PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Report of the Monte Rosa Expedition of 1911

J. Barcroft, M. Camis, C. G. Mathison, Ff. Roberts and J. H. Ryffel

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II. *Report of the Monte Rosa Expedition of* 1911.

By J. Barcroft, *F.R.S.*, M. Camis, C. G. Mathison, Fr. Roberts, *and* J. H. Ryffel.

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Part I.—Factors affecting the Reaction of the Blood of the Resting Individual.

1. *Introductory.*

The work undertaken by this expedition arose out of that which was done in Teneriffe by Barcroft (1) on the properties of the dissociation curve of human blood at various altitudes.

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The results arrived at by BARCROFT were that, in spite of obvious alterations in the alveolar pressure of CO_2 at 7000 and 11,000 feet, the dissociation curve of the individual remained unaltered. This could only be the case if some other acid was thrust into the blood to replace the CO_2 which had left it. It seemed, therefore, desirable to test for such an acidosis on Monte Rosa; this was carried out by MATHISON and ROBERTS. The first portion of our work, then, deals with the verification of the results obtained in Teneriffe and the extension of them which has been indicated.

The main object of the Monte Rosa expedition, however, was to extend the work in another direction. In Teneriffe the effect of altitude on the dissociation curve was studied only in the resting subject. On Monte Rosa the effect of altitude upon the organism when taking exercise was made the subject of enquiry. The exercise undertaken was that afforded by climbing. Before the effect of climbing in the Alps could be compared with that of climbing at low levels it was necessary to carry out a series of observations in which the effect of exercise on the dissociation curve was not complicated by that of altitude. This investigation was carried out for the most part at Carlingford (2) by BARCROFT, PETERS, ROBERTS, and RYFFEL; some experiments also were performed by MATHISON at Abergavenny.

These points will be treated of in detail.

The name of the author of each section is given in brackets at the head of the section, the whole has been edited by BARCROFT.

2. *The Degree of Hæmacidosis which takes place at High Altitudes.* (MATHISON and ROBERTS.)

In view of the well-known production of lactic acid (3) or similar acids under conditions of oxygen want—conditions certainly existing at an altitude of 11,000 feet upon Teneriffe—and of the influence of lactic acid upon the dissociation curve observed by BARCROFT (1) and ORBELI (4), BARCROFT felt justified in suggesting that the changes observed were probably due to lactic acid production. By observing the effects of adding small quantities of lactic acid to the drawn blood of one member of the Teneriffe expedition, he was able to form a rough estimate of the amount of lactic acid—or rather of hæmacidosis* expressed in terms of lactic acid—present at 11,000 feet. As one of us (MATHISON) had been working for some time upon changes in the acidity of the blood (5) it seemed desirable to continue these researches. The effect of acid on the dissociation of hæmoglobin is to increase the velocity of the reaction

$$Hb + O_2 \longrightarrow HbO_2$$

relatively to

$$Hb + O_2 \longleftarrow HbO_2.$$

This effect may be measured quantitatively by observing the final equilibrium which is attained in the presence of a standard concentration of oxygen. On the

* The word "hæmacidosis" throughout the present paper signifies the addition of abnormal acid, exclusive of CO_2, to the blood within organism. Such acid radicals may be abnormal in kind or only in degree.

score of convenience a method was adopted based upon the final equilibrium between the relative quantities of HbO_2 and Hb in blood exposed to a standard oxygen pressure.

Method.—Blood was taken, sometimes from an arm vein, sometimes from the finger, of an individual. It was at once defibrinated by whipping, and shaken vigorously for some minutes to get rid of free carbon dioxide. The percentage saturation at a given oxygen tension (17 mm.) and at 37° C. was determined. To different samples of this blood varying quantities of lactic acid were added, and the dissociation at 17 mm. oxygen tension again determined. In this way a curve was obtained showing the dissociation of the blood at 17 mm. oxygen tension, with quantities of lactic acid up to 0·12 per cent. added.

This curve exhibited the degrees of dissociation of the blood of a person to which successive quantities of lactic acid were added, always exposed to 17 mm. oxygen pressure in the absence of CO_2. The ordinate represents the degree of dissociation of the hæmoglobin, 100 corresponding to blood which contains entirely oxy-hæmoglobin and no reduced hæmoglobin, and 0 to blood which contains entirely reduced hæmoglobin and no oxy-hæmoglobin; the intermediate figures represent the intermediate percentage saturations of the hæmoglobin with oxygen. Along the abscissa are plotted the successive quantities of lactic acid added to the normal blood. These curves, shown in fig. 1, were used as scales, by reference to which the increased acidity of the blood could be determined at different altitudes (in equivalents of lactic acid), by the simple process of determining the percentage saturation of his blood with oxygen at 17 mm. oxygen pressure and reading off on the curve the quantity of lactic acid to which this corresponds.

Such curves were constructed for the blood of every member of the party at sea-level at Pisa, where the barometer was 765 mm. and the laboratory temperature was 27°. It will be seen on reference to fig. 1 that there are differences between the curves of different individuals; the significance of these will be discussed later. The error of the method is not more than 3 per cent. in the dissociation curve, corresponding to about 0·005 per cent. lactic acid.

The blood of any one person, with the CO_2 shaken out, gives extremely constant figures for the percentage saturation on different occasions. The following figures were obtained by Barcroft and Boothby (6):—

Percentage Saturation at 17 mm.

Barcroft's blood	78, 77, 73, 74, 75, 76.
Boothby's blood	79, 77, 76, 77.

The method of determining the dissociation curve was that already described by Barcroft and Orbeli (4), with a few modifications; the details of an experiment are as follows:—

The aërotonometer was roughly cylindrical (7), and had a capacity of 318 c.c. It was filled with hydrogen prepared electrolytically by the Knowles Oxygen Company, of Wolverhampton. Analysis showed this to contain only 0·4 per cent. oxygen; 30 c.c. air at a barometric pressure of 765 mm. and temperature 27° were put in, giving an oxygen tension of 17 mm.

At other pressures and temperatures the calculated amounts of air to give the same oxygen tension were employed; for example, at Col d'Olen with barometric pressure 542 mm. and temperature 16°, 41 c.c. were used.

About 2–3 c.c. of blood, which had been vigorously shaken for about 10 minutes to free it of CO_2, were then introduced and well mixed with the contained atmosphere by rotating the aërotonometer for 10 minutes in a water-bath at 37°. At the end of this time a sample, about 1 c.c., was withdrawn, and its percentage saturation with oxygen determined by means of the large Barcroft-Roberts (8) blood gas apparatus. The percentage saturation is ascertained by determining the amount of oxygen absorbed by the blood on simple shaking and the amount given off by it after addition of potassium ferricyanide.

For example, if the manometer registers 16 mm. pressure as the result of O_2 absorbed, 40 mm. pressure as the result of O_2 given off after addition of ferricyanide, then percentage saturation $= 100 \times (40 - 16)/40 = 60$ per cent. To this 4 per cent. is added to correct for changes which take place in the analysis due to gases physically dissolved in the blood. If the blood had to be kept for any length of time after it was drawn, it was kept at about 0° in carefully stoppered glass phials, so that no evaporation occurred.

The curves obtained at sea-level will first be considered, then the variations in the blood of each individual at high altitudes will be discussed.

Exposed to an atmosphere of 17 mm. O_2 the blood of various individuals taken at sea-level gave the following results:—

	Percentage saturation.
Ryffel	79
Roberts	77·5
Camis	76
Barcroft	74
Mathison	65, 68·5

When various amounts of lactic acid were added the individuals still came in much the same order; of the curves drawn through the points determined that of Ryffel remained the highest and that of Mathison the lowest. Thus Mathison started with his blood more dissociated at a given oxygen tension; at present we can only say that this might be due to a greater acidity or, in part, to a less salt concentration of his blood. We are unable to say with what bodily condition it can be correlated. The curves are shown in figs. 1A–E with the determinations from which they were obtained at Pisa. In fig. 1F they are placed in the one diagram. There is little

doubt that had a greater number of points been determined in the case of each curve the slight want of parallelism which exists in the figure would disappear.

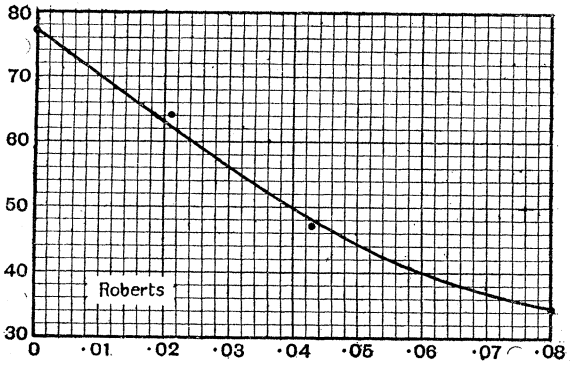


FIG. 1A.

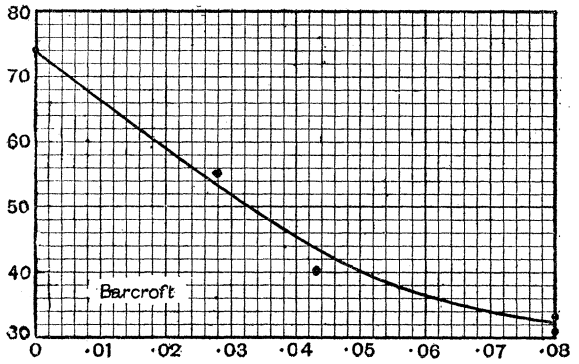


FIG. 1D.

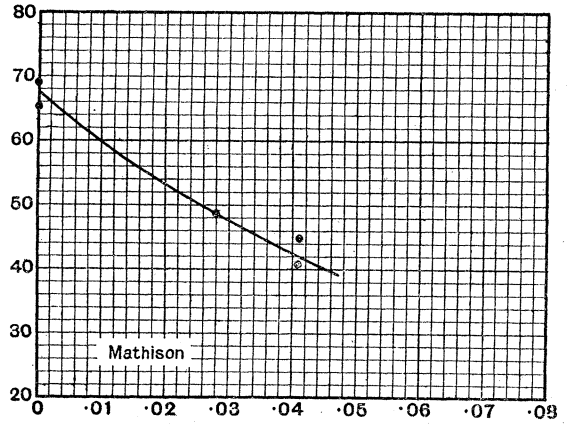


FIG. 1B.

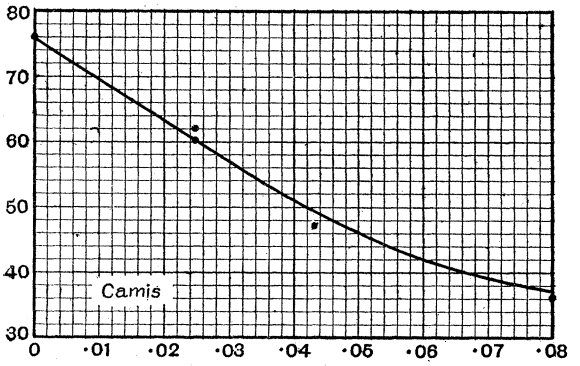


FIG. 1E.

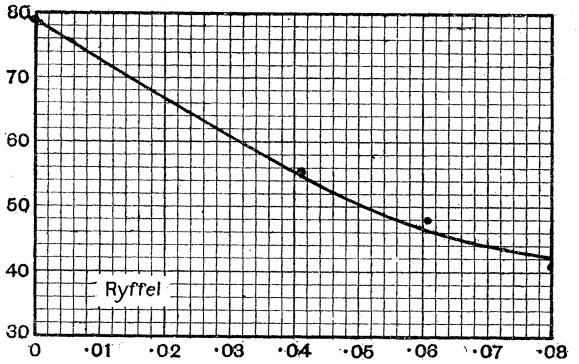


FIG. 1C.

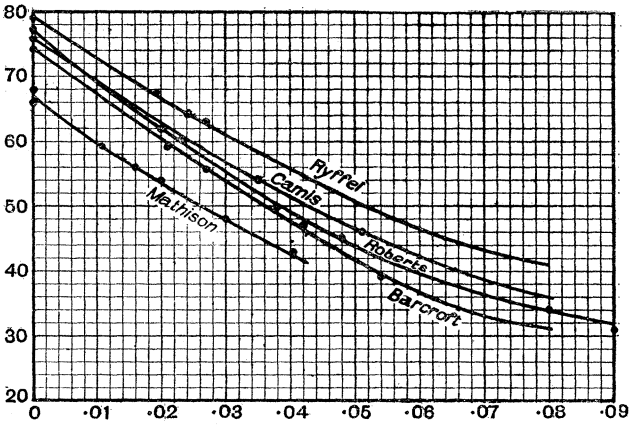


FIG. 1F.

FIG. 1.—Effect of Lactic Acid upon the Dissociation of Blood at 17 mm. O_2 and 37° C.
Ordinates = Percentage saturation; abscissæ = Percentage of lactic acid added.

Points in MATHISON's curve determined on return to London corresponded with those taken at Pisa.

The percentage saturation is given in the following table :—

TABLE I.

Subject.	Per cent. lactic acid added.							
	0.	0·021.	0·025.	0·028.	0·041.	0·043.	0·061.	0·08.
Ryffel . . .	79·0				55·5		48·0	41·0
Roberts . .	77·5	64·0				46·5		34·0
Camis . . .	76·0		62·0			46·5		36·0
			60·0					
Barcroft . .	74·0			55·0		40·0		31·0
								33·0
Mathison . .	65·0			49·0		45·0		22·5
	68·5					41·0		24·5

3. *The Changes in Acidity and Alveolar Carbon Dioxide at High Altitudes.*

The changes in the dissociation of the blood of the various individuals in conditions of rest and of activity are shown in figs. 2, 3, 4, 5, and 6. The points determined upon blood taken under the various conditions are marked thus ●. Table II (pp. 56 and 57) gives a summary of the conditions and the results.

These results show that there is a considerable "hæmacidosis" at high altitudes even in the resting individuals. This is shown both at Col d'Olen and still more at the Capanna Margherita—in the former case by persons who for several days had done extremely little physical work. In order that our results might not rest on a single method some confirmation of them was attempted by another.

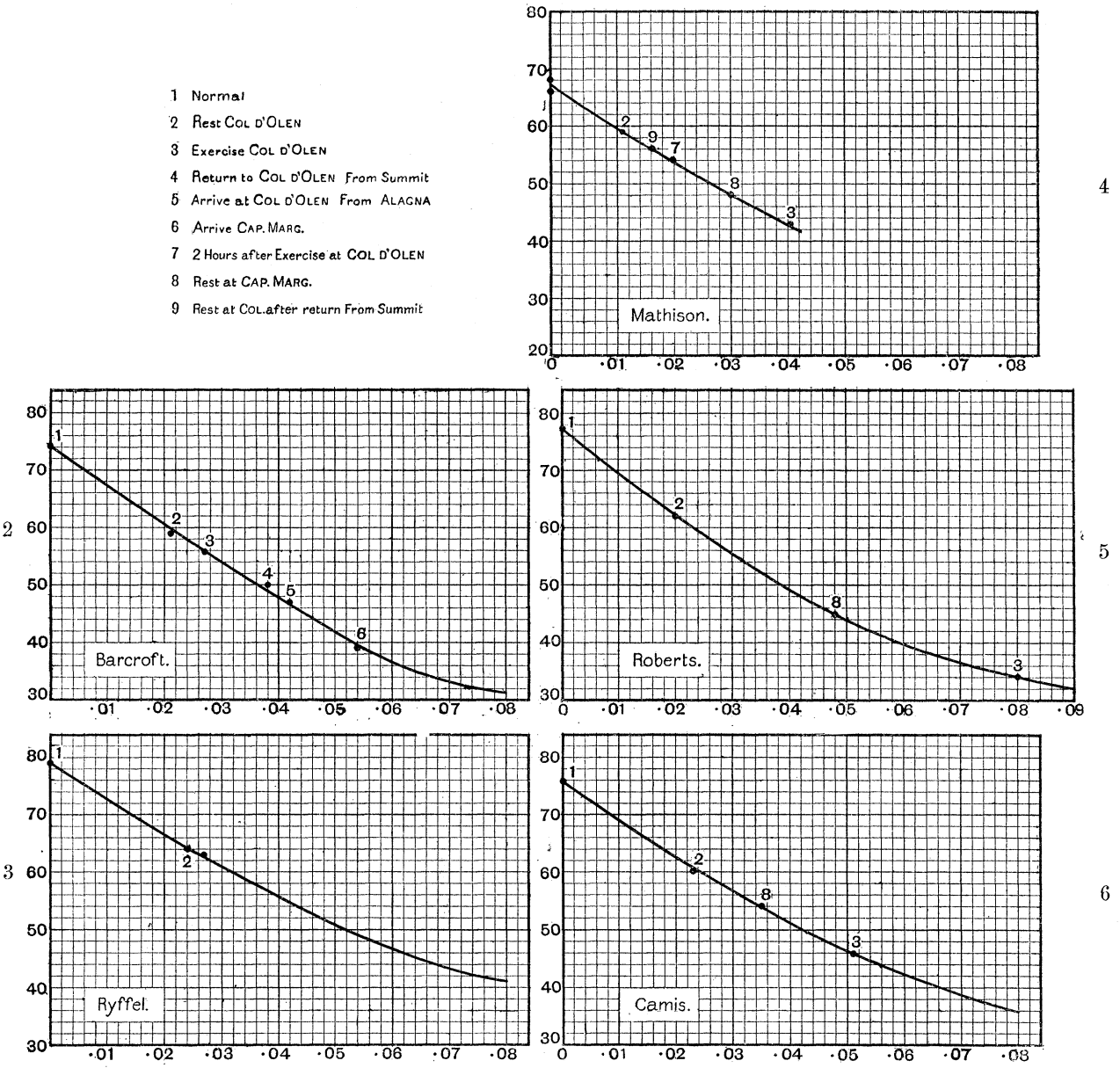
4. *Determination of Hæmacidosis in Resting Subjects by the Method of* BOYCOTT *and* CHISOLM. (RYFFEL.)

As a further demonstration that the acidosis in the blood apart from carbonic acid is increased at high altitudes, determinations of the alkalinity of the blood were made by BOYCOTT and CHISOLM'S (9) method at Pisa and at Col d'Olen.

This method consists in adding, by means of a small pipette, one drop of blood (0·02 c.c.) drawn from the finger to a series of tubes containing quantities of N/1000 sulphuric acid ranging from 0·5 to 1 c.c., diluted to 2 c.c. with distilled water, and then heating the tubes at about 45° C. for an hour. A flocculent precipitate of nucleoprotein derived from the laked red corpuscles of the blood forms in those tubes to which more than a certain amount of acid has been added.

With the blood of RYFFEL at Pisa a precipitate formed in the tubes containing 0·8 c.c. and more of N/1000 acid. At Col d'Olen, on August 15, the precipitate formed in that containing 0·7 c.c. as well. The decrease in alkalinity was therefore equivalent to 0·1 c.c. N/1000 acid in 0·02 c.c. blood, or about 0·04 grm. lactic acid

per 100 c.c. This figure shows a somewhat greater formation of acid than that shown in Table II, in which the addition of acid is equivalent to 0·27 and 0·24 on two occasions. It is quite probable that the combined experimental errors of the two methods account for the observed difference. Clearly, however, the difference is at most one of degree.



Figs. 2, 3, 4, 5, and 6.—The Percentage Saturation, at 17 mm. oxygen tension, of the blood of members of the expedition, at various high altitudes and under conditions of rest, the points observed being placed upon the standard curve obtained by observing the dissociation after addition of quantities of lactic acid to blood taken at sea-level.

It is clear from the results of Mathison's method and of Boycott and Chisolm's method that there is an increased quantity of acid radicals (exclusive of CO_2)

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TABLE II.

Subject.	Date.	Place and height in metres.	Barometric pressure.	Saturation of blood at 17 mm. O_2.	Equivalent lactic acid.	Alveolar CO_2.	Alveolar O_2.	Remarks.
			mm. Hg.	per cent.	per cent.	mm. Hg.	mm. Hg.	
Roberts—								
Resting	Aug. 5	Pisa	765	77·5	0·00	39·5	[100]	Felt the heat, otherwise well.
Immediately after climb to Col d'Olen	„ 10	Col d'Olen 2900	542	34·0	0·08	—	—	Marked dyspnœa and fatigue.
Resting	„ 12	Col d'Olen	542	62·0 62·0	0·02	32·5	59·5	Still cyanosed, dyspnœic on slight exertion. Slightly apathetic.
On arrival after climb to summit	„ 17	Capanna Margherita, 4560	440	31·5	0·09	28·0	—	Fairly fit during climb.
Resting	Aug. 18, 11 A.M.	Capanna Margherita	440	45·0	0·048	28·0	48·5	Great discomfort from cold, dyspnœa on movement, fairly fit mentally.
Two hours after descent	Aug. 18, 6 P.M.	Col d'Olen, 2900	540	—	—	28·0	67·0	Condition good.
Resting	Aug. 19, 10 A.M.	Col d'Olen	540	62·0 62·0	0·02	28·0	65·5	Much better than before ascent. Condition normal.
Camis—								
Resting	Aug. 5	Pisa	765	76·0	0·000	39·0	—	Permanent resident in Pisa. Climate suits him.
Resting	„ 11	Col d'Olen	542	—	—	35·5	58·0	Slightly cyanosed, slightly apathetic.
Resting	„ 14	„	542	60·0	0·023	—	—	Condition good.
Immediately after 1000 feet climb	„ 15	„	542	44·5 49·5	0·051	—	—	Experienced ordinary exercise dyspnœa.
Resting	„ 17	Capanna Margherita	440	—	—	—	—	Condition good during climb.
	„ 18	„	440	54·0	0·035	—	—	

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Barcroft—								
Resting	„ 4	Pisa	760	74·0	0·000	35·0	[100]	
Immediately after climb from Alagna	„ 10	Col d'Olen	542	47·5	0·042	—	—	Marked dyspnœa during ascent.
Resting	„ 11	„	542	—	—	31·5	61·0	Not at all fit. Marked dyspnœa.
						30·5	63·5	Intellectually not alert.
Resting	„ 14	„	542	59·0	0·021	—	—	Condition better.
After 1000 feet climb	„ 14	„	542	54·0 57·0	0·027	—	—	Climbed very slowly, 45 minutes. Sweated very little.
Immediately after ascent	„ 17	Capanna Margherita	440	39·0	0·054	28·5	—	Severe dyspnœa during ascent; felt the cold very acutely.
Resting	„ 18	„	440	—	—	28·0	48·0	Still feeling unwell.
Resting, 7 P.M. . .	„ 18	Col d'Olen	540	50·0	0·038	—	—	Feeling very well.
Resting	„ 19	„	540	—	—	31·5	70·0	Not quite so well.
Ryffel—								
Resting	„ 7	Pisa	765	79·0	0·000	39·5	—	
Resting	„ 12	Col d'Olen	542	63·0	0·027	31·0	59·0	Condition not at all good, physically or intellectually.
Resting	„ 14	„	542	64·0	0·024	—	—	Took some exercise, condition better.
Mathison—								
Resting	„ 3	Pisa	765	65·0 69·5	0·000	34·5	[96]	Condition good.
Resting	„ 11	Col d'Olen	542	65·0	0·000	31·75	70·0	Condition good during climb and afterwards.
Immediately after climb of 1000 feet	Aug. 11, 6 P.M.	„	542	42·5	0·040	34·5	66·5	Climbed 1000 feet in 20 minutes. Great dyspnœa but no distress. Sweated profusely.
Resting, two hours later	Aug. 11, 8.30 P.M.	„	542	52·5	0·018	32·5	70·0	Feeling very fit.
Resting	Aug. 13	„	542	59·0	0·011	—	—	Condition good.
Resting after climb	„ 17	Capanna Margherita	440	—	—	27·0	—	Dyspnœa during climb. Quite well at the summit, but Cheyne-Stokes breathing readily induced by exercise.
Resting	„ 18	„	440	48·0	0·030	27·5	49·5	Well intellectually.
Resting	„ 19	Col d'Olen	542	56·0	0·016	27·0	70·0	Condition good.

relatively to bases in the blood. We made some attempt to find out the nature of the acid in question, starting on the assumption, which was *a priori* probably, that the acid was lactic.

5. *Investigation of the Nature of the Acid added to the Blood of Resting Subjects by Estimation of the Lactic Acid in the Blood and Urine at High Altitudes.* (RYFFEL.)

Evidence has already been given to show that at high altitudes there is an increase in the acidity of the blood in spite of a fall in carbonic acid. The suggestion has been made first by GALEOTTI (3), and later by BOYCOTT and HALDANE (10), that this increase of acidity is due to lactic acid. The production of lactic acid in surviving frogs' muscles was carefully investigated by FLETCHER and HOPKINS (11), who showed that, when the muscles are inactive, they do not produce lactic acid unless they are insufficiently supplied with oxygen, and that, when the muscles are stimulated, lactic acid is produced in them, which is partially removed in course of time when oxygen is supplied. Thus there appear to be two causes of the accumulation of lactic acid in muscle, muscular activity and lack of oxygen. ARAKI (3) obtained an increase of the lactic acid in the blood and an active excretion in the urine when warm-blooded animals were kept in the later stages of asphyxia for considerable periods, but muscular activity was not excluded. RYFFEL (12) demonstrated a considerable increase of lactic acid in the blood and an active excretion in the urine in man as a result of hard exercise, but found only minute increases in the blood and no increase in the urine as a result of shortage of oxygen as great as could be voluntarily endured for short periods, and obtained similar results after staying for four hours at rest in a ventilated chamber with an atmospheric pressure of 460 mm. of mercury. Clearly, then, muscular activity is a much more powerful cause of the production of lactic acid in the intact body than is lack of oxygen of the order that is met with at the highest altitudes in the Alps. However, during residence at high altitudes, the diminished supply of oxygen is endured for much longer periods than in these experiments, and muscular activity is not excluded, especially if the ascent is made on foot, so that it was deemed desirable further to investigate the matter.

Lactic acid production might increase the acidity of the blood in two ways: the addition of the acid to the blood would increase its acidity, or the excretion of considerable quantities of lactic acid in the form of lactates in the urine would rob the blood of bases, and so increase its acidity. Accordingly, estimations of lactic acid were made both on the blood and on the urine.

The method employed was one previously described by RYFFEL (12). A measured quantity of blood (15 to 20 c.c.), drawn by means of a hollow needle from a vein of the forearm, is mixed with ten times its volume of 0·5-per-cent. potassium hydrogen phosphate and coagulated by heat. The coagulum is filtered off and washed very thoroughly by boiling with water and filtering, and then repeating the process. The

total filtrate is then rendered alkaline with sodium carbonate and evaporated to small bulk. It is then mixed with rather more than an equal volume of sulphuric acid, and heated at about 155° in a current of steam. This causes the lactic acid to decompose, giving a quantitative yield of acetaldehyde. The distillate containing the aldehyde is rendered slightly alkaline with caustic soda and redistilled, and the aldehyde in the second distillate estimated by diluting to a known volume with the addition of a known proportion of standard Schiff's reagent, and comparing the colour developed in the liquid with standard coloured solutions previously prepared by adding Schiff's reagent to various quantities of dilute formaldehyde solution. This method of estimating the aldehyde has the advantage of being very sensitive, so that, by making the second distillate up to 50 c.c., a fairly accurate estimation can be performed on 0·0025 grm. of lactic acid. To obviate the carriage of a colorimeter, the comparisons of colour were made in two Nessler glasses of approximately equal bore graduated in linear millimetres.

Estimations of lactic acid in urine were made by the same distillation method after treating with basic lead acetate and ammonia and filtering to remove glycuronic acid and pigment, and evaporating a measured part of the filtrate to small bulk.

The determinations at Pisa were made directly. At Col d'Olen some estimations were made directly; in others, the filtrate, after coagulation of the blood, was evaporated to small bulk and transferred to a bottle with the addition of thymol in chloroform as a preservative, the actual estimation being performed later in London. The blood taken at the Capanna Margherita was kept in ice till the return to Col d'Olen. The determinations made at Pisa, Col d'Olen, and London were standardised by making determinations on known quantities of lactic acid at each place. This procedure ensured that the error in the determinations was certainly less than one-tenth of the result.

Schiff's reagent reacts only with aldehydes, so that a result is obtained only with those substances which are not volatile in neutral solution and which decompose at 155° C. with sulphuric acid, yielding aldehydes. Lactic acid and other similar α-hydroxy-acids decompose in this way, of which lactic acid alone is known to occur in the body. Pentoses and glycuronic acid give a small yield of furfuraldehyde when treated in this way, but in the urine they have been removed by previous treatment, and they do not occur appreciably in the blood.

The results of determinations made on the blood were as follows.

The lactic acid is expressed in grammes per 100 c.c. blood.

The blood was withdrawn during ordinary occupation in the laboratory :—

TABLE III.—At Pisa.

Subject . . .	Roberts.	Camis.	Ryffel.	Mathison.	Barcroft.
Lactic acid	0·012	0·013	0·014	0·015	0·024

Blood taken since from RYFFEL, in London, gave the result 0·014 grm. lactic acid per 100 c.c. That taken from the finger of BARCROFT (11·7 c.c.), at Carlingford (sea level), contained 0·0214 grm.

TABLE IV.—At Col d'Olen.

Subject.	Date.	Lactic acid.		Increase in acid from Pisa expressed in terms of lactic acid (Mathison, Table II).
		Total.	Difference from total at Pisa.	
Roberts . . .	August 12	0·018	+0·006	0·020
Camis . . .	„ 14	0·017*	+0·004	0·023
Ryffel . . .	„ 12	0·018	+0·004	0·027
	„ 14	0·019	+0·005	0·024
Mathison. . .	„ 19	0·013*	−0·002	0·016

* Actual estimation performed in London.

The ascent to Col d'Olen took place on August 10, that to the Capanna Margherita on August 17, and the return to Col d'Olen on August 18.

The blood of the first three subjects shows an increase in lactic acid which is very small and is inadequate to account for the hæmacidosis. That of MATHISON, which was taken after the return from the summit to Col d'Olen, when he was thoroughly compensated, shows actually a small decrease of lactic acid (within the region of experimental error), but a definite increase in acidity (see Table II).

TABLE V.—At the Capanna Margherita.

Subject.	Date.	Lactic acid.		Increase in acidity from Pisa in terms of lactic acid (Mathison).	Difference from Col d'Olen.	Increased acidity from Col d'Olen in terms of lactic acid (Mathison).
		Total.	Difference from Pisa.			
Camis . .	August 18	0·036*	0·021	0·035	0·019	0·012
Roberts .	„ 18	0·039	0·027	0·048	0·021	0·028

Here the increase in lactic acid is more definite, but is again inadequate to account for the whole of the increase in acidity. It is conceivable that if the peripheral circulation was reduced, owing to the low temperature, the blood from the forearm might contain more lactic acid than that of the general circulation. Our experiments furnish no data on this point.

Taking the figures as they stand, however, the increase of lactic acid does account for the increased acidity of the blood as between Col d'Olen and the Capanna Margherita. The effects of high altitudes in this connection on resting individuals would then fall into two stages—(1) that of moderate altitude (10,000 feet), in

which there is an acidosis not due entirely or even mainly to lactic acid which is in some unexplained way an indirect effect of oxygen want; and (2) an extreme effect which is obtained at higher altitudes which is no doubt the direct effect of oxygen want upon metabolism.

It is to be regretted that we have not data of the lactic acid in the blood and in the urine of more persons after a much longer residence at 15,000 feet, for the data which we possess, taken as they were on the day after the ascent, may have been to some extent vitiated by the effects of exercise, of which we shall speak later.

6. *On the Equivalence of the Acid added to the Blood and the Carbonic Acid Displaced from it.* (Barcroft.)

Taking the affinity of hæmoglobin for oxygen as an "indicator" of reaction it appeared in Teneriffe that the reaction of the blood was the same in resting subjects at high and at low altitudes. That is to say that points on the dissociation curve determined always in the presence of the alveolar CO_2 pressure fell on the same curve. If the total reaction of the blood including the CO_2 were to become more acid the hæmoglobin would take up a less quantity of oxygen at any given oxygen pressure and the curve depicted by the notation used throughout the paper would be depressed and would appear below the normal curve, whilst on the contrary, were the blood more alkaline, the curve would move in the opposite direction. As, however, change of reaction (5), though it is the most potent factor in moving the curve, is not the only one conceivable, it is desirable to have a definite nomenclature for these movements of the curve. A curve which is shifted in the direction which would be produced by acid, *i.e.* in which the hæmoglobin takes up less oxygen (at a given oxygen pressure) than it normally would in the body is called "meionectic," that in which it takes up more oxygen is called "pleonectic,"* whilst that in which it takes up the normal amount is called "mesectic." It will be clear that the curve may be mesectic under conditions in which the blood is abnormal, for instance, when an acid radical usually present is replaced in equivalent amounts by one which is usually absent.

Expressing the result of the Teneriffe enquiry in the nomenclature it would be that in spite of the decreased alveolar pressure of CO_2 the curve remained "mesectic."

We have been at some pains to find out whether this result, which was gleaned merely from inspection of the points determined with reference to the curves, was accurately true, or whether it was only true as a first approximation.

In order to carry the research further than can be gauged by mere inspection it is necessary to have some numerical method of expressing the position of a certain point with reference to a certain curve.

* πλεονεκτικός, disposed to take more than one's share. From πλεονεξία, a disposition to take more than one's share (Liddell and Scott). We are indebted to Dr. W. M. Fletcher and Mr. Harrison for this nomenclature.

The researches which have been performed within recent years on the physico-chemical significance of the dissociation curve of blood fortunately furnish a suitable notation.

The most recent writers (13) on the subject are in agreement on the following points :—

(1) That the reaction between hæmoglobin and oxygen is essentially a chemical one.

$$Hb + O_2 \rightleftarrows HbO_2.$$

(2) That the differences between observed dissociation curves of hæmoglobin and blood can be explained on the assumption that the molecules of hæmoglobin can exist in various states of aggregation.

(3) That the effect of slight changes in reaction is to alter the equilibrium constant of the reaction, with but little change in the state of assumed aggregation of the molecules.

Of the two formulæ which have been put forward to express the facts (those of J. B. S. Haldane and A. V. Hill) my reasons for preferring that of Hill are given in another place.* It is superfluous to re-argue the point here, rather let me say that so far as the present investigation goes it is immaterial which formula is used.

The general expression for the curve representing the equilibrium between oxygen and hæmoglobin is, according to Hill,

$$y/100 = \frac{Kx^n}{1+Kx^n},$$

where x is the pressure of oxygen, y the percentage saturation of hæmoglobin with oxygen, K the equilibrium constant of the reaction, and n the average number of molecules which are aggregated into a single group. Now, so far as is known experimentally, n does not vary as the result of slight changes in reaction and may be taken as 2·5, so that the curve is completely defined by a statement of K. Taking n as 2·5 K, can, of course, be found out from a single point (with such accuracy as the experimental determination of the points admits of).

If the blood is more acid than normal, K will be less than usual and a meionectic curve will result; if the blood is less acid, K will have an abnormally large value.

The Teneriffe results showed that the value of K for points determined at high altitudes appeared sometimes greater and sometimes less than the normal value, the experimental error in the process of determining a single point being considerable. That is to say the points fell on both sides of the line which represented the dissociation curve at the sea-level. The question which we now wish to answer is this: Is the mean value for K as derived from a large number of points the same at high altitudes as at the sea-level? The enquiry of course relates to resting individuals, the carbonic acid present being taken as that of the alveolar air.

* "Oxy- and Carboxy-hæmoglobin.—I and II," 'The Biochemical Journal.'

Before going into the actual results some statement should be made as to the accuracy of the method. The percentage saturation can be determined to within about 3 per cent. of the correct figure; what error does this amount to in calculating the value of K? The answer to this question is not simple, for the error varies at different portions of the curve.

In the following table the values of K are determined with reference to a curve for which K is 0·00029. The percentage saturations for which K is calculated are each respectively 3 per cent. below or above the correct values for the pressure given.

TABLE VI.

	(1)	(2)	(3)	(4)	(5)	(6)	(7)
Oxygen pressure, mm.	10·0	15·0	20	30	40	50	60
True percentage saturation.	9·0	20·3	34	58	74	84	90
3 per cent. too low	6·0	17·3	31	55	71	81	87
3 „ high	12·0	23·3	37	61	77	87	93
K, true value	*0·000290	290	290	290	290	290	290
K calculated from inferior value	0·000202	240	251	248	242	241	235
„ „ superior „	0·000420	349	328	318	331	376	476

Fig. 7 will show the distribution of these errors. Clearly it is inadmissible to consider points of very high or very low pressure of oxygen above 40 mm., and below 20 mm. a very small difference in the percentage saturation makes a comparatively large difference in K. Indeed the best points to take are at or near the two pressures

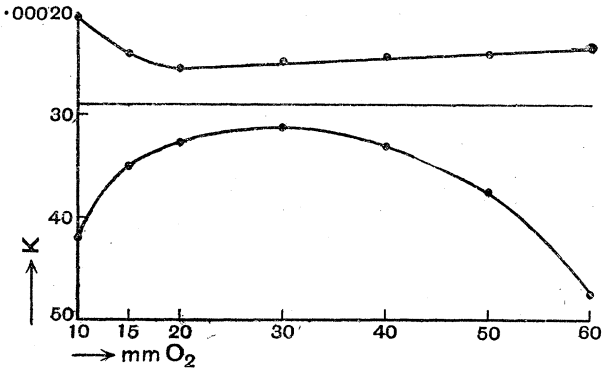

FIG. 7.—Shows the error produced in the value of K by an error of ± 3 per cent. in the measurement of the percentage saturation at various pressures of oxygen.

mentioned, for in addition to the errors being almost minimal they are about equally distributed on both sides of the line, a point of some importance if the arithmetic mean of the value of K is going to be taken at the end. Our results were obtained for the most part near these pressures.

* The 0's are omitted in all but the first column for the sake of brevity.

TABLE VII (14).

Subject.	Height.	Pressure.	Saturation.	K.	Normal.
			per cent.		
Barcroft . . .	Alta Vista, 11,000 ft.	18·5	31·5	0·000311	
		28·5	54·0	273 } 0·000298	0·00029
		38·5	74·0	310	
Zuntz	Alta Vista, 11,000 ft.	25·0	50·0	320	
		35·0	64·5	250 } 0·000274	0·00032
		45·0	75·0	250	
Douglas . . .	Alta Vista, 11,000 ft.	33·5	44·0	250 } 0·000253	0·00021
		42·5	67·0	257	
Camis	Capanna Margherita, 15,000 ft.	20·4	33·0	242	
		20·4	34·0	255 } 0·000264	0·00029
		33·0	65·0	296	
		34·0	64·0	264	
Roberts . . .	Capanna Margherita	19·0	32·0	300	
		19·0	37·0	376 } 0·000297	0·00033
		41·0	70·0	223	
		41·0	76·0	293	
Roberts . . .	Col d'Olen	21·0	40·0	344	
		21·0	44·0	330 } 0·000282	0·00033
		33·0	59·0	228	
		33·0	59·0	228	
Barcroft . . .	Col d'Olen	39·0	67·0	234 } 0·000240	0·00029
		39·0	70·0	245	

The normal values for K in the cases of DOUGLAS' and BARCROFT'S blood were calculated from known data (15), namely, for

DOUGLAS . . . 0·000212
BARCROFT . . . 0·00029

That these do not vary appreciably in the resting individuals seems also to be ascertained.*

It is only necessary to give the data which exist with regard to the normal value of K for ROBERTS, CAMIS, and ZUNTZ.

* See Chapter XIV, 'The Respiratory Function of the Blood.'

TABLE VIII.

Subject.	Place.	Pressure of oxygen.	Percentage saturation with oxygen.	K.	Mean K.
Camis	Pisa	21·0	36·0	0·000279	
		21·0	34·0	258	
		21·0	36·0	279	0·000289
		36·0	71·7	326	
		36·0	70·6	306	
		36·0	69·2	289	
Roberts . . .	Cambridge	21·0	43·0	0·000373	
		21·0	41·0	344	
		41·5	77·0	301	0·000327
		41·5	74·0	257	
	Carlingford	25·0	51·0	333	
		25·0	51·0	333	
Zuntz	Berlin	26·5	58·0	0·000380	
		37·2	75·0	374	
		37·2	68·0	252	0·000322
		25·0	50·0	252	
		32·5	63·0	353	

Let us now compare the values for K which have been obtained at high altitudes with those obtained at or near sea-level. The points in the following table, which were determined on Monte Rosa, are shown in fig. 8 :—

TABLE IX.

Subject.	K′.	Height.	No. of determinations for K′.	K at sea-level.	K′/K.
		feet.			
Barcroft.	0·000298	11,000	3	0·000290	0·97
Zuntz	274	11,000	3	322	0·85
Douglas.	253	11,000	2	212	1·19
Camis	264	15,000	4	289	0·91
Roberts.	297	15,000	4	322	0·92
	282	10,000	4	322	0·88
Barcroft.	240	10,000	2	292	0·82

The mean ratio K′/K may be found for the whole series of 22 determinations by multiplying the ratio K′/K for each person by the number of determinations on which it is based, adding the quantities so obtained and dividing by 22. The ratio so obtained is 0·92.

The only question which could be raised with regard to the legitimacy of this proceeding is whether 22 determinations is sufficient for the purpose. Whilst the actual ratio 0·92 may not be accurate, it seems to be clear that the value for K at

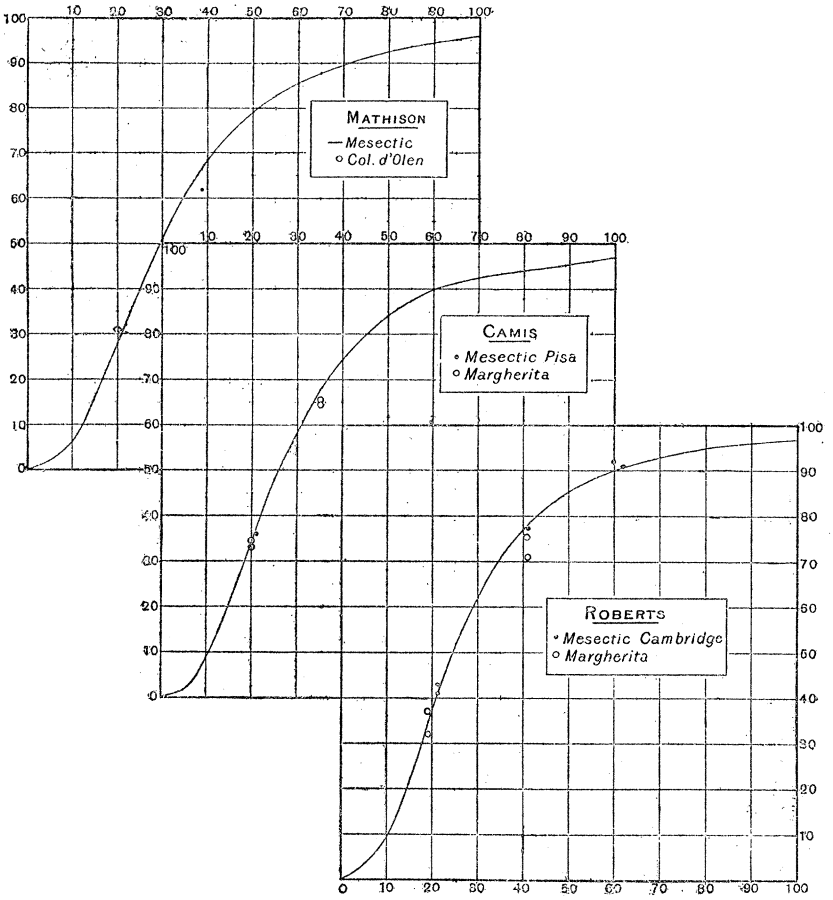

FIG. 8.—Showing Points determined at High Altitudes in relation to Mesectic Curves, the CO_2 pressure in every case being that of the individual at the place.

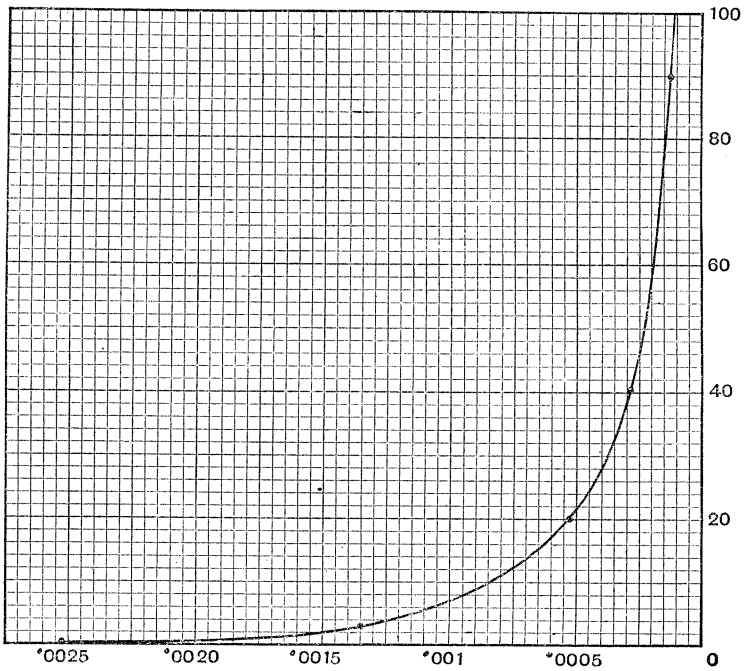

FIG. 9.—Ordinate = CO_2 pressure in millimetres; abscissa = K.

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high altitudes is somewhat less than it is at the sea-level, the probable cause of the slight decrease in K being a corresponding increase in the hydrogen-ion concentration.

We can get an idea of the change in reaction of the blood by enquiring what increase in the amount of carbonic acid in the blood would be required to produce the observed change in the value of K.

For my own blood Poulton (13) and I worked out a relationship between the CO_2 pressure to which my blood was exposed and the value of K for me; this relation is shown in fig. 9.

Taking my normal value for K as ·00029, the value at over 10,000 feet would be approximately ·000267, the difference K being ·000023. At this portion of the curve such a decrease in K would correspond to an increase of the order of 3 mm. in the alveolar carbonic acid. This is a very rough measurement, for the curve in fig. 9 is only based on a few determinations of K, still it probably gives an indication of the order of change in the hydrogen-ion concentration of the blood at high altitudes. Such a change would of course tend to increased ventilation. It is not necessary to go into the literature of this question, the increased ventilation is well known to exist and is in fact the counterpart of the decrease in the alveolar CO_2. The actual amount of CO_2 which leaves the body is not reduced. The whole question is discussed in a paper by Campbell, Douglas, Haldane and Hobson ('Journ. Physiol.,' vol. 46, p. 316), to which the reader is referred. These authors conclude that the difference in reaction of the blood at Pike's Peak and at Oxford should correspond to the addition of 0·8 mm. CO_2. In this there are considerable individual differences, but it is at least satisfactory to find that two methods so widely different should have given results of the same order. It seems clear that in the blood of the resting individual there is a trifling increase in hydrogen-ion concentration at high altitudes, but this is small as compared with the change that can be induced by exercise.

Though no actual measurements of hydrogen-ion concentration were made by us on Monte Rosa, Peters undertook the task of investigating whether or no any relation could be found between the hydrogen-ion concentration of my blood and the value of K in the equation

$$y/100 = \frac{Kx^n}{1+Kx^n}.$$

In the case of blood, over a great range of CO_2 pressures, n may be regarded as constant, so that the only variable in the equation is K. Peters' method is described in detail elsewhere (16), and it has been considerably improved since the determinations here quoted were made; it is only necessary, therefore, to say that some 4 c.c. of my blood were placed in a vessel consisting of two chambers separated by a tap.

The larger of these chambers is the tonometer, the smaller is the electrode vessel. The tonometer is 250 c.c. in capacity; it is fitted with a rubber cork and that with a three-way tap of capillary bore, so that gas can be taken out for analysis or put into

the tonometer without contamination with air. The electrode vessel is of about 10 c.c. capacity, it is also fitted with a rubber cork through which go the connection of the platinum-hydrogen electrode and a glass tube fitted with a stopcock, the fluid

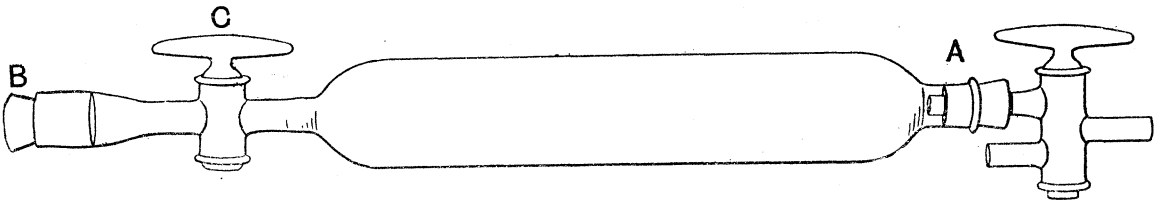

FIG. 10.—Apparatus for Determination of Hydrogen-ion Concentration. The electrode is replaced by cork B.

in which forms a connection, by means of a saturated solution of KCl, with the calomel electrode outside the apparatus. The method of using the apparatus is very simple. After the blood is put in it is corked up at A. The tonometer is then evacuated, filled with hydrogen and rolled round and round in water at 37° C. The blood then becomes reduced, or nearly so. The electrode is now put in its place at B (being exposed to air for the minimal time), the whole apparatus is evacuated and refilled with hydrogen.

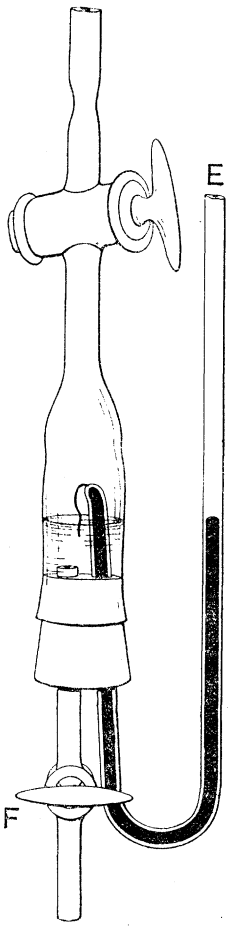

FIG. 11.—Electrode in cell.

If the blood is thoroughly reduced the hydrogen-ion determination is rapidly made. The apparatus is rotated for 10 minutes in the bath at 37° C., it is then placed with the cell downwards, while still in the warm bath, the blood then runs from the tonometer into the cell (the bore of the tap C must be large enough to allow of this). C is then closed and the apparatus is transferred to a bath of potassium chloride at 37° C. in a thermostat. This bath is in contact with the calomel electrode. The tap F (fig. 11) is opened, the wire making contact with the platinum electrode is placed in the mercury contained in the glass tube E (fig. 11). Equilibrium is reached in two minutes and a constant reading obtained which may be measured to one millivolt or less.

Proceeding with this apparatus we first determined the hydrogen-ion concentration of my blood with no CO_2 present. Then we added successive quantities of CO_2, on each occasion letting out some gas for analysis in the Haldane apparatus and replacing in the tonometer the hydrogen left at the end of the analysis. Thus we obtained the CO_2 pressure in the tonometer corresponding to each hydrogen-ion determination which we observed. We thus obtained a curve relating the concentration of hydrogen ion to the CO_2 pressure to which the blood was exposed. This curve is very similar to those already published by LUNDSGAARD and HASSELBALCH (18), but slightly more

acid.* We verified it with two subsequent determinations on another sample of my blood.

The following is the curve, in it the CO_2 pressure forms the abscissa and the exponent of the hydrogen-ion concentration the ordinate :—

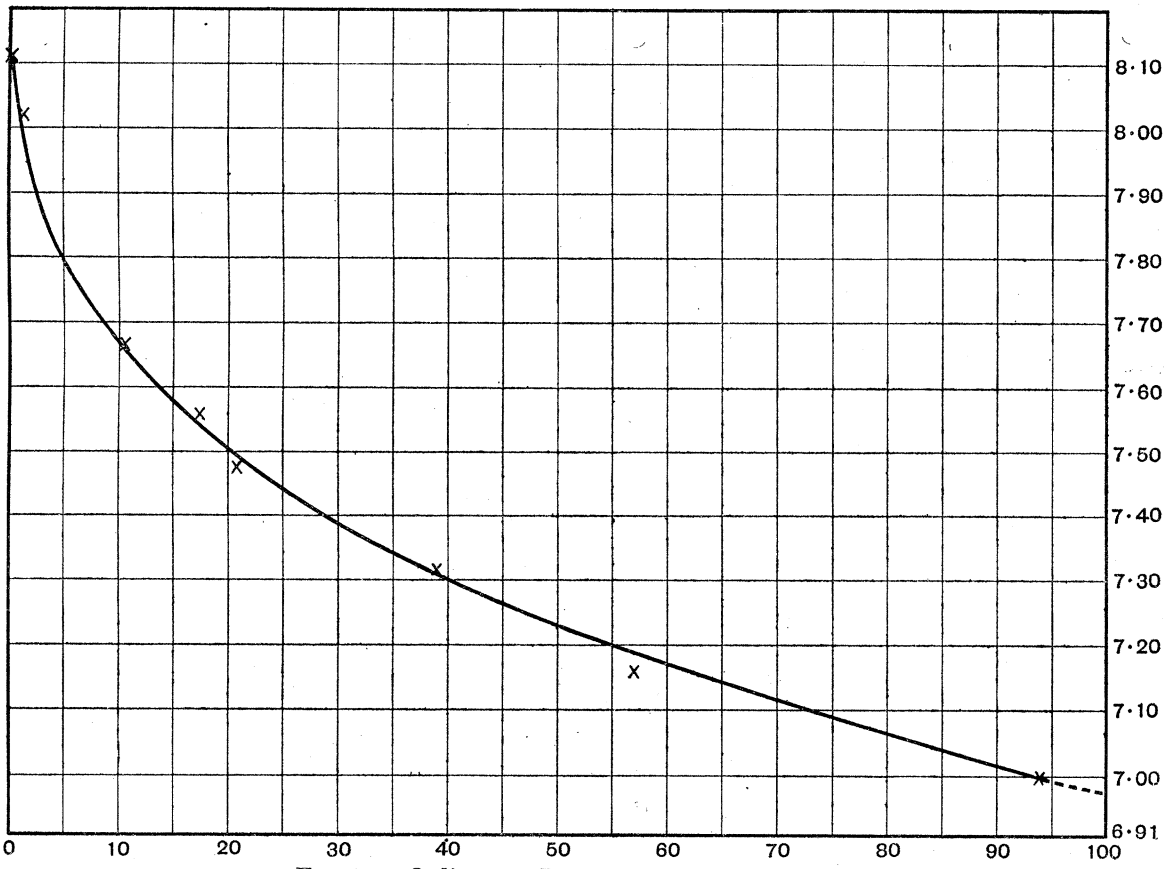

FIG. 12.—Ordinate = P_H; abscissa = CO_2 pressure.

The question now arises, can any direct comparison be made between the value of K, which also varies in relation to the CO_2 pressure, and the hydrogen-ion concentration ? The answer is in the affirmative. Fig. 13 shows the relation between the CO_2 pressure and the logarithm of K.

If fig. 13 be applied to fig. 12 it will be seen at once that the two curves are the same, from which we arrive directly at the important conclusion that the value of K varies inversely as a power of the hydrogen-ion concentration.

* Upon the slight difference between the determinations of HASSELBALCH and others for the P_H of blood exposed to 40 mm. of CO_2 and those of our own we lay no stress at present. We were not concerned with the absolute P_H of blood at 40 mm. CO_2 so much as with the comparative P_H of BARCROFT'S blood exposed to different CO_2 pressures, and therefore the standardisation of the calomel cell was not carried to any great degree of accuracy. It is possible also that the slight traces of acid formed in blood during incubation at 37° C. may have a slight effect upon the hydrogen-ion concentration.

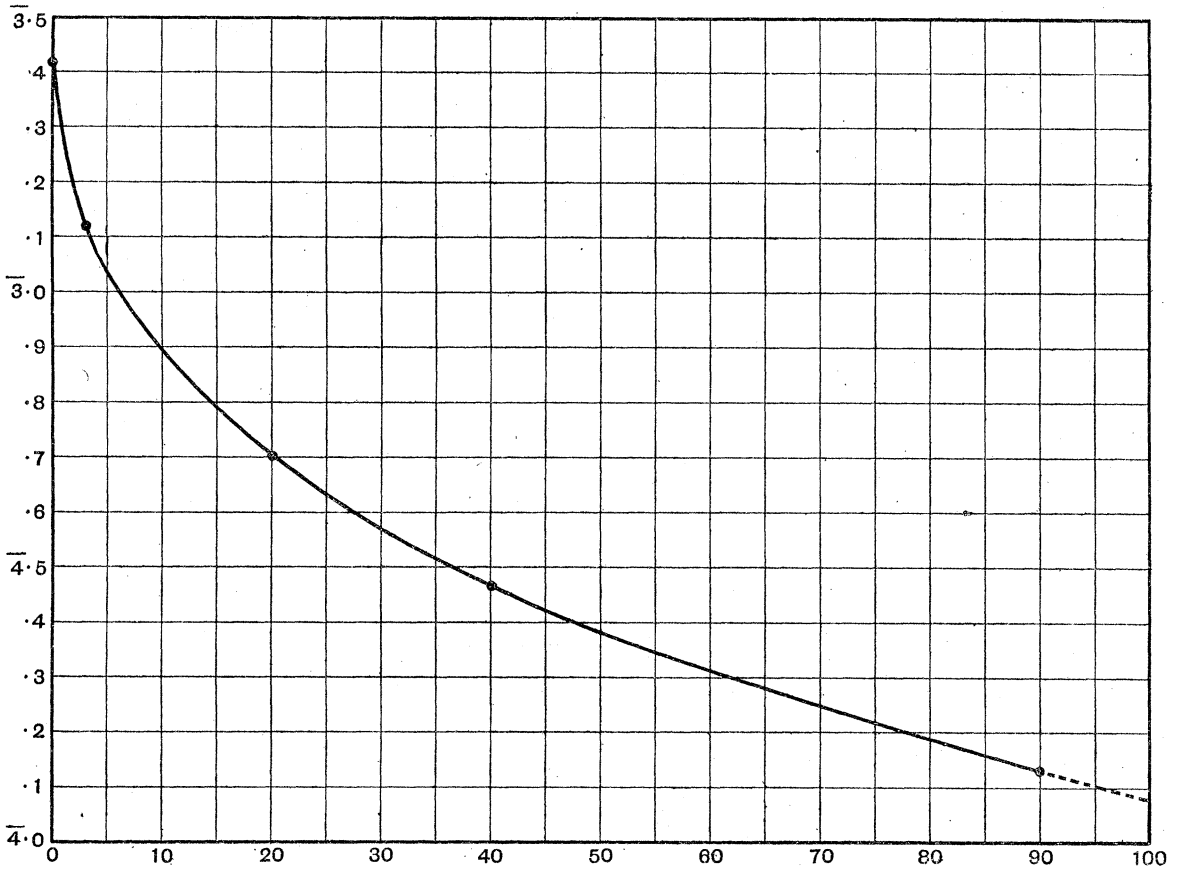

FIG. 13.—Ordinate = log K; abscissa = CO_2 pressure in millimetres.

Putting on one side the theoretical importance of this conclusion, it is clear that it gives us a means of expressing the changes in reaction of BARCROFT'S blood on Monte Rosa and Teneriffe in terms of hydrogen-ion concentration.

Above it was stated that his normal value for K was 0·00029 ($\log K = \bar{4}\cdot4624$), whilst above 10,000 feet it would be about 0·000267 ($\log K = \bar{4}\cdot4200$); these would correspond to the following values for P_H, namely, −7·284 and −7·250 respectively, the difference being approximately 0·03.

This observation may be compared with the change which would have taken place in the opposite direction if no acidosis had taken place to compensate for the withdrawal of the CO_2. At the Margherita Hut the CO_2 pressure in BARCROFT'S alveolar air was 28 mm., the corresponding value for P_H being 7·39. Thus the acid added to his blood changed a difference in P_H of 0·1 in the alkaline direction into about 0·03 in the acid direction.

Whilst some slight change in hydrogen-ion concentration of the above order probably takes place, it must be remembered that it has not been observed with certainty in any one person, and the only evidence which we had of it at altitudes as low as 10,000 feet was obtained after we had come down from the Margherita Hut. I have, therefore, taken the normal values of K in the following portions of the paper

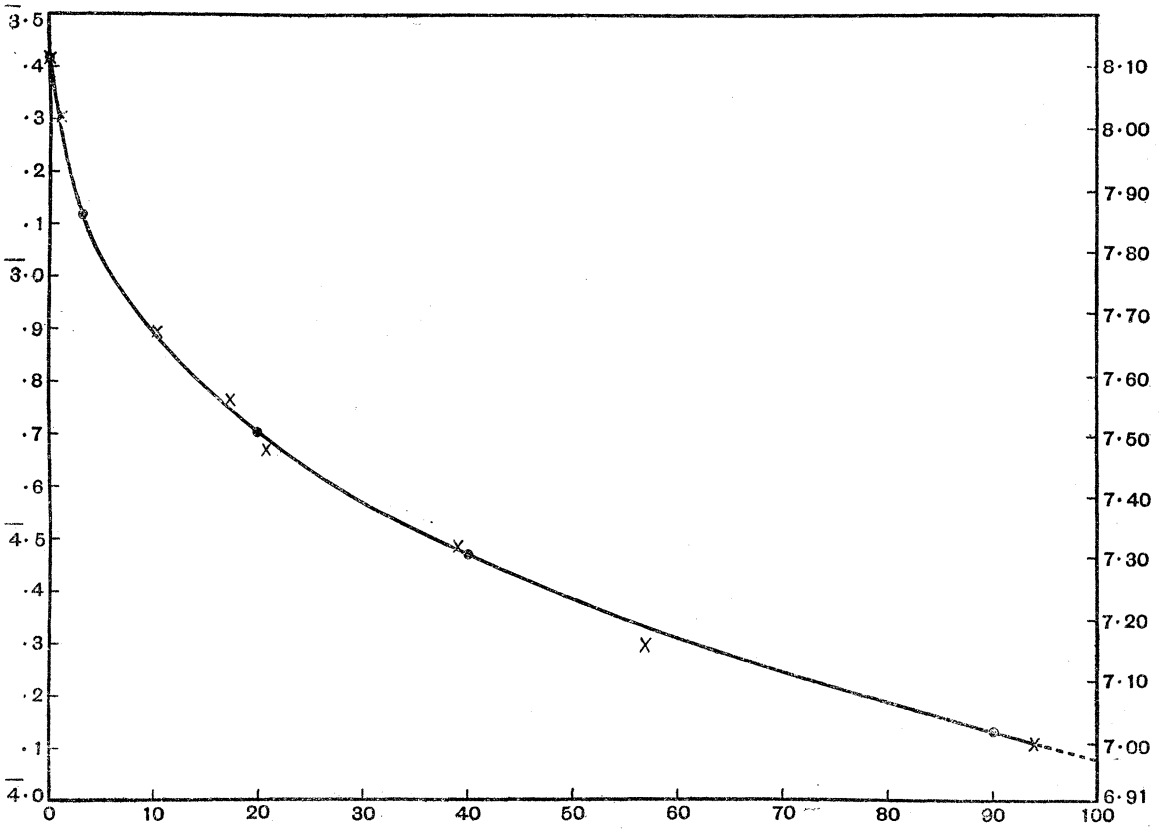

FIG. 14.—Showing the Relation of P_H to log K.

as more nearly representing the condition at Col d'Olen before the ascent to the Margherita Hut.

Part II.—The Effect of Exercise on the Reaction of the Blood.

1. *Introductory.*

This enquiry has been carried out along the same lines as that of the effect of altitude on the resting individual.

In the first place the data will be given with reference to the effect of exercise uncomplicated by that of altitude. The exercise in question consisted of a climb of 1000 feet. This research was undertaken in January, 1913; the steepness and general nature of the climb was as nearly as might be the same as the 1000 feet immediately below Col d'Olen. The locality chosen was Carlingford Mountain (*i.e.*, Slieve Foy), which is particularly suitable, as the mountain rises practically from the sea-shore. The apparatus used was that which had been taken to Monte Rosa, with the exception of the bath for rotating the tonometer, this was of a different design. The laboratory used proved to be exceedingly efficient, it was the bathroom of a lodging-house, containing a bath provided with hot and cold water, a wash-hand basin with the same equipment, and a water-closet, with the addition of a pail for the solid

things which we wished to throw away. This equipment left little to be desired, and the luxury of hot water was felt to be very great in view of the difficulty which we had encountered in heating it at high altitudes. The party at Carlingford consisted of BARCROFT, PETERS, ROBERTS, and RYFFEL, three of the four being the same as were at Col d'Olen.

2. *The Effect of Exercise upon the Alveolar Air.* (RYFFEL.)

This has been the subject of so much work carried out by so many observers that it is only necessary to observe that our results, in which the measurement of the CO_2 pressure in the alveolar air was an incidental determination, agreed with those of other workers.

At the end of 1000-foot climb, if undertaken slowly the CO_2 in the alveolar air was sensibly lower than at the beginning.

TABLE X.

Height climbed.	Time.	CO_2 in alveolar air.		Subject.
		Normal.	At end.	
feet.	mins.	mm.	mm.	
1000	30	40	36	Barcroft.
1000	20	40	36	Roberts.
1000	45	40	38	Barcroft.

3. *The Acidosis Produced by Exercise.* (BARCROFT.)

This lowering of the CO_2 pressure in the alveolar air as the result of continued exercise of a not very severe character is, of course, accompanied by increased ventilation, and is explained by BOYCOTT and HALDANE (10), and others in the following way :—Carbonic acid is not the only acid produced by the exercise, but as has been shown by RYFFEL (12) and others lactic acid is produced as well. The combined effect of these acids in the blood is the factor which regulates the respiratory centre. The subjects in the present case are conceived of as having an abnormally high hydrogen-ion concentration in the blood, at the same time the CO_2 has been to some extent replaced by lactic acid, hence the CO_2 pressure in the alveolar air is lowered.

There are, of course, those (18) who do not accept the theory of the respiratory centre being actuated by the increased hydrogen-ion concentration of the blood, but regard CO_2 as a specific stimulus. Such would suppose that lactic acid production has a secondary effect on the respiratory centre, liberating CO_2 from its combinations in the centre, and thus forming increased quantities of CO_2 in the centre itself which

act as a stimulus. Such a theory would account for the facts up to a certain point. This point seems to me to be the one at which a fresh equilibrium is established in the body. So long as lactic acid is accumulating in the body it is possible to conceive of fresh liberation of CO_2 in the respiratory centre, but at the end of a long slow grinding climb it is difficult to suppose that such accumulation is taking place. Further experiments might be performed on the time at which this equilibrium is reached, but once the lactic acid loss becomes equal to the lactic acid production it is not easy to see how the respiratory centre can be stimulated in the presence of decreased carbonic acid in the alveolar air if carbonic acid is the specific stimulus. One explanation might be forthcoming, namely, that in view of the increased rate of blood flow and of respiration during the exercise the pressure gradient of CO_2 between the respiratory centre and the alveolar air might become steeper. No doubt it does so, but in view of the great solubility and diffusibility of CO_2 it seems unlikely that the pressure of CO_2 should be abnormally high in the respiratory centre and 4–5 mm. below the usual figure in the alveolar air merely as the result of an increased pressure gradient.

But it is important to recollect with regard to both theories that the accumulation of acid in the sense of change in the reaction of the blood heretofore has been purely conjectural. The increased quantities of lactic acid found by RYFFEL furnish no evidence of changed reaction. The lactic acid may be present entirely as lactate, for which bases are provided either by tissue breakdown or by altered excretion. It seemed, therefore, to us to be of importance to go into this question and ascertain whether there was evidence of changed reaction in the blood during exercise, and if so to what extent the change occurred.

The tests which we performed were of the same nature as those performed during rest on Monte Rosa—

(1) Estimation of the acids thrown into the blood exclusive of CO_2.
(2) Estimation of the lactic acid radicals in the blood.
(3) Estimation of the change in the dissociation curve of the individual.

The methods of estimation, etc., were roughly similar to those on Monte Rosa.
The results obtained were as follows :—

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TABLE XI.—Degree of Hæmacidosis which takes place as the Result of a Climb of 1000 feet.

Subject.	Date.	Place.	Percentage saturation of blood at 17 mm.	Equivalent of lactic acid.	Rate of climb of 1000 feet.
					mins.
Mathison . .	Sept. 27, 1912	Abergavenny	52·5 50·0	0·022 0·025 } 0·024	20
Barcroft . .	Aug. 17, 1912	Carlingford	58·0 55·0	0·023 0·027 } 0·025	30
Roberts . .	Jan. 3, 1913	,,	53·5 56·5	0·034 0·031 } 0·033	20
Barcroft . .	,, 6, 1913	,,	64·0 59·0 60·0	0·016 0·021 } 0·018	45

The figures in the column "Equivalent of lactic acid" are derived from the scales made out at Pisa (fig. 1). But, in the cases of ROBERTS and myself, control experiments were carried out either at Carlingford or just before going there, which showed that our normal blood had not appreciably altered in the 18 months which elapsed between the two sets of determinations.

TABLE XII.—Percentage Saturation of Normal Blood at 17 mm. O_2.

Date.	Place.	Subject.	Saturation.
			per cent.
Aug. 5, 1911 . .	Pisa	Roberts	78·5
Jan. 2, 1913 . .	Carlingford	,,	77·0
,, 2, 1913 . .	,,	,,	79·5
,, 2, 1913 . .	,,	,,	79·0
Aug. 4, 1911 . .	Pisa	Barcroft	74·0
July, 1912 . . .	Cambridge	,,	75·0

4. *The Relation between the Degree of Hæmacidosis and the Appearance of Lactic Acid in the Blood.* (RYFFEL.)

At Carlingford the blood was taken from the forearm at rest and immediately after climbing 1000 feet. The urine excreted during the climb and for 40 minutes after was also collected. The blood was diluted, coagulated by heat, and preserved by the addition of thymol in chloroform. The urines were also preserved with the same antiseptic precautions.

The actual estimations of lactic acid were made on returning to London. The results were as follows ;—

TABLE XIII.

Subject.	Lactic acid per 100 c.c. blood.		Difference.	Time taken for climb.
	At rest.	After climb.		
				mins.
Roberts . .	0·014	0·046	0·032	20
Peters . .	0·016	0·080	0·064	19

A comparison of the quantities of actual lactic hæmacidosis in ROBERTS' case, with the total hæmacidosis expressed in equivalents of lactic acid, is as follows :—

TABLE XIV.

Subject.	Actual lactic hæmacidosis.	Total hæmacidosis expressed in equivalent of lactic acid.	Climb.
	per cent.	per cent.	
Roberts . . .	0·032	0·034, 0·031 } 0·033	1000 feet in 20 mins.

It is clear, then, that in this one case the total hæmacidosis is entirely accounted for by the increase in the percentage of lactic acid in the blood. There can be little doubt that in PETERS' case, in which the increased lactic acid was twice as great, the same would have been the case.

As regards the urine, the following estimations were made :—

TABLE XVI.

Subject.	Lactic acid in urine secreted during climb and in 40 minutes subsequently.	Increased lactic acid in blood.	Time of climb.
	grm. per hour.	per cent.	mins.
Peters . . .	0·395	0·08	19
Ryffel . . .	0·0025	—	25

5. *The Change in the Dissociation Curve of the Blood.* (BARCROFT.)

From what has been said it is clear that the CO_2 in the blood had a less concentration at the end of the climb than at the commencement, whilst the lactic acid had a greater concentration. What, then, was the ultimate balance between

the two? Using the dissociation curve as an indication, the following data were forthcoming as the result of three climbs.

The following figures have been repeatedly proved to represent BARCROFT'S normal dissociation curve :—

Oxygen pressure . . .	5	10	15	20	25	30	35	40	50	60	80	100 mm.
Saturation	1·5	9	20·3	34	48	58	68	74	84	90	94	97 per cent.

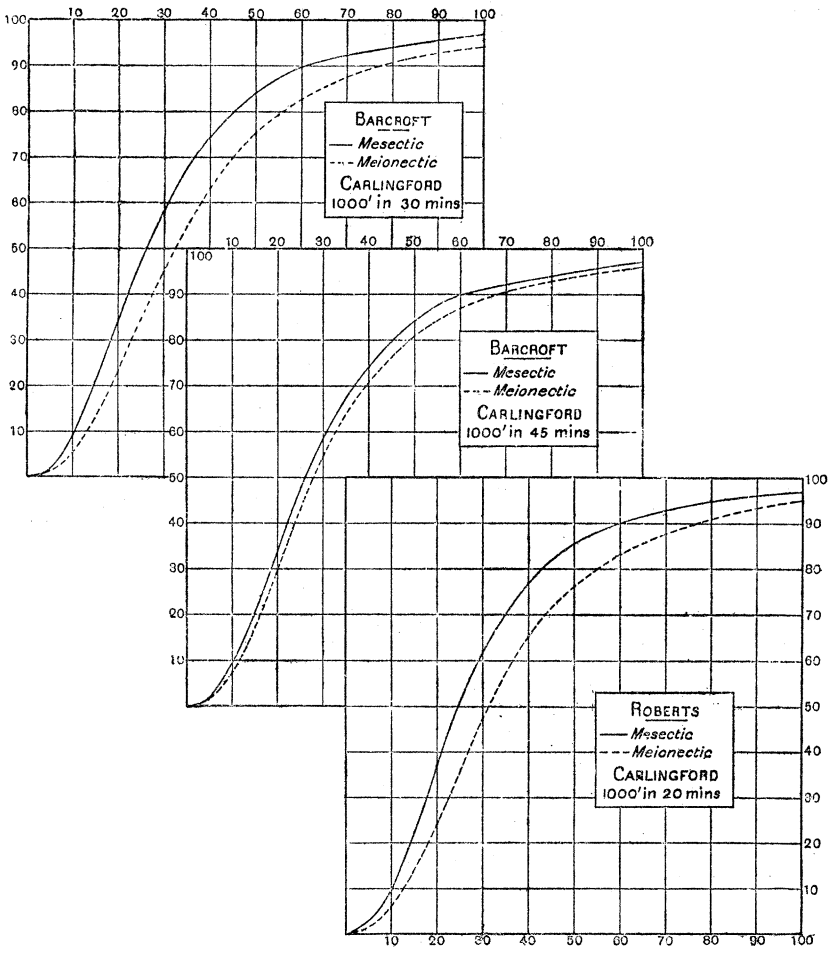

FIG. 15.

They correspond to the following constants, $n = 2{\cdot}5$, $K = 0{\cdot}000292$.

Two climbs were made by BARCROFT, one of the 1000 feet in 45 minutes, the other of the 1000 feet in 30 minutes. In each case the blood became meionectic, the degree of meionexy observed being in proportion to the quickness of the climb. In the case of the slower climb it was only just apparent.

The following were the points on the dissociation curve which were obtained :—

TABLE XVII.

Subject.	Rate of climb, 1000 feet in—	Pressure of oxygen in tonometer.	Percentage saturation.	Mean value of K.
	mins.	mm.		
Barcroft . . .	30	27·5	37, 43 } 40·0	0·000168
	45	30·9	55, 56 } 55·5	0·00024
	Normal	—	—	0·00029

These values for K give the following curves :—

Climb of 1000 feet in 30 mins., K = 0·000168, log K = $\bar{4}$·2252.

Oxygen pressure . . .	5	10	15	20	25	30	40	50	60	80	100 mm.
Saturation	0·7	4·5	10	19	29	39	57·4	70·4	78	88	93 per cent.

Climb of 1000 feet in 45 mins., K = 0·00024, log K = $\bar{4}$·3820.

Oxygen pressure . . .	5	10	15	20	25	30	40	50	60	80	100 mm.
Saturation	2·5	7	17	30	43	55	71	81	87	93	96 per cent.

These curves are shown in fig. 15, from which it will appear that the blood became more meionectic the more rapid the ascent.

It is, perhaps, worth noting that the speed of the latter climb—that in which the meionexy is just, but only just, discernible—is about as fast as proficient climbers usually climb when the climb is to be maintained.

The Carlingford climb was also done by ROBERTS with the following results :—

TABLE XVIII.

Subject.	Rate of climb.	Alveolar CO_2.	Pressure of oxygen.	Percentage saturation.	Mean value of K.
		mm.	mm.		
Roberts	Normal 1911	39	21·0 41·5 62·0	43, 41 77, 76 90, 92	0·00033
	Normal 1913	41	25·0	51·0	0·00033
	1000 feet in 20 mins.	35 36	33·0	53·4 54·0 51·0 } 53	0·00018

ROBERTS' normal curve (K = 0·00033, log K = $\bar{4}$·5185) is : –

Oxygen pressure . . .	10	15	20	25	30	40	50	60	80	100 mm.
Saturation	9·4	22	37	50·7	62	77	83·5	90	95	97 per cent.

His curve after climb of 1000 feet in 20 mins. ($K = 0{\cdot}000184$, $\log K = 4{\cdot}2562$) is:—

Oxygen pressure . . .	10	15	20	25	30	40	50	60	80	100 mm.
Saturation	6	14	24	35	47	65	76	83	91	95 per cent.

The actual curves are shown in fig. 15. They confirm those obtained from BARCROFT'S blood.

The physiological significance of this change in the dissociation curve demands some discussion.

Looked at from the point of view of pulmonary respiration it seems indeed strange that the hæmoglobin should take up oxygen less readily during exercise than during rest. Pulmonary respiration is not, however, the final process in the complex respiratory machine, the object and end of respiration is the supply of oxygen to the tissue. If in the reaction

$$Hb_n + nO_2 \rightleftharpoons Hb_nO_{2n},$$

we suppose that n does not change with an alteration in the reaction we may suppose that we have the same reaction before and after the exercise, but the equilibrium constant of the velocity changes.

Now, we know nothing of the absolute velocity of the reaction

$$Hb_n + nO_2 \rightarrow Hb_nO_{2n},$$

and the same is the case of the reaction

$$Hb_n + nO_2 \leftarrow Hb_nO_{2n},$$

but a decrease in K, the equilibrium constant, argues a relative increase in the velocity of the forward phase of the reaction.

Since K decreases in the last case quoted from $0{\cdot}00033$ to $0{\cdot}00018$ as the result of exercise, the velocity of the dissociation is almost doubled relatively to the velocity of association, or in other words the hæmoglobin parts with its oxygen much more readily at the time when the tissue wants to take the oxygen more rapidly. The blood is, of course, at a corresponding disadvantage in lungs, but this can, of course, be met to some extent by the augmentation of the mechanical processes of respiration, which tend to increase the oxygen pressure in the lungs, and so increase the pressure gradient between the blood and the alveolar air. Moreover, a very slight drop in the degree of saturation of the blood in the lung, whilst reducing the quantity of oxygen taken up only very slightly, would greatly increase the pressure gradient in the lung, and would correspondingly increase the rate of diffusion through the pulmonary alveoli.

It remains to translate the changes observed in the dissociation curve into changes in hydrogen-ion concentration. The following table gives the data for BARCROFT'S blood :—

TABLE XIX.

	Log K.	P_H.
1. Normal	$\bar{4}\cdot4652$	7·29
2. After climb of 1000 feet in 45 minutes	$\bar{4}\cdot3820$	7·22
3. After climb of 1000 feet in 30 minutes	$\bar{4}\cdot2252$	7·09

Part III.—The Effect of Altitude on that of Exercise.

1. *Introductory.* (Barcroft.)

The most systematic series of our climbs were conducted at Col d'Olen. Here we traversed a specified course, which entailed an ascent of 1000 feet, the altitude was from 9000 to 10,000 feet. The measurement of the heights was by an aneroid, the same which was used for a similar purpose at Carlingford. It was checked by the mercury barometer at Col d'Olen and the Margherita Hut.

2. *The Degree of Hæmacidosis which takes place as the Result of the Climb from* 9000 *to* 10,000 *feet.* (Mathison *and* Roberts.)

The methods of estimation were those already recounted. The following were the results obtained :—

TABLE XX.

Subject.	Date.	Percentage saturation of blood at 17 mm.	Equivalent of lactic acid.	Rate of climb of 1000 feet.
			per cent.	mins.
Barcroft	August 14 . .	54·0 57·0	0·027	45
Camis	„ 15 . .	44·5 49·5	0·051	35
Mathison	„ 11 . .	42·5	0·04	21

In the case of Camis unfortunately we have no corresponding data at low levels.

The following comparison may be made in the case of the other two :—

TABLE XXI.—Data at End of Climb of 1000 feet.

Subject.	Rate of climb of 1000 feet.	Percentage saturation at 17 mm.		Hæmacidosis expressed in equivalents of lactic acid.	
		Sea-level to 1000 feet.	9000–10,000 feet.	Sea-level to 1000 feet.	9000–10,000 feet.
	mins.	per cent.	per cent.	per cent.	per cent.
Barcroft	45	64 59	54·0 57·0	0·018	0·027
Mathison	20	52 50	42·5	0·024	0·04

The hæmacidosis was in each case greater at the end of the climb at Col d'Olen than at the low level. MATHISON's case is particularly striking, for before this climb at Col d'Olen his blood was normal. The effects of the two climbs are the more directly comparable, that at the low level producing an acidosis of 0·024 per cent. *whilst the effect of the altitude was to increase the acidosis induced by a similar piece of work to* 0·040 *per cent. lactic.*

MATHISON's blood did not return completely to the old condition whilst we were at Col d'Olen ; but of this we shall speak later.

In addition to these determinations several others were made at the end of longer climbs. Although the climbing was in most cases much slower the amounts of acid in the blood were often much more considerable.

TABLE XXII.

Subject.	Date.	Climb.	Percentage saturation of blood at 17 mm.	Hæmacidosis in equivalents of lactic acid.	Time taken for climb.
				per cent.	hrs.
Barcroft . .	Aug. 5	Alagna to Col d'Olen	47·5	0·042	5
Roberts . .	,, 5	,, ,,	34·0	0·08	5
Barcroft . .	,, 17	Col d'Olen to Capanna Margherita	43·0	0·054	8
Roberts . .	,, 17	,, ,,	31·5	0·09	8

At Col d'Olen, both in the case of BARCROFT and of ROBERTS, there was an acidosis corresponding to about 0·02 per cent. lactic acid, so that the degree of acidosis produced by the climb would be obtained by deducting 0·02 from the figure given above. The corrected figures would be for BARCROFT 0·034 and for ROBERTS 0·07 per cent.

The net figures then would be as follows for the two climbs :—

TABLE XXIII.

Climb.	Height of ascent (approximate).	Time.	Rate per hour.	Hæmacidosis.	
				Barcroft.	Roberts.
	feet.	hrs.	feet.		
Alagna to Col d'Olen .	5600	4	1400	0·042	0·08
Col d'Olen to Capanna Margherita	5300	$7\frac{1}{2}$	700	0·034	0·07

These data yield the same type of result as the comparisons of MATHISON's blood in the 1000-foot climbs at different levels. Here the heights ascended were nearly the same, acidosis nearly the same, but the rate of climbing at the higher altitudes was only half what it was at the lower one.

3. *The Relation between the Degree of Hæmacidosis and the Actual Quantity of Lactic Acid in the Blood.* (RYFFEL.)

On this point we have but few data; what there are go to show that the acidosis due to exercise at high altitudes, as at low ones, is essentially a lactic acidosis. The following determinations were made :—

TABLE XXIV.—Col d'Olen immediately after climbing 1000 feet.

Subject.	Date.	Time taken.	Lactic acid.		Increased hæmacidosis due to climb in terms of lactic acid (Mathison).
			Amount.	Increase due to climb.	
		mins.			
Camis. . .	Aug. 15	35	0·043	0·026	0·028
Barcroft . .	„ 14	45	0·028	0·004	0·006

In the case of CAMIS, in which the rate of climbing was sufficient to produce a well marked acidosis, this was entirely a lactic acidosis.

4. *The Effect of Exercise on the Lactic Acid in the Urine.* (RYFFEL.)

The results of determinations made on *urine* were as follows :—

RYFFEL.—Urine secreted during five hours, including three out of the four hours' climb from Alagna to Col d'Olen and two hours after arrival, contained lactic acid equivalent to 0·003 grm. per hour.

That secreted from midway in the climb to the Capanna Margherita until two hours after arrival at the summit contained 0·0022 grm. lactic acid per hour.

That secreted from 9.15 P.M. to 7 A.M. in bed at Col d'Olen on August 19–20 contained 0·0012 grm. lactic acid per hour.

Barcroft.—Urine secreted from beginning of climb to Col d'Olen till 7.30 next morning contained 0·0025 grm. lactic acid per hour.

Mathison.—Urine secreted for four hours from beginning of climb of 1000 feet to Col d'Olen in 19 minutes on August 11 contained 0·0027 grm. lactic acid per hour.

The normal amounts of lactic acid in the urine are about 0·002 grm. per hour during an ordinary day and 0·001 grm. during sleep, so that the figures given above are very slightly above normal, but do not indicate any active excretion of lactic acid.

Discussion of Results.—In only one of the experiments described was the lactic acid in the urine appreciably greater than normal, and this was the result of a climb from sea-level involving an intensity of exertion for the individual which would be impossible in an ascent, or in even a fairly short climb, at high altitudes. Moreover, the occasions on which there was no active excretion of lactic acid in the urine include two when on Monte Rosa Ryffel had considerable dyspnœa, and one when Mathison climbed very rapidly, and showed considerable dyspnœa and sweating, so that clearly there is no excretion of appreciable quantities of lactic acid by the kidneys as the result of reasonable climbing, whether at sea-level or at high altitudes.

5. *The Change in the Dissociation Curve of the Blood.* (Barcroft *and* Camis.)

Firstly, the data of climbs on the 1000-foot course at Col d'Olen may be dealt with. Four such climbs were made.

Table XXV.

Subject.	Rate of climb of 1000 feet.	Pressure.		Percentage saturation.	Mean value of K.
		Oxygen.	CO_2.		
	mins.	mm.	mm.		
Barcroft	45	21	33	26·0	
		21	33	28·0	
		40	33	62·0	0·000191
		40	33	67·0	
		40	33	63·0	
Camis	35	20	36	28·0	
			36	24·5	0·000161
			36	64·0	
		45	36	59·5	
Mathison	20	24	37	35·0	
		24	37	30·5	
		42	37	65·0	0·000151
		42	37	60·0	
		42	37	60·0	
Roberts	33	16	34	18·0	
			34	23·0	0·000161
		29	34	40·0	
			34	37·0	

If these values of K be compared with the normal ones, the comparison would be as follows :—

TABLE XXVI.

Subject.	Normal value of K.	Normal $P_{H.}$	Value after climb.	After climb $P_{H.}$
Barcroft	0·000292	−7·29	0·000191	−7·14
Camis	0·000299		0·000161	
Mathison	0·000212		0·000157	
Roberts	0·000324		0·000161	

The change in the value of K does not correspond with the rate at which the climbing was performed by the various individuals. Arranging the climbs in order of their speed—

TABLE XXVII.

Subject.	Rate of climb of 1000 feet.	K′/K.
	min.	
Mathison	20	0·7
Roberts	33	0·5
Camis	35	0·55
Barcroft	45	0·65

The discrepancy depends upon the individual fitness of the climber and the effect which the altitude had upon his powers of climbing. The most interesting question which arises is, of course, the last. In the case of two of the four, BARCROFT and ROBERTS, control climbs of 1000 feet were undertaken at Carlingford, which are directly comparable with those at Col d'Olen.

The following table gives the data which are available on this subject :—

TABLE XXVIII.

Subject.	Rate of climb.	Normal value of K.	K′ (after climb).		K′/K.	
			At Carlingford.	At Col d'Olen.	At Carlingford.	At Col d'Olen.
Barcroft . . .	min. 45	0·000292	0·00024	0·00019	0·8	0·65

These two observations show that a greater reduction in the value of K is produced by a similar piece of work at high altitudes than at low ones.

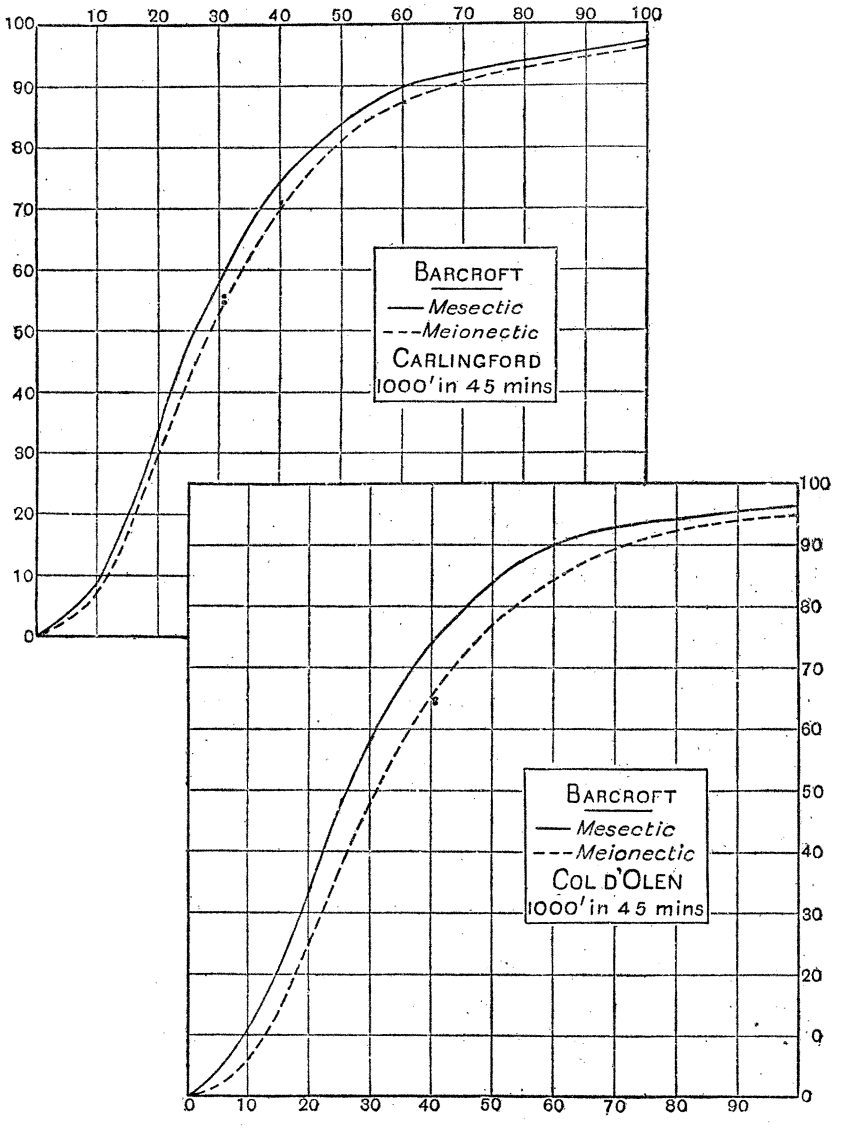

FIG. 16.

The same fact was brought out in another way. Instead of performing the climb at the same speed in the two cases, the speed was so regulated that the value of K′ was approximately the same in the case of the two climbs.

TABLE XXIX.

Subject.	Place.	Rate of climb.	Normal K.	K′.	K′/K.
		mins.			
Barcroft	Carlingford	30	0·00029	0·00017	0·6
	Col d'Olen	45	0·00029	0·00019	0·65
Roberts	Carlingford	20	0·00033	0·00018	0·6
	Col d'Olen	33	0·00033	0·00016	0·5

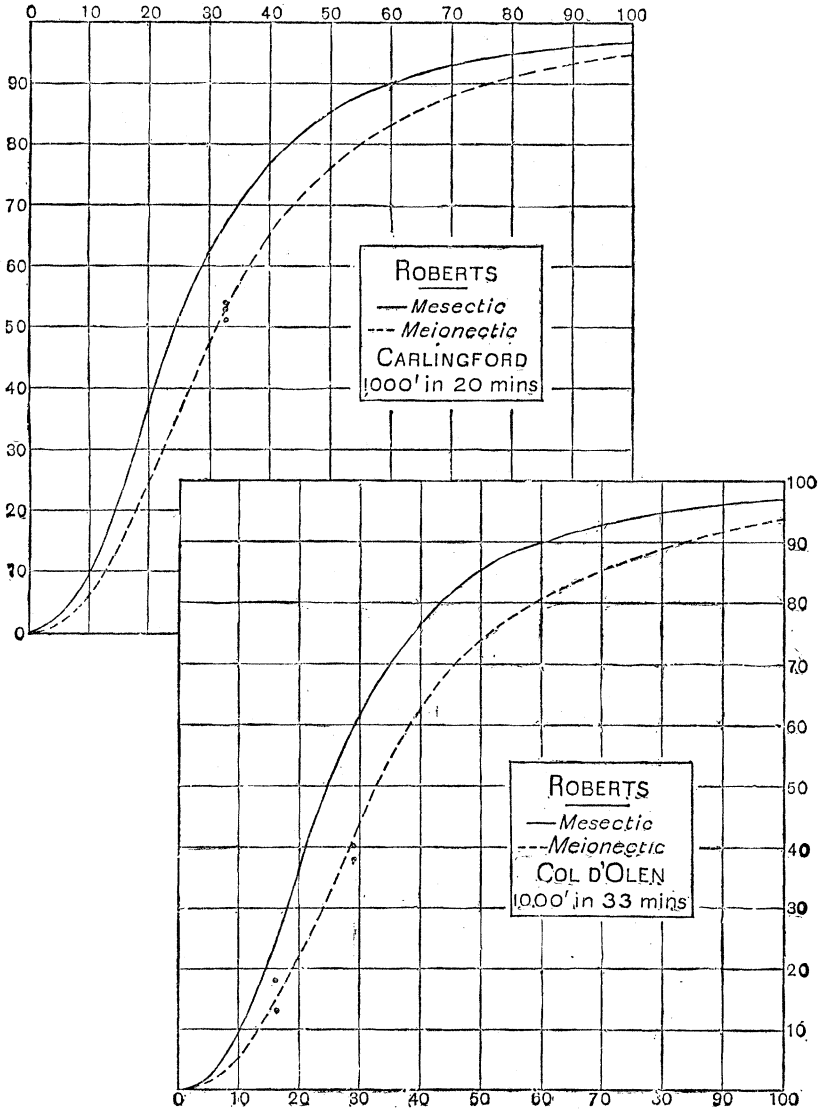

FIG. 17.

TABLE XXX.—Data of Hydrogen Ion Determinations.

Subject.	Place.	Rate of climb.	P_H normal.	P_H after climb.
		mins.		
Barcroft . . .	Carlingford	30	−7·29	−7·09
	Col d'Olen	45	−7·29	−7·14

In this case the effect of the altitude is that about the same change in the reaction of the blood is produced in each case, but with a much slower ascent at the high altitude.

So much for the short climbs; 1000 feet in three quarters of an hour on a pretty

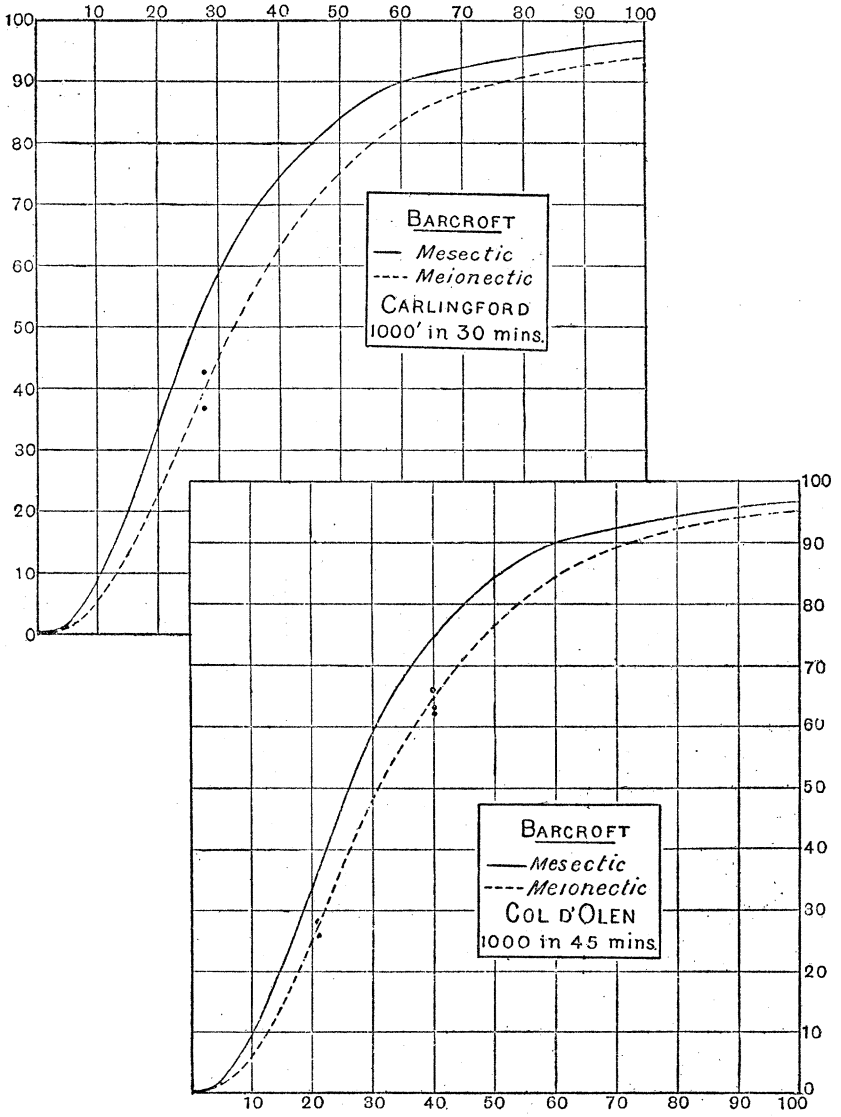

FIG. 18.

steep ascent is very quiet walking in this country, but, of course, it is regarded as quite the reverse when kept up for long ascent in the high Alps. At Col d'Olen there is clearly a well-marked acidosis at this speed; taking the blood of the body as 3·5 litres, the amount of lactic acid which accumulates in it is about 1 grm. This appears to be secreted only very slowly, therefore the opportunity occurs for the accumulation of considerable quantities of lactic acid as the result of long but not rapid climbs. The following data with regard to the alteration of the dissociation curve for climbs of about 5000 feet were obtained :—

TABLE XXXI.—Data obtained at End of Climb of about 5000 feet.

Subject.	Climb.	Rate.	Pressure of		Percentage saturation.	Mean value of K′.	P_H.
			Oxygen.	CO_2.			
		hours.					
Roberts . .	Alagna to Col d'Olen, 5600 feet	5	22		31	0·00022	
			22		34		
			22		36		
			40		67		
			40		68		
			40		71		
	Col d'Olen to Capanna Margherita, 5300 feet	8	21		14	0·00013	
			40		57		
			59		82		
Barcroft . .	Col d'Olen to Capanna Margherita, 5300 feet	8	27		32	0·00013	−7·02
			27		28		
			39		55		
					56		

From the above table one sees that the diminution in the value of K in these climbs of 5000–6000 feet is very considerable; the normal values being—BARCROFT 0·00029, ROBERTS 0·00033.

For instance, the value K′/K was considerably smaller as the result of eight hours' climbing of 5300 feet (600–700 feet per hour) than as the result of 1000 feet in 45 minutes at Col d'Olen, or, indeed, in ROBERTS' case as the result of 1000 in 33 minutes. To the cumulative effect of this acidosis we shall refer later.

Another point to which I would draw attention is the greater degree of meionexy which took place at the higher altitude, even though the rate of climbing was so much slower.

TABLE XXXII.

Subject.	Climb.	Rate.	Normal value of K.	K′ at end of climb.	K′/K.
		hrs.			
Roberts . . .	Alagna to Col d'Olen, 5600 feet.	5	0·00033	0·00022	0·66
Roberts . . .	Col d'Olen to Capanna Margherita, 5300 feet.	8	0·00033	0·00013	0·4

In the case of long, slow climbs, therefore, as also in that of quick ones of short duration, the effect of altitude is to cause a much greater degree of meionexy than would be the case were the climb performed at lower levels.

6. *The Duration of the Changes produced in the Blood by Exercise at High Altitudes.* (Barcroft, Camis, Mathison, Roberts.)

We have no knowledge of the length of time for which the ordinary meionexy of exercise persists. On Monte Rosa, however, we did perform some experiments on the duration of meionexy after exercise. The first of these was upon Mathison, and was made after his climb of 1000 feet.

The following are the data which we obtained. The climb of 1000 feet was made in 20 minutes. The dissociation curve of the blood and the composition of alveolar air were determined :—

(1) 5 minutes after the climb.
(2) 20 minutes after the climb.
(3) About $2\frac{1}{2}$ hours after the climb.

Table XXXIII.

Subject.	Determinations of curve.	Pressure in tonometer of		Percentage saturation of blood with oxygen.	Mean value of K.
		Oxygen.	CO_2.		
		mm.	mm.		
Mathison . .	Cambridge (mesectic)	34	39	55·0	
		34		59·0	
		34		57·0	0·000211
		21		27·5	
		21		33·0	
	5 mins. after ascent of 1000 ft. at Col d'Olen in 20 mins.	24	37	35·0	
		24		30·5	
		42		65·0	0·000151
		42		60·0	
		42		60·0	
	20 mins. after same ascent	24	27	35·0	0·000209
				39·0	
	$2\frac{1}{2}$ hrs. after same ascent	20	32	31·0	0·00025

The degree of meionexy induced by this exercise would be—

K′/K.		
After 5 minutes.	After 20 minutes.	After $2\frac{1}{2}$ hours.
0·7	1·0	1·2

The striking fact is that after 20 minutes the meionexy had passed off; the figure obtained after two and a half hours depends upon a single determination, but it is probably of value as showing that MATHISON was not meionectic, though not sufficient to establish pleonexy.

Although 20 minutes sufficed to bring the reaction of MATHISON's blood back to approximately its normal value, the blood itself was profoundly altered. The pressure of carbonic acid was much less than it had formerly been. The question naturally arises, What evidence was there of increase of other acid to take its place?

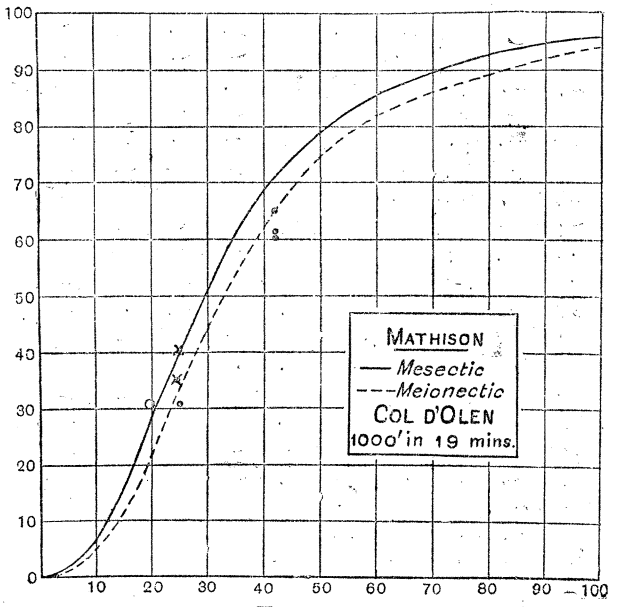

FIG. 19.

The following data for the hæmacidosis were obtained by MATHISON's method :—

Acid added to Blood in Equivalents of Lactic Acid.

Before.	After 5 minutes.	After 20 minutes.	After 2½ hours.
0·000	0·04	—	0·018

Unfortunately there are no data of the acidosis 20 minutes after the ascent, but considering how slowly lactic acid is secreted, the amount was probably 0·04–0·02 per cent. For the purpose of visualising the changes in (1) the reaction, (2) the CO_2 pressure, (3) acidosis, the following figure (20), in which the acid is supposed to be secreted at a uniform rate, may be useful.

The CO_2 determinations are such as have been obtained in ordinary cases of exercise (see p. 57). Although the blood rapidly arrived at approximately its former reaction, this change from meionexy to mesexy was not arrived at by

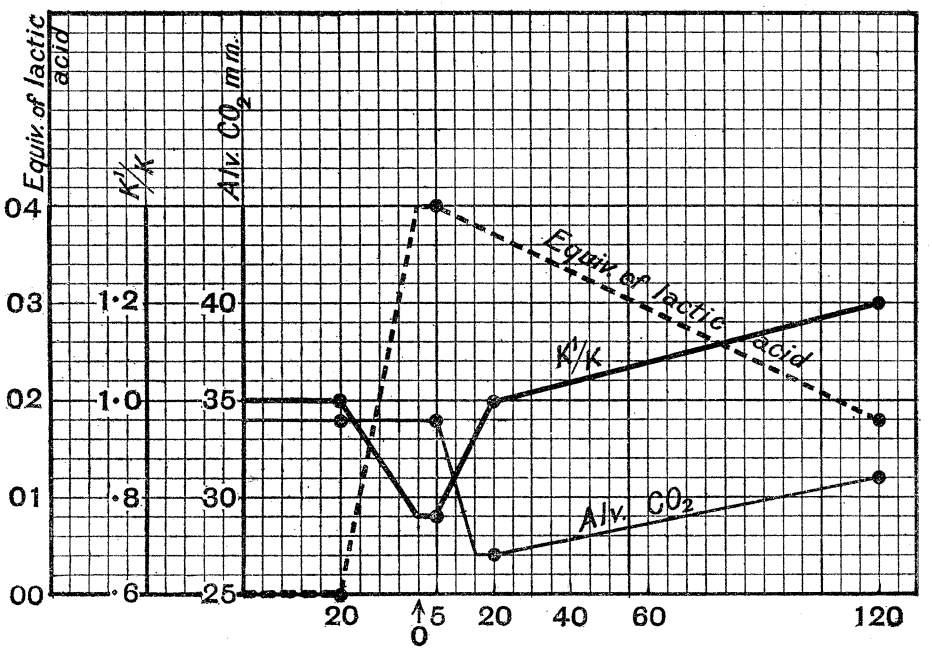

FIG. 20.—Ordinates: (1) Acidosis in equivalents of lactic acid, per cent.; (2) K′/K; (3) Alveolar CO_2 pressure. Abscissa: Time in minutes before and after the end of the climb (O).

a simple return of the blood to its former condition. It was arrived at by a replacement of carbonic acid by lactic acid; this replacement showed signs of readjustment, and at the end of two and a half hours a considerable degree of approximation to the original values had taken place on the part of both the acids involved. But MATHISON's blood never, the whole time he remained at Col d'Olen, actually returned to its former condition, as far, at least, as our measurements showed.

Another phase of the problem of "recovery," if I may so call it, presented itself when we came down from the Margherita Hut to Col d'Olen. At the Margherita Hut, as we have seen, our bloods lost CO_2 and gained lactic acid, but remained, roughly speaking, mesectic. The question which was thrust upon us was, How long did it take at the lower level for the CO_2 and the lactic acid to return to the values which had existed before we made the ascent? It was previously known by the observations of WARD that the CO_2 in the alveolar air remained low for some little time; this result was confirmed by the Pike's Peak party at the same time that we were at Col d'Olen.

Taking the CO_2, the acidosis, and the dissociation curves in order.

Part IV.—THE AFTER-EFFECTS OF ALTITUDE.

1. *Carbonic Acid in Alveolar Air after Descent from Col d'Olen.* (MATHISON.)

The following data were obtained:—

TABLE XXXIV.—Pressure of CO_2 in Alveolar Air.

	Col d'Olen.						Capanna Margherita.		Col d'Olen.	
	Aug. 11.	Aug. 12.	Aug. 13.	Aug. 14.	Aug. 15.	Aug. 16.	Aug. 17.	Aug. 18.	Aug. 18.	Aug. 19.
Mathison . .	32	—	32	—	—	—	27·0	27	—	27
Barcroft . . .	31 32	—	—	—	—	—	28·5	28	—	32
Roberts . . .	—	32·5 34·0	—	—	—	—	28·0	28	28*	28

* 6 P.M., two hours after arrival at Col d'Olen.

So far as our observations went they tended to confirm those of WARD (20), in two out of the three cases they did so, whilst in the third only a single observation had been made. The members of the Pike's Peak (21) expedition, which was at work in California at the same time that we were in the Alps, observed the same phenomenon.

2. *The Hæmacidosis after Descent.* (MATHISON *and* ROBERTS.)

The question naturally arose as to whether with the fall of CO_2 in the alveolar air there was a corresponding acidosis.

TABLE XXXV.—Hæmacidosis in Equivalents of Lactic Acid.

	Col d'Olen.						Capanna Margherita.		Col d'Olen.	
	Aug. 11.	Aug. 12.	Aug. 13.	Aug. 14.	Aug. 15.	Aug. 16.	Aug. 17.	Aug. 18.	Aug. 18.	Aug. 19.
Mathison . .	0·000* 0·018†	—	0·011	—	—	—	—	0·030	—	0·016
Barcroft . . .	—	—	—	0·021	—	—	0·054‡	—	0·038	—
Roberts . . .	—	0·020	—	—	—	—	0·09‡	0·048	—	0·02

* Before climb. † Two hours after climb. ‡ Immediately after climb.

Just as on the whole there was evidence of fall of CO_2 at Col d'Olen as the result of our short sojourn at the 15,000 altitude, so the evidence on the whole is in favour of an increased acidosis: it appears in two out of the three cases, but it

should be noted that the case which showed no rise was ROBERTS, while the case which showed no fall of CO_2 was BARCROFT.

3. *The Dissociation Curve after the Descent.*

The following observations were made after the descent :—

TABLE XXXVI.—Data of Observations on Dissociation Curves, made at Col d'Olen after Descent from Margherita Hut.

Subject.	Oxygen pressure.	CO_2 pressure.	Percentage saturation.	K.	Mean K.
Barcroft . . . . (four hours after arrival)	18	32	34	0·000378	0·000291
	18	32	30	312	
	39	32	69	234	
	39	32	70	245	
Roberts	21	27	44	0·000330	0·000282
	21	27	40	344	
	33	27	59	228	
	33	27	59	228	

On the face of it neither of these sets of determinations inspire much confidence on account of the great variations in the value of K. We, therefore, do not propose to build anything upon them, more especially as the changes which took place after the descent were no part of our original plan ; the fragmentary observations which we give here suffice to show that the matter is well worthy of systematic observation, and there we must leave it for the present at all events.

Part V.—ON THE POSSIBLE AGGREGATION OF HÆMOGLOBIN MOLECULES. (BARCROFT.)

In the preceding portions of this paper the assumption has been made that the average value of n is constant and is 2·5. This assumption is sufficiently near to the truth for the purposes of our argument heretofore. Nevertheless it seemed desirable to investigate the apparent constancy of n in the equation

$$y/100 = \frac{Kx^n}{1+Kx^n},$$

with considerable care ; the result has been a demonstration that n increases by a measurable amount in the presence of high hydrogen-ion concentrations. On the physical conception on which the formula is based this would indicate an increased clumping of the molecules of hæmoglobin.

The argument in terms of this conception is as follows :—

The effect of carbonic acid on a pure dialysed solution of hæmoglobin is to cause very active clumping of the molecules. In the pure solution the molecules exist as single molecules, in the presence of the carbonic acid, however, the dissociation curve of oxyhæmoglobin varies as follows :—

TABLE XXXVII.

Pressure of CO_2 at 40° C.	n (Average number of molecules in a clump).	K (Equilibrium constant of reaction $Hb_n + nO_2 = Hb_nO_{2n}$).
mm.		
0	1·0	0·111
7·5	1·8	0·0062
17·0	2·2	—
33·0	2·5	0·000492
67·0	2·7	0·000192

The salts present in the red corpuscles, however, produce clumping up to about 2·5 molecules on the average, and above this figure CO_2 has relatively little effect. It is clear that the salts add stability to the whole system. The question is : Can the effect of acids in the quantities present in blood alter the degree of clumping of the hæmoglobin molecules in the red corpuscle to an extent which can be measured quantitatively ? This is a matter which can only be settled by experimental determination.

Fig. 21 shows three dissociation curves of blood, these curves have the following values of K and n from left to right :—

TABLE XXXVIII.

CO_2 pressure at which curve was determined.	3 mm.	20 mm.	90 mm.
n	2·5	2·5	2·5
K.	0·00130	0·000505	0·000135

The argument centres about the distribution of the points determined experimentally with reference to the last of the three curves. Those determined at a low oxygen pressure tend to fall below the curve, whilst those at higher oxygen pressures such as 62 mm. tend to fall above it. The value of K for each of the four points given in the figure, on the assumption that n is constant, works out as follows :—

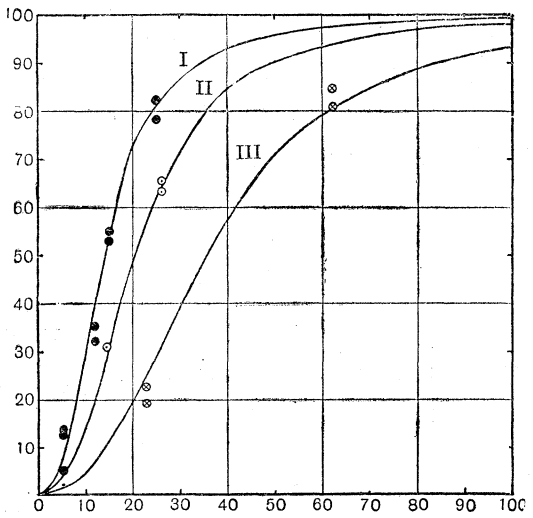

FIG. 21.

TABLE XXXIX.

Pressure of oxygen .	62	62	23	23
Percentage saturation .	81	84·5	22·5	1·7
K	0·000135	0·000180	0·000112	0·00093
Mean K	0·000158		0·000106	

Note then :—

(1) The apparent values of K obtained from the points at 62 mm. oxygen pressure are higher than those obtained at 23 mm. pressure, and consequently

(2) The mean of those obtained at high oxygen pressures is above 0·000135, whilst the mean of those obtained at 23 mm. is below 0·000135.

There is nothing at all remarkable about the distribution of the points with reference to a single set of determinations. The remarkable point is that this distribution takes place in the case of every set of determinations which has been made in which the mean value of K is 0·000135 or less.

Another instance of the same distribution is to be found in the published determinations of the dissociation curve of DOUGLAS' blood in the presence of considerable quantities of acid. This may be seen in fig. 22, A and B. There the points shown are either in the presence of 41 mm. CO_2+0·075 lactic acid or drawn at the Alta Vista hut (and therefore containing considerable quantities of adventitious acid) exposed also to 41 mm. CO_2. The heavy line is the line drawn by free-hand through the points copied from figs. 6 and 7, p. 52, of the 'Journal of Physiology,' vol. 42. The dotted line is drawn from the equation—

$$y/100 = \frac{Kx^n}{1+Kx^n}.$$

$$n = 2{\cdot}5, \qquad K = 0{\cdot}000135.$$

The apparent values for K if worked out for each point separately would, on the whole, decrease with decreased oxygen pressure.

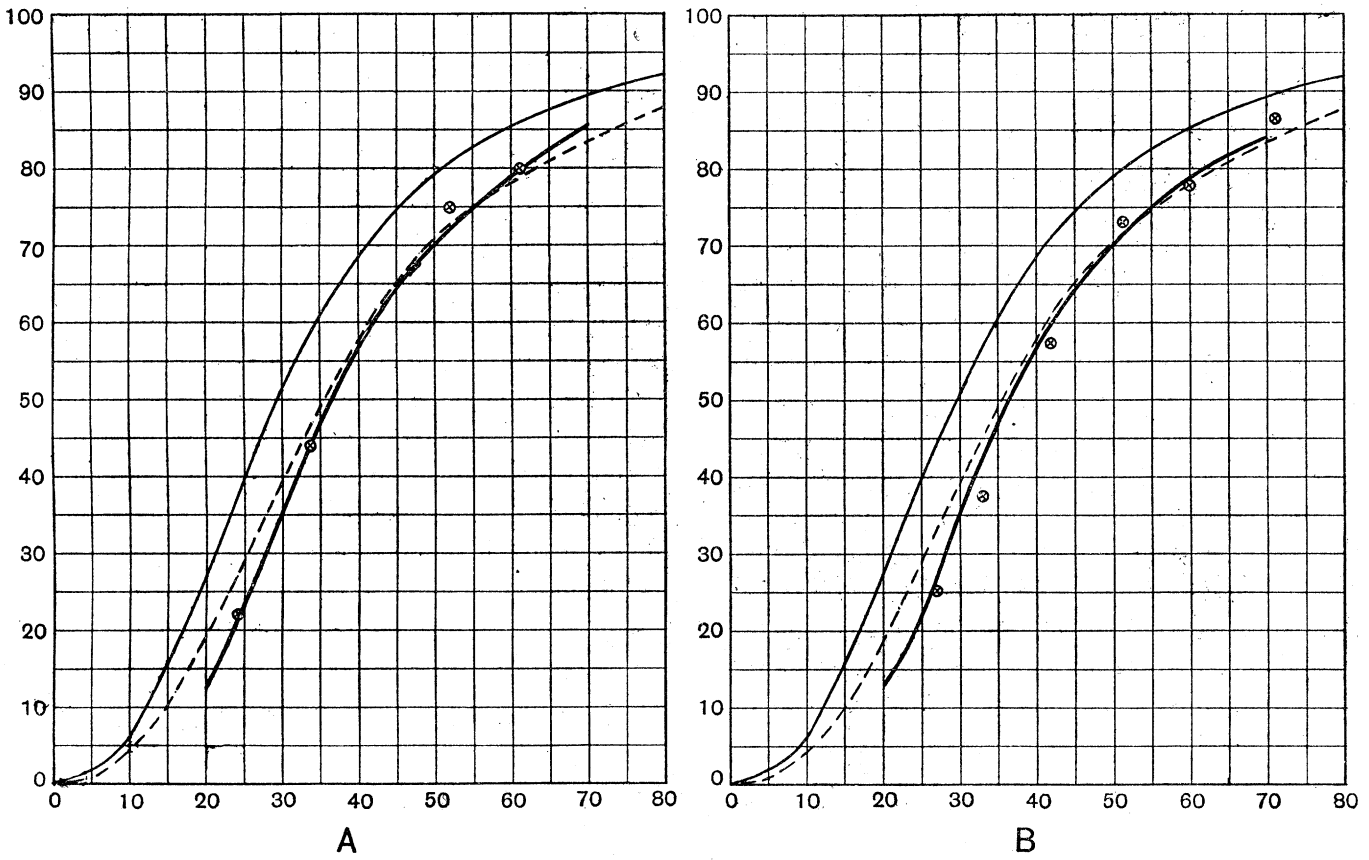

FIG. 22.

Apart from the data acquired on Monte Rosa and those given above, two other observations are relevant, those made by HALDANE, HALDANE, and DOUGLAS on the effect of CO_2 on the carboxyhæmoglobin dissociation curves, and some made by me upon patients of Dr. LEWIS at University College Hospital. The former are particularly valuable because the method by which the percentage saturations were obtained (that of carmine titration) is so different from that by which the percentage saturation of oxygen was determined in my own experiments on oxyhæmoglobin dissociation curves.

The observations made at University College Hospital on patients who were very meionectic were as follows :—

(1) H. C., April 8—

Pressure of oxygen . . .	37·7	37·7	32·0	32·0
Percentage saturation . .	52·0	48·5	34·0	29·0
K (apparent)	0·000124	0·000107	0·000089	0·000070

(2) C., February 5, 1913—

Pressure of oxygen . . .	40·0	27·0
Percentage saturation . .	63	26
K (apparent)	0·000164	0·000090

The following points are those of the cases of meionexy observed on Monte Rosa in which the mean value of K is 0·000135 or less, n being taken as 2·5 :—

(1) BARCROFT on arrival at the Margherita Hut (K = 0·00013).

Oxygen pressure	39	37	27	27
Percentage saturation . .	56	53	32	28
K (apparent), $n = 5$ . . .	0·000135	0·000130	0·000121	0·000103
	0·000133		0·000112	

(2) ROBERTS on arrival at the Margherita Hut.

Oxygen pressure	59	40	21
Percentage saturation . .	82	57	14
K (apparent), $n = 2{\cdot}5$ . .	0·00017	0·00013	0·00006

It is impossible to escape the conclusion that the dissociation curve of blood which is very meionectic crosses the curves drawn from the formula

$$y = \frac{Kx^n}{1+Kx^n}, \quad \text{where } n = 2{\cdot}5,$$

assuming that the two curves cross at about 50-per-cent. saturation. The interpretation to be placed upon this crossing is that n is greater than 2·5.

We may then proceed to enquire what values of n would furnish correct curves in the last two cases cited.

The points determined on ROBERTS' and my blood when we reached the Margherita Hut fall on curves with the following constants :—

Blood on arrival at Margherita Hut.

Subject.	n.	K.	log K.
Barcroft. . .	2·9	0·000029	$\bar{5}$·4634
Roberts. . .	3·0	0·000019	$\bar{5}$·3161

These curves are shown in figs. 23 and 24 ; with them are shown—first, the normal (mesectic) dissociation curves of the two individuals ; and, secondly (dotted), the dissociation curves which would have occurred if there had simply been a change in the value of K without any change in the value of n. In the latter case it has been assumed that these hypothetical curves and the actual ones cross at about 50-per-cent. saturation.

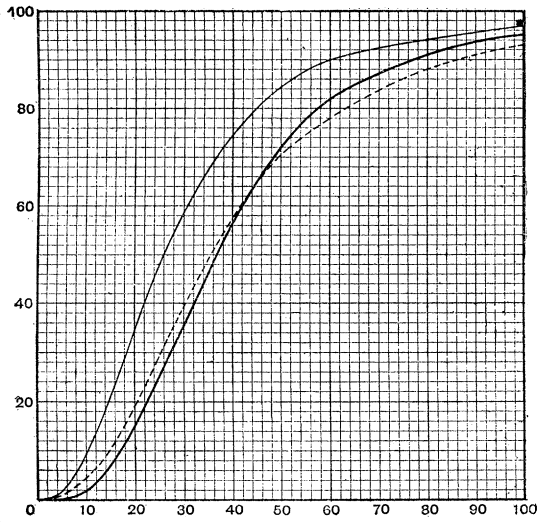

FIG. 23.

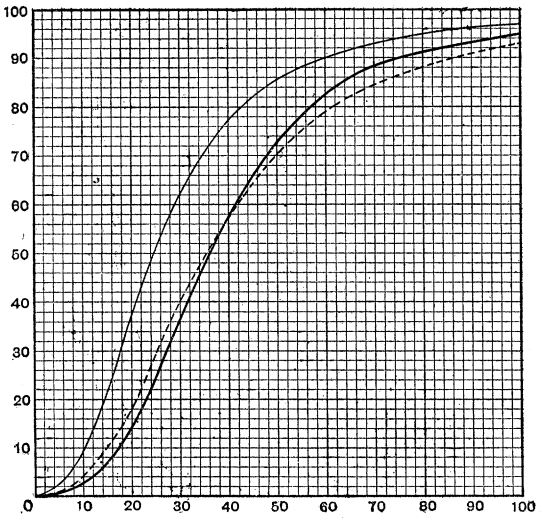

FIG. 24.

FIG. 23.—Thick line: dissociation curve of BARCROFT'S blood on arrival at Capanna Margherita, $n = 2{\cdot}9$, K = 0·000029. Dotted line: $n = 2{\cdot}5$, K = 0·00013. Thin line: mesectic curve.

FIG. 24.—Thick line: dissociation curve of ROBERTS' blood on arrival at Capanna Margherita, $n = 3{\cdot}0$, K = 0·000019. Dotted line: $n = 2{\cdot}5$, K = 0·00013. Thin line: mesectic curve.

The Significance of the Possible Aggregation of the Hæmoglobin Molecules.

The effect of aggregation is to increase the percentage saturation corresponding to any given pressure at oxygen pressures above about 35–40 mm., and to increase the pressure corresponding to a given percentage saturation at below 35–40 mm. In both cases the effect is beneficial to the process of respiration. The former effect would not appear to be very important, since the alveolar oxygen pressure of the persons in question was only about 50 mm. at the Margherita Hut. If further research substantiates the view of HALDANE and his collaborators, that there is oxygen secretion at high altitudes, this part of the curve would acquire importance, and would form an adaptation whereby the efficiency of the secretory system was increased. Moreover, the same changes in the curve may take place in violent exercise, in which case the upper portion of the curve is important. The chief interest in the change produced is its bearing on tissue respiration. Some blood taken from a vein in CAMIS' arm at the Margherita Hut proved on analysis to be 10 per cent. saturated with oxygen. If the heavy line in fig. 24 were to represent the dissociation curve, the oxygen pressure corresponding to this saturation would be 18 mm. Therefore, assuming that the pressure in the tissue was nil, the minimal difference of pressure between the oxygen in the plasma of the capillary blood and that in the tissues was 18 mm. The amount of oxygen which diffuses out from the capillary in a given time depends upon the difference of oxygen pressure within and without the capillary, the same quantity of oxygen then could diffuse out under the circumstances at the Capanna Margherita as would diffuse out from

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capillary when the oxygen pressure in the vein was 18 mm., whatever the percentage saturation might be. In the case of normal blood (CAMIS, ROBERTS) the percentage saturation at 18 mm. is about 30 per cent.

We may arrive at some idea of the effect of the adaptation which has taken place by instituting the following direct comparison of figures taken from analyses of ROBERTS' blood on arrival at the Margherita Hut and under more normal conditions, say at Col d'Olen; we will assume (1) arbitrarily that in each case oxygen is removed from the blood to the extent of 55 per cent. of the total oxygen capacity; (2) that the venous blood is 10 per cent. saturated at the Margherita and 30 per cent. saturated normally; and (3) that the arterial blood is, therefore, 65 per cent. saturated at the Margherita Hut and 85 per cent. saturated at Col d'Olen. The following would be the corresponding pressures at the arterial and venous ends of the capillary in each case :—

	Percentage saturation.		Corresponding pressures.		Mean.
	Art.	Ven.	Art.	Ven.	
	per cent.	per cent.	mm.	mm.	mm.
Arrival at Margherita . . .	65	10	45	10	23
Leaving Col d'Olen	85	30	50	10	25

The capillary pressure would be practically the same in each case and therefore the tissues would be in as strong a position to get the amount of oxygen stated in the one case as in the other. So far as tissue respiration was concerned, therefore, the conditions obtaining at Col d'Olen would only prove advantageous in so far as they enabled the blood to yield up more than 55 per cent. of its oxygen, for this is about the maximum amount with which it could readily part at the Margherita Hut. Below 10 per cent. the blood would be reduced with considerable difficulty, whilst it would not get oxidised much above 65 per cent., the alveolar pressure of oxygen being 48 mm. in ROBERTS' case at the Margherita Hut.

However interesting the aggregation of the hæmoglobin molecules may be as leading to an adaptation for the purpose of facilitating respiration, it is evident that the phenomenon of aggregation, if it exists at all, has a much more far reaching interest than this. So far as we know the acid causes aggregation of the molecules of hæmoglobin to take place in virtue of the fact that these molecules are protein molecules. There is no reason to suppose that they stand alone among the proteins of the body in respect of the effect of reaction upon them. Presumably their aggregation is typical of some other proteins, whilst in others under conditions of acidosis the aggregates would break down. We have a picture before us then of a change permeating the whole system; where there was an average of 2·5 molecules in clump before

there are now 3, where there were 3 clumps there are now but 2·5; every functional process that is communicated by the impacts of the clumps must be altered, for if there are fewer clumps there will be fewer impacts, but this is not all, for the velocity of movement of each clump will be in inverse proportion to the square root of its mass; the number of impacts will therefore receive a further diminution owing to the reduced velocity of the clumps. Something of this kind may be going on more or less everywhere. Little wonder then that acid intoxication brings abnormal phenomena in its train. We are in the dark as to whether such a phenomenon as the conduction of the cardiac impulse down the bundle of His is something propagated from molecule to molecule, but at least we cannot be surprised that, other things being equal, the A–V interval should be prolonged by acid; we are in the dark as to whether the tone of the heart is dependent upon the contiguity of the molecules, but we cannot be surprised that acid should cause this tone to relax if the number of clumps decreases and each becomes further removed from its neighbour; we are in the dark as to whether the acuteness of the mental processes is dependent upon the correct number of clumps in the nerve cell vibrating at the correct speed, but we cannot affect surprise if the finer cerebral functions become dulled—as indeed they do—when the molecules become inert and the number of vibrating aggregates becomes diminished. We must not, however, push the theory of aggregation too far, and our last word in this section must be one which distinguishes fact from hypothesis. The determinations stand, whatever construction be put upon them. The curves given express the properties of hæmoglobin in relation to oxygen, and their physiological significance, as regards respiration, is independent of theory. The formula $y/100 = Kx^n/(1+Kx^n)$ fits the known curves, and therefore provides a useful method of notation, but the assumption that n represents the mean number of molecules in a clump is hypothesis.

Summary.

1. Although there is a marked fall in the CO_2 pressure at high altitudes the blood does not become pleonectic. This fact is due to an acidosis, the specific nature of which has not been completely discovered at altitudes below 10,000 feet, though it is in part a lactic acidosis, but above 10,000 feet is largely a lactic acidosis. It is probable that the acidosis which takes place below 10,000 feet is less due to any acid abnormal in kind than to a fresh adjustment of the usual acid and basic radicals. This readjustment is probably set up by the kidney.

2. The question of whether the blood becomes meionectic at high altitudes is more difficult to answer. The mean of over 20 observations on different persons at rest, taken at and above 10,000 feet, indicates a trifling degree of meionexy which corresponds to a diminution of 7 per cent. in the equilibrium constant of the reaction $Hb_n + nO_2 \rightleftarrows nHbO_2$; or, when applied to Barcroft's blood, of 0·03 in the exponent

of the hydrogen-ion concentration. This very trifling departure from the mesectic condition would, according to HALDANE and his colleagues, suffice to explain the increased pulmonary ventilation.

3. Sustained exercise causes meionexy, in spite of a fall in the alveolar carbonic acid pressure. The exercise consisted in climbing 1,000 feet. The degree of meionexy and the degree of acidosis depended upon the rate of the climb. Estimations of lactic acid in the blood showed that the acidosis was entirely a *lactic* acidosis. Relatively little lactic acid was secreted in the urine, the acid therefore accumulated in the blood, displacing the carbonic acid. The degree of meionexy observed in BARCROFT's blood corresponded to a change in P_H from $-7{\cdot}29$ to $-7{\cdot}09$ when the climb was made in 30 minutes, and to $-7{\cdot}22$ when the climb was made in 45 minutes.

4. At high altitudes the effects of exercise are the same as at low ones, namely, meionexy and acidosis. The acidosis is, moreover, entirely a *lactic* acidosis; but, on account of the altitude, a relatively small amount of exercise produces a given degree of meionexy; the lactic acidosis is very evident, even as the result of a quite slow ascent, and, being cumulative, a long slow ascent at high altitudes produces marked symptoms.

5. An acidosis, so marked, may produce an appreciable aggregation of the molecules of hæmoglobin, and doubtless, therefore, of other protein molecules in the body. It is by no means improbable that many of the functional abnormalities of the mind and of the body which are observed at high altitudes are referable to this result of acid intoxication.

6. The acidosis produced by residence at high altitudes to some extent outlasts the residence.

7. The meionexy which takes place during exercise forms a physiological adaptation by which the blood can be more easily reduced in the capillary tissues and the oxygen can diffuse more rapidly from them. This adaptation is heightened by the degree of aggregation of the molecules of hæmoglobin which we observed.

We would like to take this opportunity of thanking the Royal Society and the British Association for grants which defrayed the expenses of the expedition, and also the former for placing their tables in the Col d'Olen Laboratory at our disposal.

Our thanks are due in an especial degree to Professor ADUCCO, who allowed the expedition to use the laboratory at Pisa as a base. He placed the whole laboratory and its staff of attendants at our disposal—a kindness which enabled us to get through a great deal of work in the short space of time at our disposal.

The Italian and French Ambassadors in London most kindly passed our boxes through the custom-houses of their respective countries; our apparatus, therefore, arrived in Italy intact—another great saving of our time and resources.

Lastly from Professor AGGAZZOTTI and from all at Col d'Olen, whether officials in

the laboratory or otherwise, we received a helping hand and we have carried away the happiest and most grateful memories.

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