some cases skiagrams showed an actual diminution in the size of the heart, in others they did not. Such an individual variation would indicate, along the lines laid down by STARLING and his pupils, a corresponding individual variation in the efficiency of the heart. In the hearts, the fibres of which elongated in diastole to the same extent at Cerro as at the sea-level, there would be a loss of efficiency; for with the same strain on the heart at each beat there are more beats. In the hearts which dilate less, the smaller elongation of the fibres goes to counterbalance the more rapid pulse.

It had been our intention to make observations on the blood volume at high altitudes; this intention was not carried out, for a reason which probably proved to be more illuminating than our original programme would have been. There appears to be a temperature factor in the blood volume. On the voyage to Peru, and to a less extent on the voyage home, the blood volumes of three persons were observed to change with the external temperature; increasing in the warm climates. A similar increase has subsequently been observed in chamber experiments of two or three days' duration (Appendix I), in which the temperature factor was the only alteration of circumstance to which the subjects were exposed. The experimental procedure in these chamber tests were carried out by three different methods. The significance of the change in volume of the blood would appear to be that in hot climates much of the blood is in the skin; the circulation in the arm may in the most extreme cases be increased fifty-fold by a change of skin temperature. Under circumstances where the whole skin is affected, such as very hot climates, the increase in the vascular bed may be considerable, and the volume of blood increases to preserve the relation between the quantity of vascular fluid and the bed which contains it.

There remain three principal factors which appear to have a positive influence in acclimatisation:—

(*a*) The increase in total ventilation, which usually raises the alveolar oxygen pressure 10 or 12 mm. higher than it would otherwise be.

(*b*) The rise in the oxygen dissociation curve, so that at any oxygen pressure the hæmoglobin will take up more oxygen than before.

(*c*) The rise in the number of red corpuscles and correspondingly in the quantity of hæmoglobin.

These three factors may be regarded at first as independent variables and an attempt made to appraise their relative importance. The attempt has necessitated an enquiry into the laws which govern diffusion in the lungs and the tissues. This enquiry makes it obvious that:—

(1) The colour of the blood in the lungs must be almost that of arterial blood, whilst the colour of blood in the tissue capillaries approach that of the venous blood which emerges from the tissue in question.

(2) An explanation is found for the fact that, at high altitudes, the arterial blood darkens when exercise is taken, whilst it does not do so to an appreciable extent at the sea-level. It is also explained why the arterial blood should darken on exercise in lung complaints in which the permeability of the lung wall, or the surface of capillaries in the lung (see Appendix VI), is diminished—either will reduce the diffusion coefficient.

Working from Bohr's method of graphic integration, it appears that fall of alveolar pressure tends to depress the region of oxygen utilisation in two ways:—

(1) It lowers limiting the percentage saturation which the arterial blood could attain if it achieved an equilibrium with the alveolar air.

(2) It increases the gap between this limiting saturation and the actual saturation which is attained in the lung. The equilibrium is not so nearly approached.

Increase of total ventilation and rise in the oxygen dissociation curve each have two effects, and these in about the same degree :—

(1) They raise the point on the oxygen dissociation curve at which an oxygen equilibrium between the arterial blood and the alveolar air could be struck.

(2) They diminish the gap between the equilibrium and the actual degree to which the arterial blood is saturated with oxygen.

The rise in hæmoglobin value (§ (*c*) above) produces little effect on the position of utilisation. It causes the arterial blood to be less saturated and the venous blood to be more saturated than would otherwise be the case. Inasmuch, however, as the average capillary pressure approximates to the venous and not to the arterial pressure, benefit accrues—this, however, is rather small, and it seems clear that the real advantage derived from increase in the red blood corpuscles is of a secondary character, as will appear.

Concerning the mechanism of the increase in total ventilation, one possibility may be ruled out during rest, namely, increased hydrogen-ion concentration in the blood, for during rest the blood is no less alkaline than at sea-level. This is shown by the limited number of readings taken by the Dale and Evans' method. Indirectly it is shown also by the method of measuring the rate of the free to the combined CO_2 in the whole blood. It is true that on the actual readings the difference in reaction was slight, but of two samples of blood exposed to 25 mm. oxygen which give the same readings by this method, that which contains the greater number of corpuscles will be the more alkaline (see Appendix II). As this result appears to be in conflict with the researches of Warburg, it will be wise to leave open the question as to whether the reaction of the blood is unchanged or becomes slightly more alkaline.

By a process of exclusion, it must be supposed that the increased activity of the respiratory centre is the result—direct or indirect—of oxygen want on the centre itself. The fall of CO_2 in the alveolar air is the effect, and so also in the relative rise in oxygen.

When exercise is taken, a given amount of exercise is found to produce a greater rise in the hydrogen-ion concentration in rare than in ordinary air, hence the urgency of the breathlessness which supervenes is due to the fact that there is not only a more irritable respiratory centre but a greater increment of hydrogen-ions, *i.e.* a greater stimulus acting upon it.

Above the three main factors in acclimatisation ((*a*), (*b*) and (*c*) above) were provisionally treated as independent variables; in reality they are not so, for blood can be made artificially to resemble high-altitude blood, by shaking out the CO_2, centrifugalising and then withdrawing a portion of the plasma so that the blood is richer in corpuscles. Such blood has been found to give at the alveolar CO_2 pressure of the Andes (27 mm. CO_2 or thereabouts) :—

(1) A reaction which is apparently almost unchanged, or even more acid as measured by the ratio of combined to free CO_2.

(2) A more alkaline reaction by the platinum electrode.

(3) An oxygen dissociation curve, which rises apparently out of proportion to the change in reaction.

Herein would appear to be the essence of the acclimatory process. The possibility of the oxygen dissociation curve altering, owing simply to a loss of CO_2, appears to be ruled out (Appendix II). There was an increase in the hæmoglobin value of the blood and in the red cell count in all cases. On making the ascent there was a marked increase in the number of reticulated red cells, after the descent these cells fell to below their normal percentage. In the natives the ratio of reticulated to unreticulated red cells was not greatly increased, but the absolute number of reticulated cells per cubic millimetre was about 50 per cent. greater than normal. We argue a hypertrophy in the bone marrow. There were no nucleated red cells. The increase in red blood corpuscles is such as to cause an absolute increase in the amount of oxygen in each cubic centimetre of blood in the majority of cases, in spite of the decrease in saturation.

In the natives (3) the saturation of the arterial blood is 80–85 per cent. ; in the members of the Expedition it was found to be 85–90 in most cases. The arterial blood, as withdrawn from the radial artery with a syringe, was always dark in appearance, as also was the colour of the lips. The cyanosis disappeared on breathing oxygen. The saturation of the arterial blood appears to be much the same as in many cases of pneumonia observed by Meakins. The "oxygen want factor" in pneumonia is worthy of abolition by oxygen respiration, and must be regarded as an important factor accessory to the toxin.

A number of mental tests of the ordinary type were performed at Cerro and at sea-level. These revealed no particular mental disability in the Andes. In our opinion, as well as in that of psychologists whom we have consulted, we have shown rather that the mental tests were inadequate than that our mental efficiency was unimpaired. Judged by the ordinary standards of efficiency in laboratory work, we were in an obviously lower category intellectually at Cerro than at the sea-level. By a curious paradox this was most apparent when it was being least tested, for perhaps what we suffered from chiefly was the difficulty of maintaining concentration. When we knew we were undergoing a test, our concentration could by an effort be maintained over the length of time taken for the test, but under ordinary circumstances it would lapse. It is, perhaps, characteristic that, whilst each individual mental test was done as rapidly at Cerro as at the sea-level, the performance of the series took nearly twice as long for its accomplishment. Time was wasted there in trivialities and "bungling," which would not take place at sea-level.

A number of tests were made for the purpose of discovering whether the pressure of oxygen in the blood was or was not higher than that in the alveolar air. In all cases they were so nearly the same that we attribute the passage of gas through the pulmonary epithelium to diffusion.

Cyanosis, whilst always more or less evident at Cerro, increased upon exercise. Cyanosis is a darkening of the colour of the mean capillary blood in the area studied. This blood approximates in colour to the venous blood from the part observed. As exercise does not increase the oxygen consumption of the blood of the lips, and as there is no reason to suppose that it induces vaso-constriction in the lips, the reason for their cyanosis must be diminished saturation of the arterial blood which reaches them. Such diminished saturation is not accompanied by any fall in the alveolar oxygen, yet it is easily explicable on the diffusion theory.

Some observations on mountain sickness are given; the principal contribution which we have made is the observation that in our own party the proneness to "soroche" corresponds pretty closely to the value of the diffusion coefficient, those persons who had a low diffusion coefficient being the sufferers. Further research is necessary before any statement can be made as to whether observation is due to more than coincidence. Such research is being carried out.

APPENDIX I. (See p. 422).

ON THE RELATION OF EXTERNAL TEMPERATURE TO BLOOD VOLUME.

J. Barcroft, J. C. Meakins, H. W. Davies, J. M. Duncan Scott, W. J. Fetter.

During the voyage from Liverpool to Callao, and again on the return journey from Callao to New York, a number of determinations were made for the purpose of measuring the blood volume of various members of the Expedition which went to Peru in the winter of 1921–22. The first set of these observations was intended merely to establish the blood volumes at sea-level for the purpose of comparison with those found at high altitudes. It very soon transpired that the blood volumes, as estimated, were not constant, and that the only factor with which they appeared to be correlated was the temperature of the environment, the blood volume increasing as the temperature rose and decreasing as it fell.

This result was in many ways so surprising, and in any case so difficult to explain, that it seemed desirable to test it by subjecting one or two individuals to high temperatures in an artificially heated atmosphere and making observations of the "blood volume."

Some further inquiry is required into the meaning of the term "blood volume," as applied to the results of estimations by the carbon monoxide method.* The individual absorbs a known volume of carbon monoxide in virtue of the high affinity of the gas for hæmoglobin. In using the term "blood volume" the hæmoglobin is assumed to be all in the blood, and the blood supposed to be so far in the circulation that all the pigment which it contains is exposed to the carbon monoxide during the duration of the experiment. Of these assumptions the first is certainly incorrect, whilst the second is certainly not true. In man, the hæmoglobin in the muscles is, however, but a small percentage of the whole, and is probably pretty constant from day to day. For the present purpose, therefore, it may be neglected, unless it could be shown that the muscles were at times cut off for 15 minutes from the circulation.

The carbon monoxide then may be assumed to unite with so much of the hæmoglobin as it has access to in the quarter of an hour during which it is inspired, and to give an index coupled with the hæmoglobin value of the volume and total O_2 capacity of

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* We did not use "vital red" to check our carbon monoxide results as we heard of two human cases in which injection of this material proved all but fatal. It would appear that some samples of the pigment may be more toxic than others or some persons more susceptible to it.

blood current in the circulation.* How far this volume is identical with the total blood volume is a matter for separate investigation. Taking the result of the carbon monoxide method as an estimate then of the volume of circulating blood we proceeded to measure what this might be: (1) before, (2) during, and (3) after exposure to high temperatures.

The principal possibility of error which we hoped to eliminate from the Peru results was that (if any) contingent on the method of estimating the percentage of CO in the blood.

On the voyage out the sole method used for this estimation was the reversed spectroscope devised by HARTRIDGE (38). This instrument has the drawbacks common to all instruments which are based on readings of a subjective character. On some occasions, for instance, the eye fatigues more easily than others, and indeed there have been times when one of us (Barcroft) has found difficulty in seeing the bands for sufficient time to ensure getting their position correctly. Such experiments made us suspicious of the instrument, and inclined to wonder whether its calibration could change under changing atmospheric conditions. Moreover, our instrument was made of wood, and it seemed possible that some such effect as warping of the box in the tropics might invalidate the readings. Before undertaking the present experiments the instrument was taken to pieces and reassembled; it was a considerable satisfaction to discover that the calibration curve was only altered in the following sense, namely, that if two hæmoglobin solutions A and B were taken—A containing no CO and B a definite percentage of CO; and, further, if the reading in each case for A were taken as zero—the reading for B exceeded the reading for A by the same number of divisions on the scale. This was so, even though the readings, before and after going to Peru, were on quite different parts of the scale.

In addition, however, to the Hartridge method of estimating CO, we employed two other methods in the present series of experiments: (1) The method of pumping out the CO with a blood gas-pump and measuring it in a Haldane gas-analysis apparatus by means of combustion and absorption of the CO produced. In the first experiment (on Davies), the Van Slyke pump was employed, and samples of 2 c.c. of blood were used for the estimation. In the second (on Fetter), the larger samples of blood were requisitioned (10–15 c.c.), and the blood gas-pump was used. (2) The method of carmine titration (45).

Throughout the course of the first experiment all three methods worked as well as could be expected, the carmine and the spectroscopic methods keeping very close to one another, while the extraction method gave results which (but for one observation) were parallel, but showed a less blood volume throughout. The probable reason for

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* In these experiments a minimum of 15 minutes was allowed between the time of introducing the carbon monoxide into the breathing circuit and the time of taking the blood sample. We have assumed that during this time the carbon monoxide has become uniformly diffused throughout the whole circulation. It is proposed, however, to test this assumption by means of further experiments.

a lower blood volume, as shown by the extraction method, was revealed when the method was operated in Experiment 2. In this experiment the CO in the blood was estimated before as well as after the blood-volume measurement, and a certain amount of combustible gas was always found to be present in the blood.

TABLE I.—Combustible Gas reckoned as CO before CO Inhalation.

Subject.	Date.	C.c. of gas per 100 c.c. of blood.	Apparatus for extraction.
Fetter	26/4/22	0·36 c.c.	Van Slyke.
	27/4/22	1·44	Blood gas-pump.
	28/4/22	0·7	,, ,,
	29/4/22	0·59	,, ,,
	30/4/22	0·36	,, ,,

Whether this gas was entirely CO, or whether there was an admixture of gas possibly absorbed from the intestine, such as marsh gas, hydrogen, etc., we are not in a position to say. The immediate point is, that from the gas volume obtained by the Van Slyke extraction from Davies' blood, a deduction should probably have been made of the order of 0·5 volumes per cent. Such a correction, had it been made, would have increased the observed blood volume throughout by about 8–10 per cent., and brought them very nearly up to the values observed by other methods. In giving the figures, we have, however, refrained from any such correction.

The carmine method at times gave results discordant with itself, and the observations made on such occasions have been omitted. In Experiment 2 a number of the observations carried out by the Hartridge method was done by two different observers and with different instruments; their results agreed very closely.

The experiments were carried out in the glass respiration chamber in the Cambridge Physiological Laboratory; the temperature was maintained at 32–35° C. throughout. The subject only emerged for short intervals—at most an hour. The air was warmed by electric heaters, and sufficient ventilation was maintained to prevent the accumulation of aqueous vapour or carbonic acid. To test the humidity, a wet-bulb thermometer was observed from time to time. The carbon monoxide was administered from a "Proto" bag, with a closed circuit and valves for respiration. Into this bag was run oxygen from a cylinder as required, the carbon dioxide expired being absorbed by sticks of soda which the bag contained. Carbon monoxide of known purity was run into the bag in measured volume by water displacement from a long cylinder graduated in cubic centimetres.

Procedure.

The supply of carbon monoxide is kept under pressure in a Winchester quart-bottle by means of a syphon arrangement. The burette A is filled from this at the top tap, a little being allowed to escape from the free limb of the tap in order to displace air. A sample of the stock supply of CO is also taken in order that its purity may be estimated by analysis.

The bag is then disconnected at F and CO passed through from the free limb of the tap of the burette in order to displace air between A and E. The oxygen is then passed from D, E being turned the other way so as to displace carbon monoxide between E and F. I is then closed, F is connected, and a few litres of oxygen are then passed into G. The subject then commences to breathe from H, inspiring room air from the free limb of I. After about two breaths I is turned thus making a closed circuit, oxygen being allowed to bubble in from CD. After about a minute, to make sure that carbon dioxide is being properly absorbed in C, E

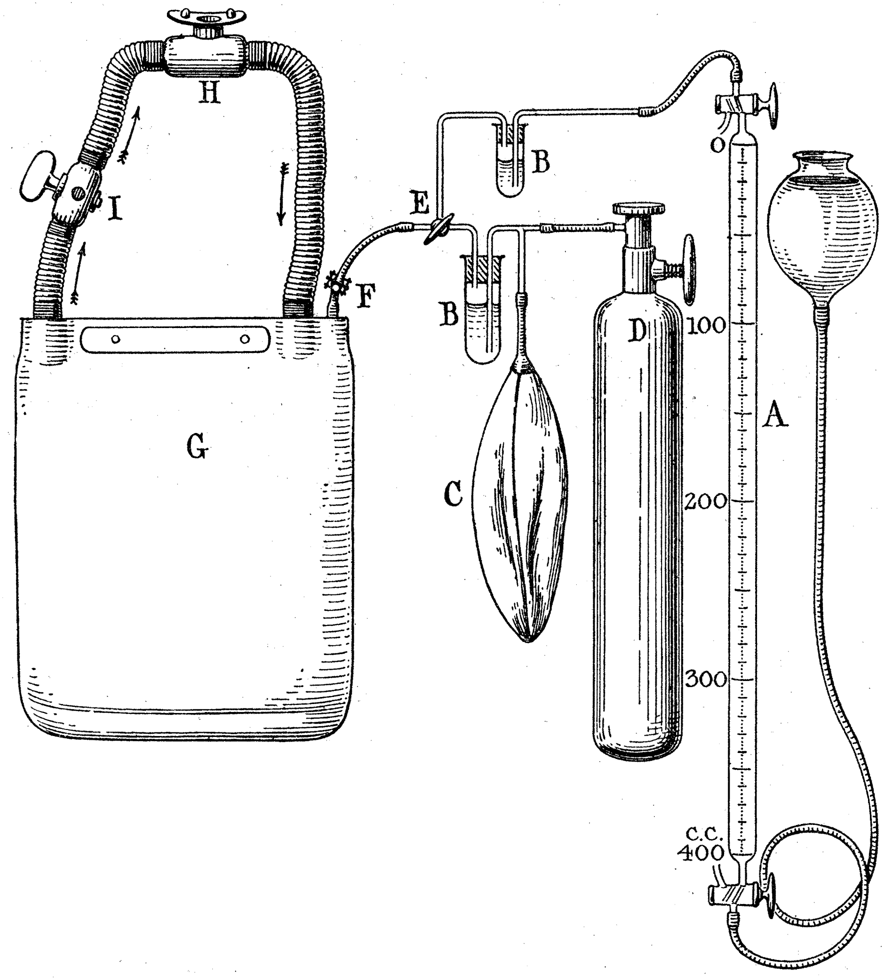


Fig. 1.—A. Burette for delivery of measured quantities of carbon monoxide. 400 c.c. capacity graduated in c.c.o. The displacing fluid is a saturated solution of common salt. BB. Water valves to show passage of gas into, and to prevent return of gas from, G. C. Bladder to act as reservoir for oxygen. D. Oxygen cylinder with reducing valve. E. Three-way glass stop-cock. F. Screw clip. G. Rubber bag of "Proto" mine-rescue apparatus about 30 litres capacity. There is a rubber partition down the centre, the inlet and outlet being on different sides of the partition. In the bottom of the bag is placed coke or pumice coated with caustic soda. H. Rosling valve set; air circuit in direction of arrows. I. Tap to prevent loss of contents of bag on inspiratory side when not breathing through H.

is turned the other way and a measured quantity of carbon monoxide passed in from A, temperature and barometer being noted. E is then turned to allow oxygen to pass in. The subject continues to breathe for at least 15 minutes, after which a sample of blood is taken for estimation of its carbon monoxide saturation. I is then turned and F clipped off and disconnected. A sample of the gas is taken from F for estimation of residual CO, and the volume of gas remaining in the bag is measured by expressing it through a "wet" meter.

Further details and calculation are shown in protocol.

Protocol.

H. W. D. 24/4/22. 11.30 A.M.

Hæmoglobin (duplicate) 79 p.c. = 14·61 c.c. p.c. oxygen capacity.

CO taken 362 c.c. T. 29° C. Bar. 750. Factor for reduction to S.T.P. 0·853.

CO 93 p.c.

Bag contains 7 litres. CO 0·12 p.c. = 7·7 c.c. residual CO. Corrected volume of CO absorbed (362 × 0·93 × 0·852). 7·7 = 279·3 c.c.

Carmine Method. (Observer, H. W. D.)

Saturation 28 p.c. = 14·61 × 28/100 = 4·09 c.c. vol. p.c. of CO in blood.

Blood volume = 279·3. 4·09 = 6·82 litres.

Hartridge Method. (Observer, J. B.)

Saturation 26·8 p.c. = 14·61 × 26·8/100 = 3·92 c.c. vol. p.c. of CO in blood.

Blood volume 279·3. 3·92 = 7·13 litres.

Extraction and Combustion Method. (Observer, J. C. M.)

2·10 c.c. blood contain 0·1050 c.c. of CO at 15° C., and 750 = 4·585 c.c. vol. p.c. of CO at S.T.P.

Blood volume 279·3. 4·585 = 6·09 litres.

The gas in the bag was analysed after the experiment. It always contained a small quantity of CO—something of the order of 10–20 c.c. This had to be deducted from the measured volume of gas put into the bag, in order to obtain the quantity absorbed by the subject.

Experiment 1.—Subject, H. W. Davies.

The course of this experiment may easily be seen from fig. 2, in which the blood volume, as given by the three methods, is plotted. The general parallelism between the methods is obvious, there being but one discordant result, namely, that given by the extraction method on the afternoon of the 25th. This result might very properly be discounted.

The deduction is, that there is a more or less gradual rise in the volume of circulating blood in the two days spent in the warm chamber, followed by a fall immediately on coming out. It must be borne in mind that in all the methods of measuring the volume of blood in circulation there is a relatively large error. In fig. 3 the top band represents the blood volume results as obtained by the Hartridge method; the breadth of the band indicates what we calculate to be the experimental error.

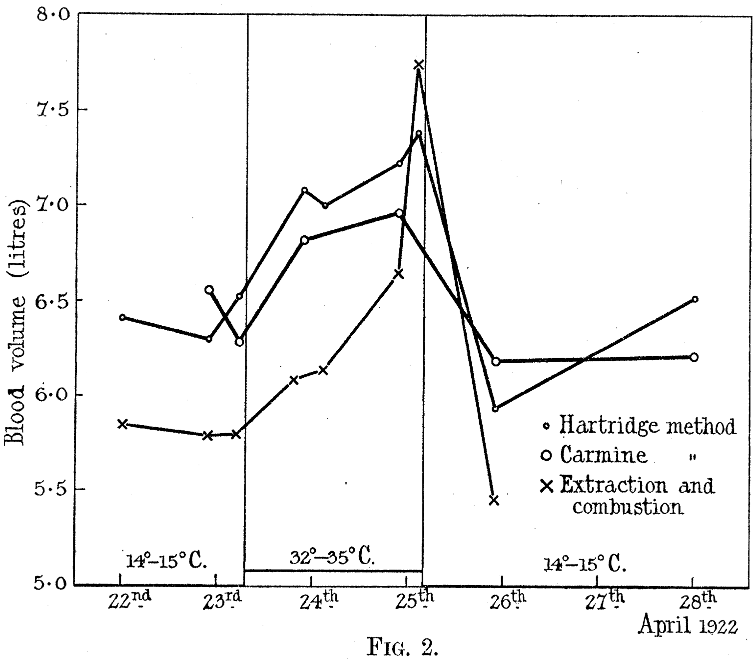


FIG. 2.

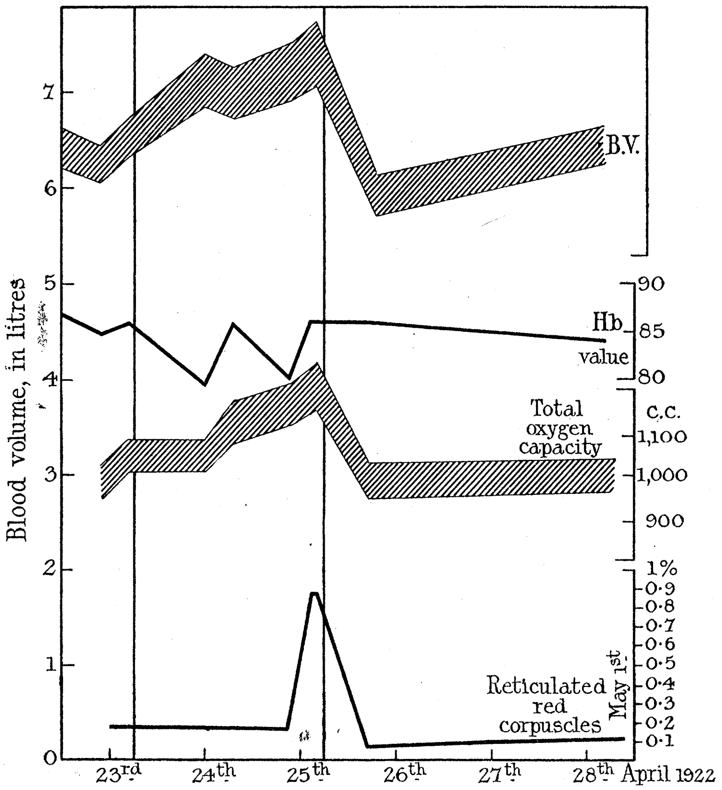


FIG. 3.

The same in the case of the lower shaded band, in which the total oxygen capacity of the circulating blood is shown in the same way. From the blood volume curve it will appear—even taking the blood volume before the experiment at the highest point which is consistent with all the determinations, namely, 6·4 litres, and that just before leaving the chamber on the 25th at the lowest, namely, 7·1 litres—there is an increase of 700 c.c. of blood. Similarly, the oxygen capacity would appear before the experiment to have been not more than 1020 c.c., and at the close of the experiment not less than 1130 c.c., a rise of about 10 per cent.

The comparison of the various curves in fig. 2 is instructive. During the night of the 23rd to the 24th there was a considerable rise in blood volume. This initial rise was accompanied by a considerable fall in the hæmoglobinometric reading, suggesting that the increased blood volume was caused mainly by dilution. This suggestion is borne out by the fact that there was no appreciable change in the total oxygen capacity. Between the morning and evening determinations on the 24th a considerable amount of exercise was taken in the warm chamber on the bicycle ergometer. There was a marked rise in the hæmoglobinometer reading; this rise was reflected in the measurement of total oxygen capacity. It would appear, therefore, that from some store or stores within the body enough corpuscles could be produced in a few hours to make an appreciable rise in the total oxygen capacity of the circulating blood. It will be noted that there was no increase in the reticulated cell-count on the 24th. On the night of the 25th–26th there was a dilution of the blood similar to that of the previous night, followed in the day by a restoration of the hæmoglobin value. On the evening of this day the number of reticulated cells in the circulation was very considerably increased. This was the first indication of a fresh production of red blood corpuscles.

Numerous determinations of the blood volume, made during March and April in Edinburgh, in which the CO was estimated in different ways, gave results between 5 and 6 litres.

TABLE II.

Date.	Time.	Hæmoglobin (per cent.).	CO c.c. breathed.	Method of estimating CO.			Total O_2 capacity c.c.
				Hartridge (litres).	Carmine (litres).	Van Slyke (litres).	
22/4/22	P.M.	87	—	6·4	—	5·85*	—
23/4/22	A.M.	85	285	6·25	6·56	5·77	982†
	P.M.	86	280	6·52	6·26	5·76	1040‡
24/4/22	A.M.	79	279	7·13	6·82	6·09	1040‡
	P.M.	86	295	7·0	—	6·13	1120‡
25/4/22	A.M.	80	259	7·22	6·96	6·65	1150‡
	P.M.	86	248	7·42	—	7·75	1185§
26/4/22	A.M.	86	261	5·93	6·19	5·54	990‖
28/4/22	P.M.	84	277	6·51	6·22	—	1000‖

* T. 14–17° C. † Entered chamber (T. 32–35° C.) ‡ T. 32–35° C.

§ Left chamber. ‖ T. 14–17° C.

The following Table gives the reticulated blood-counts.

It will be observed that, after the experiment, just as after the descent from the Andes, the reticulated blood-counts fell to below the initial reading.

Table III.—Reticulated Red Corpuscles. Davies.

Date.	Remarks.		Proportion.		Average.
			Reticulated.	Unreticulated.	
April 23 . . .	Outside	Film (1)	1–	553	
		,, (2)	1–	610	
		,, (3)	1–	581	
		,, (4)	1–	633	
		,, (5)	1–	503	1– 576
April 24 . . .	In chamber	,, (1)	1–	631	
		,, (2)	1–	576	1– 603
April 25 . . .	,,	,, (1)	1–	815	
		,, (2)	1–	491	
				521	1– 609
April 25 (evening)	,,	,, (1)	1–	120	
		,, (2)	1–	131	
		,, (3)	1–	97	1– 116
April 26 . . .	Outside	,, (1)	1–	1203	1–1203
April 27 . . .	,,	,, (1)	1–	1045	
		,, (2)	1–	1180	1–1112
May 1	,,	,, (1)	1–	816	
		,, (2)	1–	641	
		,, (3)	1–	772	1– 746

Experiment 2.—Subject, Fetter.

The following Table shows the data of blood volume, hæmoglobin, and total oxygen capacity. The observations are less complete than in the case of Davies, owing to unreliable carmine readings; moreover, the method of pump extraction was improvised, and therefore no series of normals had been obtained by it.

In the following points Experiment 2 agreed with Experiment 1:—

(1) Within the first 48 hours of the experiment there was a rise in the volume of circulating blood.

(2) The initial change in the hæmoglobinometer readings indicated a dilution of the blood in the first phase.

(3) Subsequently the hæmoglobin value rose.

(4) The maximal values for the blood volume and oxygen capacity were on the second day.

The Experiment 2 differed from Experiment 1 in the following particulars :—

(1) It lasted a day longer.

(2) In this experiment the determinations by the Hartridge method were done independently by two observers, using different instruments. These agreed to about 1 per cent. saturation, an error which means 4–5 per cent. in the "blood volume." While therefore the results of other methods are less reliable in Experiment 2 than in Experiment 1, those of the Hartridge method are more so.

(3) There was no evidence of increased formation of red blood cells as evidenced by the reticulated counts, a fact which may have to do with the fall in blood volume on the third day.

(4) On the third day there was a drop in the "blood volume." It was then by the Hartridge method (the only one which gave concordant results) about 1 litre in excess of that at the commencement of the experiment.

(5) The experiment proved a greater strain than the subject could sustain, as he became ill and had to take to bed for two days on its termination. We would like to take this opportunity of thanking him for his help in what proved to be a very exacting experiment.

TABLE IV.

Date.	Time.	Hæmoglobin (per cent.).	CO c.c. breathed.	B.V. Hartridge.	B.V. Carmine.	B.V., blood pump.	Total O_2 capacity.
26/4/22	P.M.	90	256	6·4	—	6·8*	1065
27/4/22	A.M.	86	259	6·03	6·07	—	960
	P.M.	91	260	5·3*	—	5·73	880
28/4/22	P.M.	88	244	6·52	7·13	5·2	1060
29/4/22	P.M.	85	287	8·15	7·48	6·35	1300
30/4/22	A.M.	86	307	7·14	—	—	1150
1/5/22	A.M.	91	263	6·02	—	—	1010

* Unreliable.

TABLE V.

Reticulated Red Corpuscles. Fetter.

Date.	Remarks.	Proportion.		Average.
		Reticulated.	Unreticulated.	
April 27	Outside	1–	1045	
			656	
			887	1– 863
April 28	In chamber	1–	854	
			802	
			601	1– 752
April 28 (evening)	,,	1–	843	
			884	
			1184	1– 970
April 29	,,	1–	571	
			556	
			552	1– 560
April 30	,,	1–	1118	
			1061	1–1090
May 1	Outside	1–	971	
			923	
			821	1– 905

APPENDIX II. (See p. 378.)

NOTE ON THE RELATIVE EFFECTS OF CARBONIC AND HYDROCHLORIC ACIDS ON THE AFFINITY OF HÆMOGLOBIN FOR CARBON MONOXIDE.

By J. BARCROFT and CECIL D. MURRAY.

For the interpretation of the shifting of the dissociation curve, which took place during residence at Cerro de Pasco, it was necessary to know whether—as some (46) allege—the carbonic acid has a specific effect on the affinity of hæmoglobin for oxygen, or whether its well-known effect is simply due to the alteration in hydrogen-ion concentration which it produces. Though the subject has formed the basis of much controversy, it is remarkable that the matter has never been put to the obvious simple experimental test as follows:—Take a solution of hæmoglobin; vary its reaction with (*a*) CO_2 and (*b*) another acid, say, HCl, by known amounts, so as to make up a number of solutions as different reactions which can be measured, and then ascertain whether a given increment in hydrogen-ion concentration obtained by carbonic acid has or has not a greater effect on the oxygen-combining power than the same change in reaction produced by HCl. The oxygen-combining power may be measured by exposing the various solutions to the same partial pressure of oxygen and determining the percentage saturation of the gas. For instance, if one starts with a solution of hæmoglobin pH8, and placing three portions, A, B, and C, each in a saturator exposed to a partial pressure of oxygen of 20 mm., and if B and C be also made more acid to the same extent, say, pH7, B with CO_2, and C with HCl, and if A has a percentage saturation of 80, while B and C are each 20, there can be no contention that the CO_2 has a specific effect; but if B has a percentage saturation of 20 while C has one of 60, then CO_2, as well as having an effect in virtue of its reaction, would also have a specific effect.

This experiment we performed with one variation, namely, that we used the reaction between CO and reduced hæmoglobin (excluding oxygen from the field of action) instead of oxygen and hæmoglobin. The curve given by Douglas and Haldane, when compared with those of Bohr, Hasselbalch, and Krogh, leaves no doubt that the effect of CO_2 on the reactions of hæmoglobin with oxygen and CO respectively is of the same character in each case. If in one case it is specific it will be specific in both. Parsons has shown that the effects of the two gases in the reaction of hæmoglobin are similar. We have used CO rather than oxygen, because the measurement of the reaction of CO hæmoglobin in an atmosphere of hydrogen and CO, with the platinum electrode, presents no difficulty. The plan of our experiment, then, was to expose a solution of hæmoglobin in 0·9 per cent. sodium chloride to an atmosphere of hydrogen containing 0·01 per cent. CO at 37° C., to vary the reaction in the ways indicated, and to determine the percentage saturation by the Hartridge technique.

Experimental Details.

Hydrogen was generated electrolytically in an apparatus kindly loaned to us by Mr. T. R. PARSONS (47). Oxygen was removed by passing the gas through palladiumised asbestos in a combustion tube, heated by a low flame with wire gauze interposed. The hydrogen was then collected in a 4-litre reservoir bottle, with a three-way tap at the top and an outlet below, over ammoniacal cuprous chloride solution, over which spread a thin layer of liquid paraffin. This container was controlled by another bottle, which received the cuprous chloride, and which served as a reservoir to force out the H_2 when required. A second similar pair of bottles was used for the gas mixtures. Between these two bottles was a mercury manometer, and a three-way tap in the main line to receive CO_2 or CO. Required amounts of gas were run into the system, washed into the gas-mixture bottle with H_2, and diluted to two litres. In each case 0·2 c.c CO was introduced to make 0·01 per cent.

The hæmoglobin solution was prepared as by Barcroft and Adair, *i.e.* corpuscles were washed three times with 9 per cent. NaCl by centrifugalising, then laked with ether, the ether drawn off, the hæmoglobin solution in the bottom layer pipetted off and dialysed in a collodion membrane against 0·9 per cent. NaCl for 20 hours. The hæmoglobin solution amounted to about 25 c.c. and was tightly corked in the sac attached to glass tubing of suitable size. The NaCl solution (600 c.c.) was changed four times. The whole procedure was carried out at 0° to 4° where possible. The resulting solution turned out to be 10 per cent. Hgb, but equilibration with CO was so slow that it was diluted to 1 per cent. before use. Normal NaOH (0·1 c.c.) brought 10 c.c. of the 10 per cent. solution to a *p*H of about 8, and this was our starting point. The reaction was made more acid in two ways: by adding normal HCl or by equilibrating with a gas mixture containing CO_2. 2 c.c. of the 1 per cent. hæmoglobin solution was shaken in a tonometer with the gas mixture in the cold for about 5 minutes, then equilibrated at 37° C., after which the gas was replaced by another lot of the same mixture and equilibrated for 20 minutes at 37° C. A sample of blood was then analysed for percentage saturation with CO with Hartridge's spectroscope, The remainder was introduced in the small saturator (30 c.c. capacity) of Parsons' apparatus for the measurement of hydrogen-ion concentration, more gas run through slowly, and another sample of blood analysed after 15 minutes; 15 minutes later the blood was transferred to the electrode vessel. Equilibrium was attained in about 2 minutes and the potential measured with a high-grade potentiometer. The calomel electrode was of the saturated type, and all calculations were made according to data and recommendations in Clark's book. A third analysis for CO was then made.

The main result is shown in fig. 1 and, with some some data deducible from it, in tbe following table :—

TABLE VI.

P.c. saturation exposed to 0·01 p.c. CO.	Reaction altered by		Table for (1).			
		*p*H.	(H) relative values of K.			
72	—	7·96	111×10^{-8}	39	0·026	1
55	?	7·93	1·8	81	0·012	1
45	HCl	7·50	3·16	122	0·0083	2
33	CO_2	7·10	7·94	200	0·005	2
26	CO_2	6·90	12·6	285	0·0035	2
24	HCl	6·82	15·1	315	0·0032	2
12	CO_2	6·39	41·7	730	0·0014	2
12	HCl	6·36	43·6	730	0·0014	2

Within the limits of hydrogen-ion concentration used, $1 \times 10^{-8} - 44 \times 10^{-8}$ the effect on the oxygen-combining power seems to be the same whether the reaction is controlled by HCl or by CO_2.

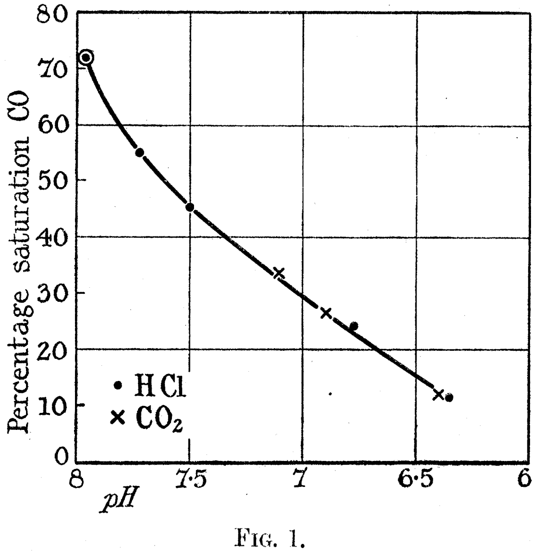


FIG. 1.

Some Theoretical Considerations.

Relative values of K, independent of the value of *n*, but assuming *n* to be constant in all determinations (which is not necessarily valid, but nearly so in 0·9 per cent. NaCl solution) can be determined by Hill's equation,

$$\frac{y}{100} = \frac{\mathrm{K}x^n}{1+\mathrm{K}x^n},$$

where y = p.c. saturation with CO (O_2 absent).
x = tension of CO.
n = a constant of uncertain significance.
K = the equilibrium constant in the reaction (Hb CO) = K (Hb) (CO).

From this standpoint these data are treated by Prof. A. V. HILL who has calculated from them the relative strengths of oxygen and reduced hæmoglobin regarded as acids. This is considered in a forthcoming paper in the 'Phil. Trans.'

Conclusion.

Carbonic acid has no specific effect on the affinity of hæmoglobin for carbon monoxide and inferentially none on its affinity for oxygen. The effect of CO_2 is not greater than is caused by a similar change in reaction produced by hydrochloric acid.

APPENDIX III. (See p. 378.)

SOME SECONDARY EFFECTS OF INCREASING THE PROPORTION OF RED CORPUSCLES IN BLOOD.

J. Barcroft and Cecil D. Murray.

Three statements have been made with regard to the blood of persons living at high altitudes which appeared to be somewhat discrepant :—

(1) The hydrogen-ion concentration judged from the ratio of fixed to free CO_2 seemed scarcely to have altered.

(2) The Dale–Evans method showed a change in the direction of alkalinity, and suggested that the oxygen-dissociation curve might move as much as it would if the CO_2 pressure of normal blood were shifted from 40 mm. to 25 or 30—the shift which takes place on going to a height of 14,000 feet.

(3) The actual shift in the dissociation curve was in some cases greater than could be accounted for by mere loss of CO_2 from the blood.

It was pointed out to us by A. V. Hill, as is also stated by Warburg, that the ratio of fixed to free CO_2 which indicated a certain hydrogen-ion concentration in normal blood did not necessarily indicate the same hydrogen-ion concentration in blood which had an abnormally large or an abnormally small number of red corpuscles. In planning an investigation of this point, it occurred to one of us (Murray) that under certain circumstances, to be detailed, the alteration in the concentration of red blood corpuscles might automatically alter the oxygen-dissociation curve, since the blood would be differently buffered.

The argument was as follows :—

Step 1.—If a large part of the CO_2 be shaken from normal blood there will, as a result, be a considerable migration of chlorides from the corpuscles to the plasma—the base remaining in the corpuscles.

Step 2.—If now the blood be centrifugalised and divided into two parts, A, rich in corpuscles, and B, rich in plasma, these parts will have different properties.

Step 3.—The difference will be shown if the CO_2 be replaced wholly or in part. In A, because there is relatively little plasma there will in the aggregate be a relative poverty in chlorides. The CO_2 will drive these chlorides into the corpuscles of which there is a great preponderance. The chlorides will have a relatively small effect on the reaction of the corpuscles. The corpuscles will, therefore, at any CO_2 pressure be more alkaline than those of the original blood. Similarly in the fraction B the corpuscles at any CO_2 pressure will be less alkaline than those of the original blood.

Step 4.—The oxygen-dissociation curve will, therefore, be displaced in the direction of greater affinity of the blood for oxygen at any CO_2 pressure in the fraction A, and of less affinity for oxygen in the fraction B.

Three experiments were performed to test the points enumerated above. The last of these three embraced all the points at issue. It will, therefore, be described at length.

Blood was taken from the arm vein into a hypodermic syringe; a small crystal of oxalate was added to prevent clotting; one portion, which shall be called N, was set aside in ice as being normal. The remainder was centrifugalised, and two portions A and B made up so that A had a reading on the Gowers-Haldane scale of 154, B of 65, while N was 108.

In the following Table the actual observations are given, and for purposes of comparison those on the oxygen-dissociation curve are reduced, so that the extrapolated reading is in every case at 27 mm. CO_2 and 20 mm. oxygen pressure :—

Blood	A.	N.	B.
Hæmoglobin value (Gowers-Haldane)	154	108	65
Oxygen-dissociation curve :			
Observed readings—			
CO_2 pressure	27	19	25·5 mm
O_2 ,,	17	19	17
Percentage saturation	60 67 } 65	39 42 } 40	34 38 } 36
1/K	620	2400	3400
Extrapolated readings—			
1/K 27 mm. CO_2	620	3200	3600
Percentage saturation with oxygen at 27 mm. CO_2 pressure and 19 mm. O_2	74	37	33
Hydrogen-ion concentration (electrode)—			
Observed at 29 mm. CO_2	7·41	7·37	7·33
Extrapolated at 27	7·39	7·36	7·31
Hydrogen-ion concentration—			
Calculated from formula $pH = 6·1 + \log \text{combined} - \log \text{dissolved } CO_2$	7·30	7·42	7·34

In the above experiment it is clear that, while the plasma of the concentrated sample (A) is the most alkaline of the three (see electrode), the ratio of free to combined CO_2 for the whole blood suggests that it is the most acid. Evidently the factor 6·1 in the equation does not hold for blood of this degree of corpuscular concentration. Another experiment confirms this result.

Blood	A.	B.
Hæmoglobinometer reading	146	66
*p*H from formula	7·29	7·44

Here again there is little doubt that in reality the sample A had the most alkaline plasma.

In confirmation of the results obtained on the oxygen dissociation curve we did one experiment on the CO dissociation curve, with the following results:—

Blood	A.	B.
Hæmoglobinometer	126	63 p.c.
Pressure of CO_2	30	30 mm.
Pressure of CO	0·08	0·08 mm.
Percentage saturation	41 p.c.	25 p.c.

In a third experiment, however, the difference in the percentage saturation was not marked; evidently we had not secured the proper conditions as regards shaking out the CO_2.

Conclusion.

1. In the case of blood with a high concentration of corpuscles the *p*H, as calculated by the formula

$$pH = 6·1 + \log \text{combined} - \log \text{dissolved } CO_2,$$

gives results that are too acid at 25 mm. CO_2 pressure.

2. If the CO_2 be properly shaken out of blood before concentration, the oxygen-dissociation curve may change in the sense of a greater quantity of oxygen in the corpuscle for any given pressure.

Note added to proof.—Since the above was sent to press, Dr. Warburg, of Copenhagen, has kindly sent us a copy of his book, in which the above formula is amended in two respects: (1) the constant 6·1 is slightly increased; and (2) a correction is made for the quantity of hæmoglobin (see equation 128). This alteration tends to make the reaction of the plasma more acid for any given $\frac{BCO_3}{HCO_5}$ ratio, and therefore is in conflict with the few experiments which we have carried out on this point. We therefore propose to make a more extended investigation of this particular point.

APPENDIX IV. (See p. 384.)

NOTES ON SKIAGRAPHS OF THE THORAX.

By Sir Arthur Keith, F.R.S.

Anyone who has examined the thoracic measurements which Mr. David Forbes made in 1870 on natives of Peru—both those living at sea-level and on the high plateau—must have realised that further observations were needed. Mr. Forbes' paper was published in the 'Journal of the Ethnological Society' (New Series, 1870, vol. 2, p. 193), and has provided the basis of all statements made regarding the great chest development of the Peruvians living on the high plateau. Many of Mr. Forbes' measurements were made by inexact methods, and in several instances are manifestly erroneous. The data brought back by the present Expedition, while confirming Mr. Forbes' contention, form the first precise data relating to the degree and kind of thoracic development in those living on the high plateau. Dr. Redfield's demonstration, that the "native" and "white" groups can be segregated by correlating certain measurements of the thorax, is a new observation, and is likely to prove of service for further anthropological investigation.

From an examination of the skiagraphs, it is possible to ascertain the influence of high altitudes on the level of the diaphragm. The level must be determined in its relationship to the vertebral column—the mid-point of the vertebral ends of the tenth pair of ribs providing a convenient level from which measurements may be made. There is a high degree of individual variation as regards the level of the domes of the diaphragm, but, notwithstanding this, I think it can be definitely stated that the right dome of the diaphragm, which furnishes a more exact index of respiratory level than the left dome, occupies a lower level in "natives" than in "whites" (see the figure). The right dome of the diaphragm, in the parasternal line, lies 27 mm. below the tenth rib (vertebral) level in whites (mean of eight), and 32 mm. below in natives (mean of eight).

In nearly all the skiagrams it is possible to identify the anterior, or ventral, end of the fifth right rib at its junction with its cartilage. During inspiration this point moves forward, upward and outward; its relationship to the vertebral column gives the data for determining the respiratory phase in which the ribs were held while the skiagraph was being taken. A line drawn transversely across the plate at the lower border of the ventral end of the fifth right rib gives a "subcostal" plane. In the "whites" this plane is situated 15·7 mm. below the tenth-rib vertebral level (see figure); in the "natives" it is 19 mm. below this level. Thus, contrary to what one anticipated, the ribs of the whites are held at a higher respiratory (inspiratory) level in the "whites" than in the "natives" of the high plateau. The true explanation of this fact will likely be found in the relatively greater antero-posterior diameter of the thorax of the natives.

It will be noted (see the figure), that the diaphragm holds the same relationship to the subcostal plane in both "whites" and "natives"; the lower position of the diaphragm in natives is due to the greater absolute slope of the ribs in them. Dr. Redfield has measured the slope of the dorsal segment of the eighth rib, and shows definitely that this segment of the eighth rib is more horizontal—has less slope—in the "natives" than in the "whites." The mean angle which the dorsal segment of the eighth rib makes with the horizontal is 16·2° in "whites" and 12·8° in "natives." The slope of the dorsal segment of a rib is not an index to the axis of movement of a costal arch, nor to the degree of slope of the arch; the axis on which ribs move is largely determined by the spinal and other musculature attached to them; the lesser slope of the dorsal segments of the ribs in natives does not necessarily signify a more inspiratory poise of their chests.

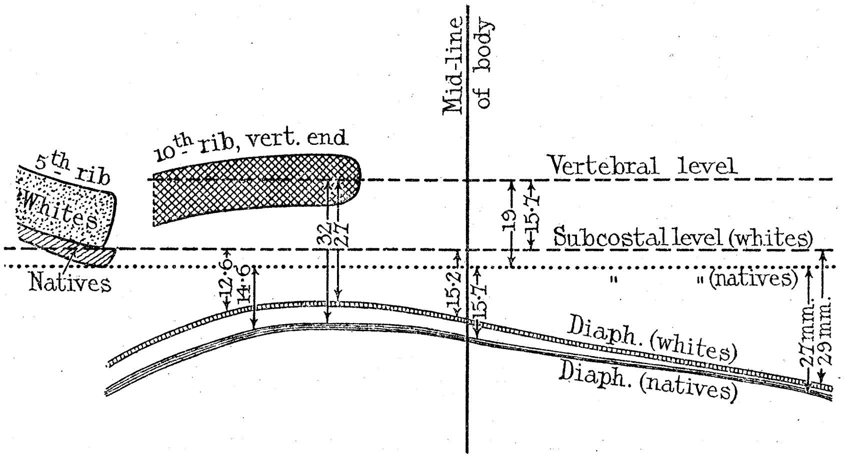


Diagram showing the mean level of the diaphragm, the positions of the vertebral and subcostal planes in whites and natives.

Another fact which shows that the ribs of natives have a greater slope as regards their anterior, or ventral ends, is the relationship of the upper end of the sternum to the vertebral column. Dr. Redfield has used a costo-clavicular plane to indicate the upper limit of the thorax; the mean position of the plane in whites is opposite the middle of the vertebral attachment of the fourth pair of ribs; in natives the plane cuts towards the lower part of the same attachment.

Turning to the changes apparent in skiagrams taken of members of the Expedition at high levels :—

In the case of Dr. Meakins, the right dome of the diaphragm at sea-level (Edinburgh) was 20 mm. below the tenth-rib plane; at Oroya it occupies the same relative level; in the first skiagraph taken at Cerro it has moved down to 30 mm.—assumed a deeper inspiratory position; in the second skiagraph it has ascended to a little above the original level, namely, 16 mm. At Edinburgh the subcostal (fifth rib) plane was 20 mm. below the tenth-rib vertebral plane. In the skiagraph taken at Oroya, although the level of the diaphragm has not moved, the ribs have assumed a higher or more inspiratory phase, the subcostal being only 3 mm. below the tenth-rib plane. In the first skiagraph taken at Cerro the diaphragm has assumed a deep inspiratory position, and with this the subcostal plane is pulled downwards, lying 25 mm. below the tenth vertebral. In the second skiagraph at Cerro the diaphragm has risen almost to its normal level, while the subcostal plane has almost reached that of the vertebral plane. In the first phase at Cerro the diaphragm was unduly called into action; in the second phase the ribs took the chief part. Dr. Redfield's measurements show that at Cerro the height of Dr. Meakins' thorax was increased while its width was slightly diminished. The vertebral segments of the ribs assumed a slightly more oblique position, accounting for the diminution in the width of the thorax.

The changes seen in the skiagraphs taken of Dr. Forbes are not unlike those seen in those of Dr. Meakins'. Taking the mean of the two records made at Boston, the right dome of the diaphragm was 32 mm. below the tenth-rib vertebral plane, the subcostal plane being only 4 mm. below the tenth vertebral plane. On going to Oroya the vertebral level of the right dome descends to 38 mm., while the subcostal plane remained as before. On going to Cerro the diaphragm assumes a still greater inspiratory phase, descending to 43 mm., while the subcostal plane also descends to 11 mm. below the subcostal plane. At Cerro, as in Dr. Meakins' case, the thorax becomes somewhat narrower and the vertebral ends of the eighth rib rather more oblique in position. The brunt of the respiration seems to fall first and foremost on the diaphragm.

In the case of Dr. Bock, the vertebral level of the diaphragm scarcely changed—descended only 3 mm.—on going from Boston to Oroya; in him the diaphragm normally occupies a high level. The subcostal plane rose from being 11 mm. below the tenth vertebral level to almost opposite this plane, showing an inspiratory elevation of the ribs. The slope of his ribs was increased but the width of the chest remained unaltered. In the first skiagraph taken at Cerro the right dome has descended to 17 mm., in the second to 26 mm., showing that later the diaphragm's tonic action was increased. With the descent of the diaphragm to 26 mm., the subcostal plane also came down to 15 mm. below the vertebral plane. Apparently over-action of the diaphragm is accompanied by a sinking of the anterior ends of the costal arches. Respiratory levels are altered.

Unfortunately there is no skiagraphic record of Mr. Barcroft's chest at sea-level. In the one taken at Oroya, the right dome of the diaphragm is situated 33 mm. below the tenth vertebral plane—a low position; but the most striking feature is the particularly low position of the subcostal plane—at the same level as the right dome—33 mm. below the tenth vertebral plane. At Oroya, Mr. Barcroft's ribs were maintained at an expiratory level. At Cerro, the positions are still more extreme; the diaphragm has taken up a lower—a more inspiratory—level, being 37 mm. below the tenth vertebral plane, while the subcostal plane has descended to what may be accounted an exceptionally low expiratory phase, namely, 49 mm. below the tenth vertebral plane. In his case I think there is clear evidence of a disturbance in the co-ordinate working of the respiratory muscles. Is this due to the primary disturbance of the respiratory centre? It is also worthy of note that at Cerro the vertebral segments of Mr. Barcroft's ribs assumed a rather more horizontal position than at Oroya; but, notwithstanding this, Dr. Redfield's measurements show that his chest at the same time became somewhat narrower.

Another skiagram was taken of Mr. Barcroft's chest at Cerro on January 10. As regards its relations to the tenth vertebral plane, the right dome has risen, so as to be situated 26 mm. below that plane, showing that the fibres of the diaphragm were less contracted—had passed more into a more expiratory phase. The anterior ends of the fifth ribs—marking the subcostal level—have risen markedly, now lying 20 mm. below the tenth vertebral plane instead of 49 mm., which they were seven days previously. The right dome of the diaphragm now occupies a normal relationship to the subcostal plane, being 6 mm. below it, in place of 10 mm. above it, as it was seven days before.

On my first survey of these skiagraphs, I carried away the impression that the ribs of the whites were markedly of greater breadth than those of natives; but on measuring the width of the eighth rib in the outer part of its dorsal segment, I found that the mean width for whites was 12·5 mm. and for natives 11·5 mm., the difference being less than I had thought.

APPENDIX V. (See p. 406.)

METHOD OF TRIPLE EXTRAPOLATION.

The following example may be given of triple extrapolation method for the simultaneous estimation of the oxygen and carbonic acid pressures in the mixed venous blood.

Bag 1.—Contains 5 mm. CO_2.
23 mm. O_2.

Routine: (*a*) Full expiration, (*b*) full inspiration from bag, (*c*) after 5 seconds expire half what is in lungs and collect sample (a_1) of alveolar air, (*d*) hold breath 5 seconds longer, *i.e.* 10 seconds in all, and collect sample (b_1) of alveolar air.

Analysis.	a_1.	b_1.
CO_2	17 mm.	23·85 mm.
O_2	38·6 mm.	37·4 mm.
(Unsatisfactory.)		

Repeat—routine the same.

Analysis.	a_2.	b_2.
CO_2	24·5 mm.	28·5 mm.
O_2	34 mm.	33·2 mm.

Bag 2.—Obtained by adding nitrogen to the gas, part of which was in Bag 1, and which therefore is richer in nitrogen, poorer in oxygen, and poorer in CO_2.

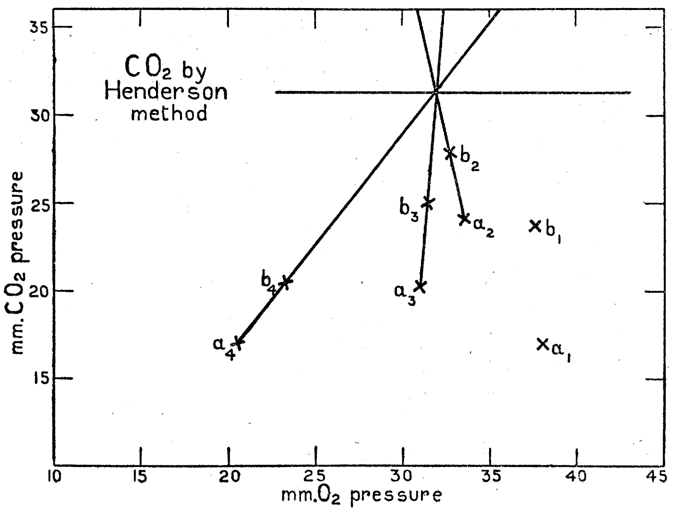
Routine same as above, interval between first and second samples 8 seconds.

Analysis.	a_3.	b_3.
CO_2	20·4 mm.	25·8 mm.
O_2	31·1 mm.	31·8 mm.

Bag 3.—Pure nitrogen.

Routine same as above, except that breath was held 6 seconds before the first sample (a_4) was taken, and 11 (*i.e.* 5 more) seconds before the second sample (b_4) was taken.

Analysis.	a_4.	b_4.
CO_2	17·6 mm.	20·5 mm.
O_2	20·6 mm.	23·2 mm.



APPENDIX VI. (See p. 434.)

EFFECT OF MUSCULAR CONTRACTION ON OXYGEN IN BLOOD.

The following figures extracted from Report No. 14, p. 19, of the Chemical Warfare Medical Committee, published in October, 1918, by the Medical Research Council, illustrate the fact that muscular contraction produces unsaturation of the arterial blood in rabbits which are suffering from bronchopneumonia caused by inhalation of sub-lethal doses of phosgene gas, whilst muscular contraction does not produce unsaturation in normal rabbits.

In each case the rabbits were anæsthetised with luminal, and the muscular contraction was induced in the lower part of the body by passing electric shocks into the skin. Rabbits 19 and 20, ungassed, lungs sound. Rabbits 21 and 22, gassed, bronchopneumonia, presumably with low diffusion coefficient.

Analyses of arterial blood were made :—

Period 1.—Before muscular contracts.
Period 2.—During 1 minute's muscular contraction.
Period 3.—15 seconds after the same.
Period 4.—20 minutes after the same.

Percentage Saturation of Arterial Blood.

Period.	1. Rest.	2. During contraction.	3. Immediately after contraction.	4. 20 minutes after contraction.
Rabbit 19 control	94	96	—	93
„ 20 „	94	—	95	—
„ 21 bronchopneumonia . .	93	83	80	84
„ 22 „ . .	93	85	87	92

The phenomenon may easily be observed with the eye. The following notes were written on the inspection of the colour of the arterial blood in another gassed rabbit—No. 16—which, after having survived $\frac{1}{4}$ minute's stimulation, died when the stimulation was repeated somewhat later. The notes apply to the first period of stimulation.

"The blood in the carotid cannula was its normal bright colour ; at 3.47 the animal was tetanised for 15 seconds, the blood grew darker in appearance, and at 3.50 it was very dark. By 3.54 it had regained its bright appearance."

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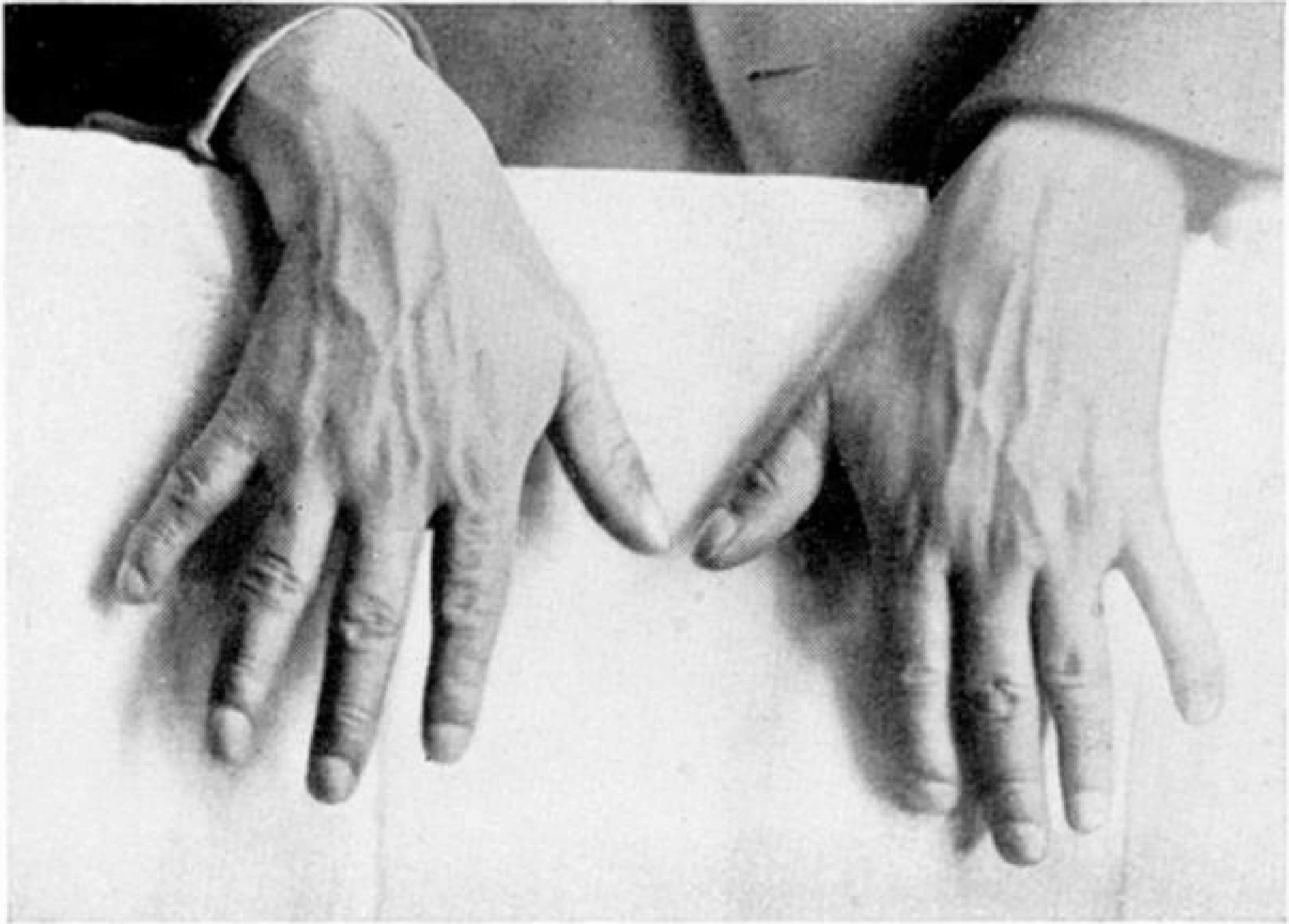

Fig. 3. Fingers somewhat "clubbed" in natives, unassociated with cardiac or pulmonary lesions (see p. 384).

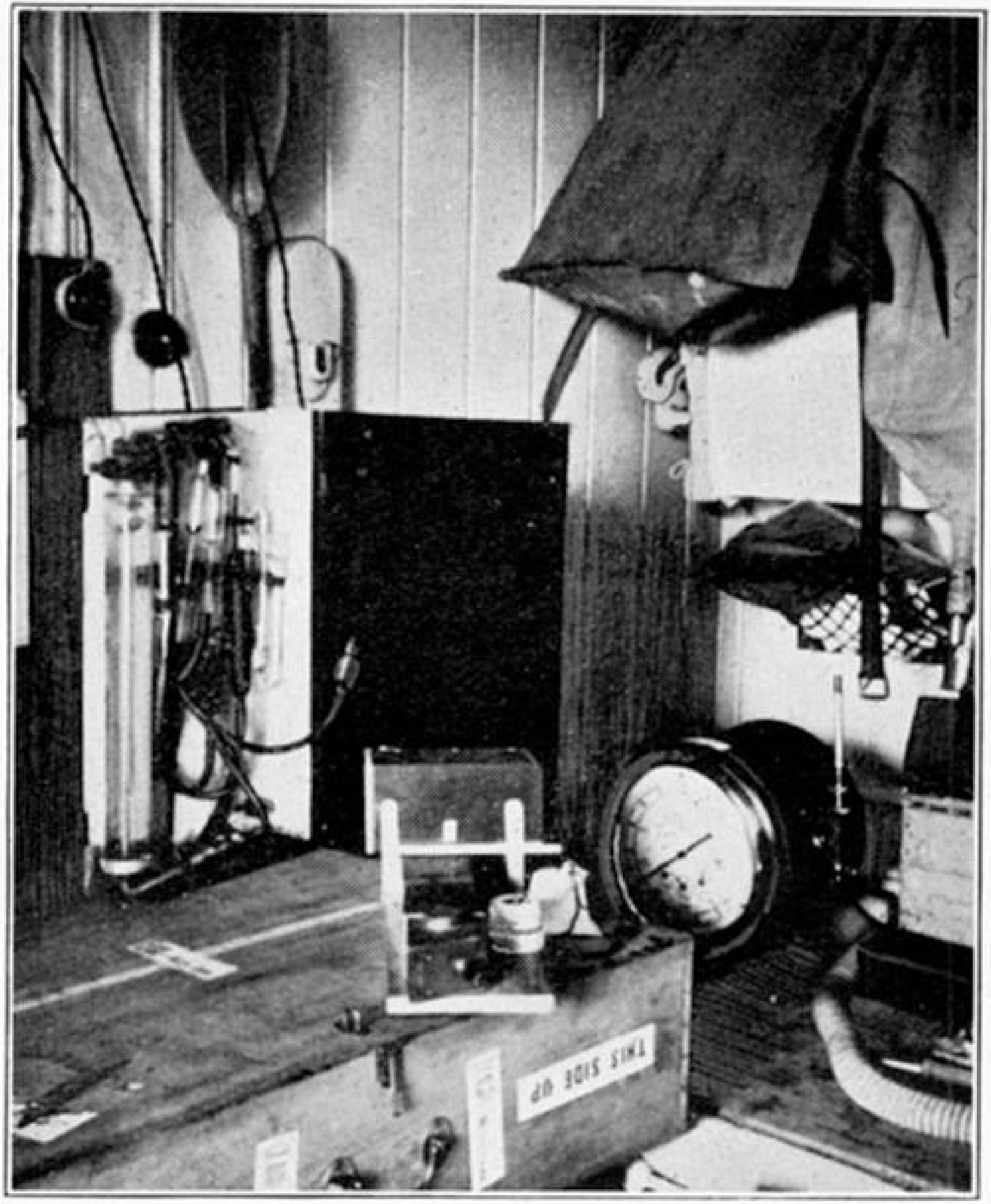

Fig. 4. Cabin on S.S. "Victoria" converted into laboratory.

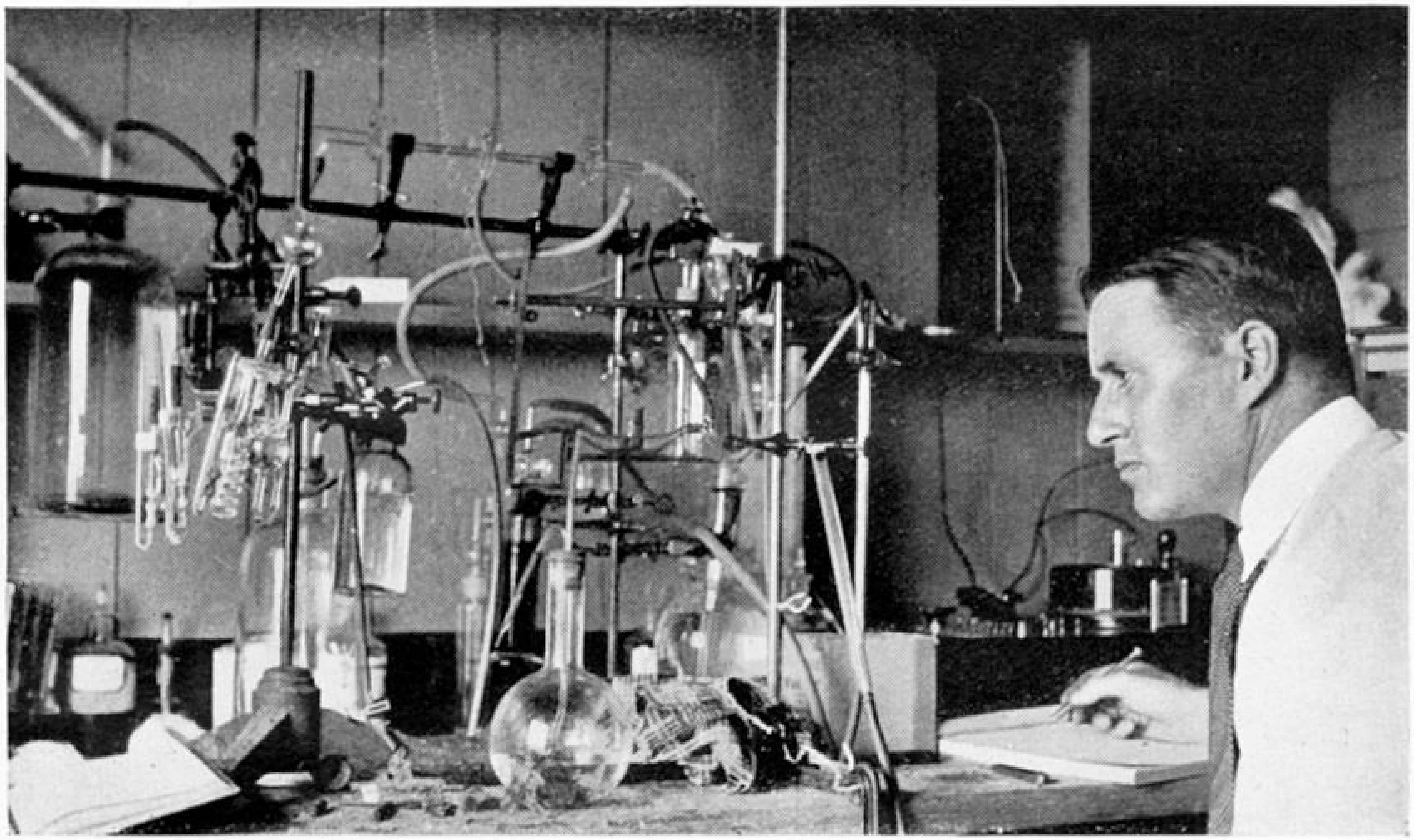

Fig. 5A.

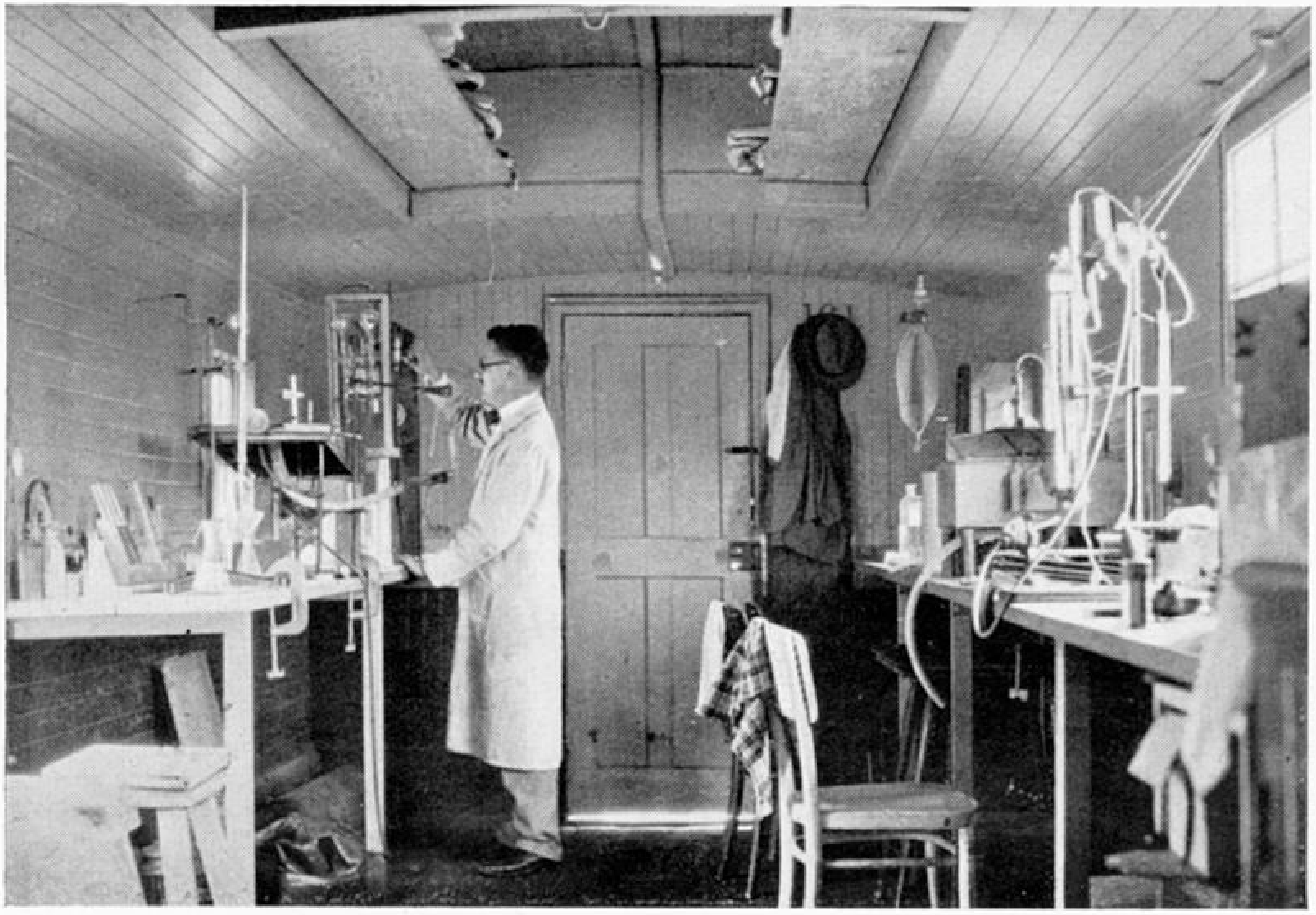

Fig. 5B.

Figs. 5A and 5B. Views inside mobile laboratory made from baggage car on Central Railway of Peru.

Fig. 6. Woman of Cerro (14,000 feet) going uphill "at a double" with burden on back.

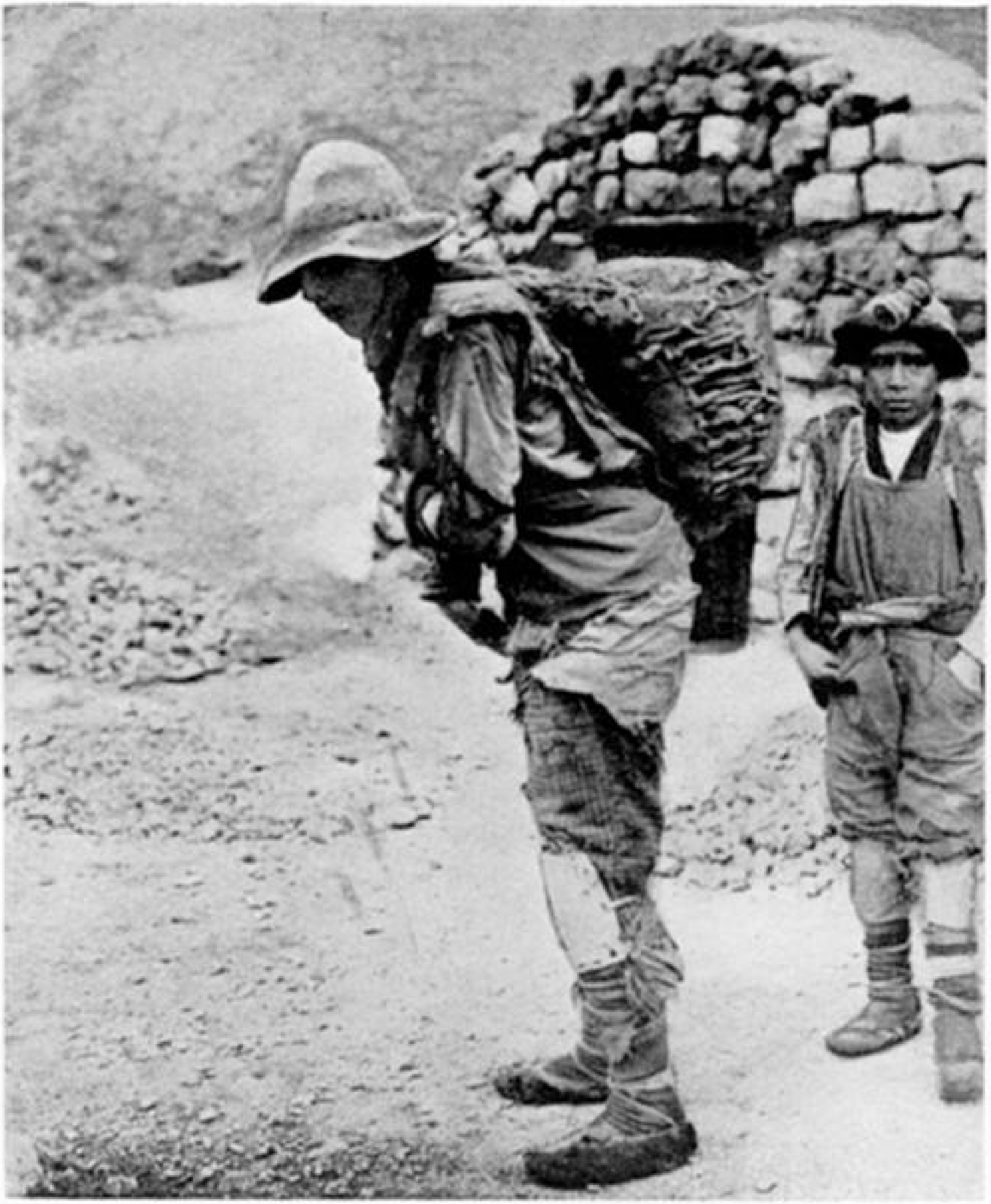

Fig. 7. Porter with load of about 80 lb. of ore which has been brought up from mine.

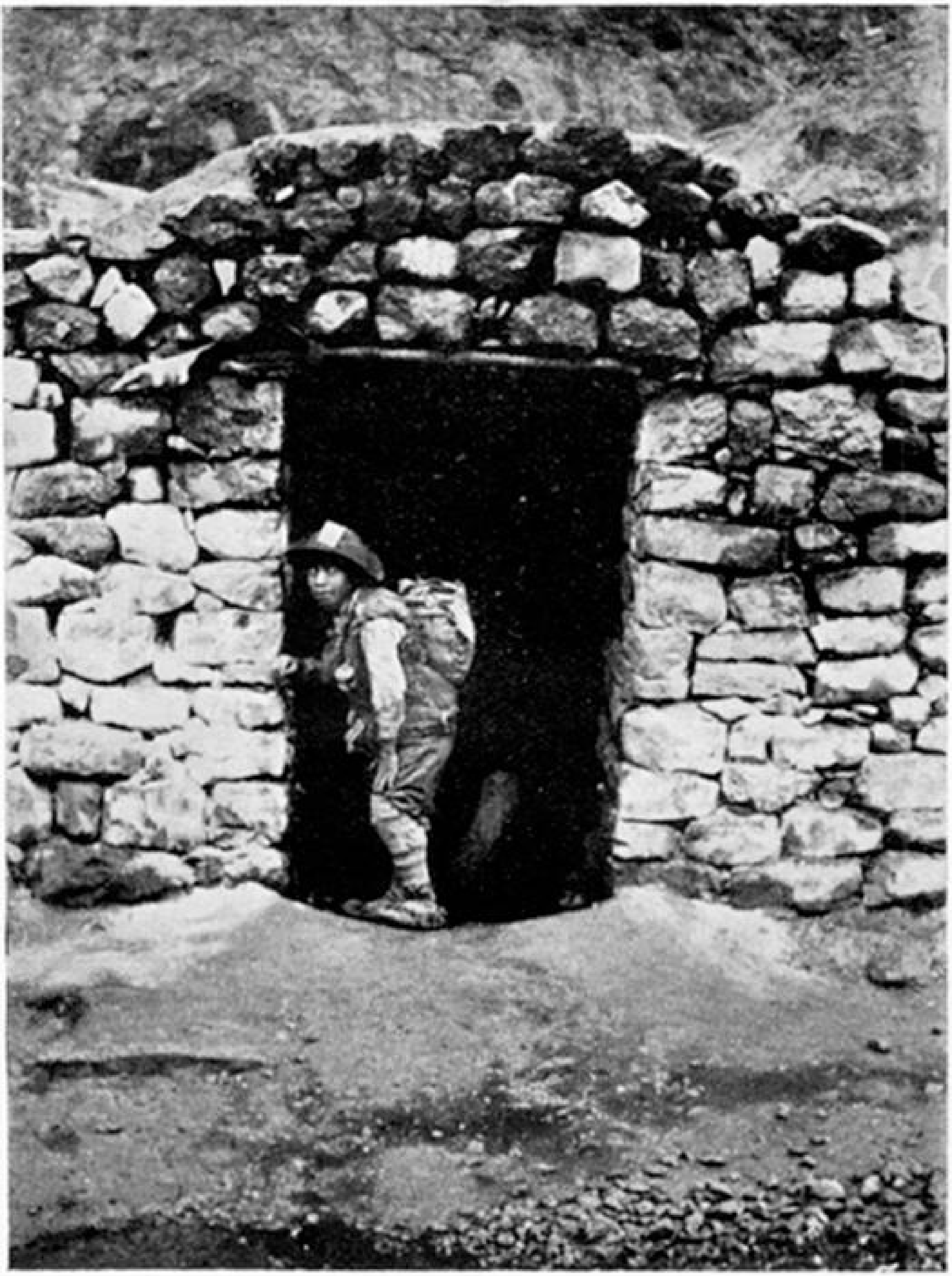

Fig. 8. Head of stairs leading to mine 250 feet below surface. Boy, aged 10(?), with load of 40 lb.

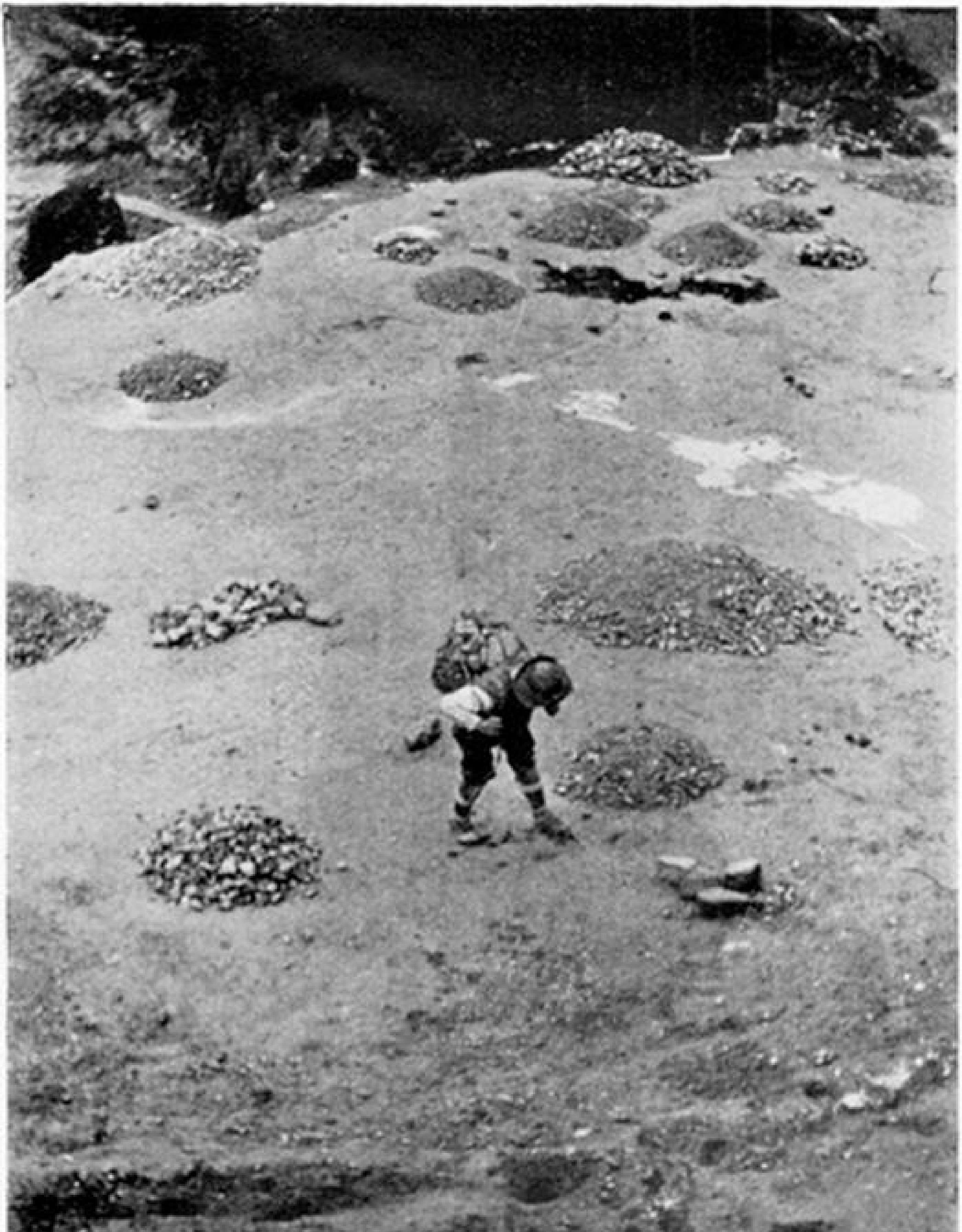

Fig. 9. Piles of ore, each representing amount raised by one porter up to 11 o'clock on day of our visit.