VI. *Physiological Observations made on Pike's Peak, Colorado, with Special Reference to Adaptation to Low Barometric Pressures.*

By C. Gordon Douglas, *B.M., Fellow of St. John's College, Oxford;* J. S. Haldane, *M.D., LL.D., F.R.S., Fellow of New College and Reader in Physiology, Oxford;* Yandell Henderson, *Ph.D., Professor of Physiology, Yale University Medical School; and* Edward C. Schneider, *Ph.D. (Yale), Professor of Biology, Colorado College.*

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Contents.

I. *Object and Organisation of Expedition, and General Conditions on the Summit of Pike's Peak.*

The Anglo-American Pike's Peak Expedition, 1911, of which we propose to give the scientific results, was planned by members of Oxford and Yale Universities, with the main object of making a thorough study of physiological adaptation to low atmospheric pressures.

It was decided to make all the observations on Man, as the conditions of respiration

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and the blood changes can be studied more satisfactorily in man than in animals. It was also essential that the physiological conditions, apart from the reduced atmospheric pressure, should be normal as far as possible, and that the observations should be continued over a considerable period. After considering the advantages and disadvantages of making the experiments in the Alps, Andes, or Himalayas, we selected Pike's Peak, Colorado, as it seemed preferable in several very important respects. The Peak is practically free from snow in summer: there is a substantial house on the summit, in which we were offered excellent accommodation; and a cog-wheel railway which ascends the mountain afforded easy transport for apparatus and supplies, and communication with the scientific laboratories at Colorado College, Colorado Springs, only about 14 miles distant. A further advantage was that large numbers of people came up daily during the summer, and furnished ample opportunities for observing the symptoms of mountain sickness in unacclimatised persons, while several persons living on the summit, besides ourselves, were available for studying the effects of acclimatisation.

In connection with the work on Pike's Peak Miss M. PUREFOY FITZGERALD carried out an extensive series of observations in towns and at mines in the surrounding districts, on the blood and alveolar air of persons living at different altitudes. The results are given in a succeeding paper, and will be referred to incidentally in the present paper. Dr. GERALD WEBB, of Colorado Springs, has kindly contributed a short appendix on the results of examinations of blood-films from members of the expedition; and in another appendix are given the results of a very interesting series of hæmoglobin determinations made at the suggestion of one of us by Mr. J. Richards, mining engineer, in connection with a journey from England to the Tatoral Mine (altitude 15,000 feet), Pazna, Bolivia, of which he was general manager.

Towards the expenses of the expedition substantial contributions were made by the Council of the Royal Society from the Donation Fund, and by Yale University from the Loomis Medical Research Fund. Part of the apparatus was purchased from a grant made to one of us from the Government Grant Fund administered by the Royal Society.

The natural summit of Pike's Peak is 14,109 feet above sea-level. The floor of our working room was 14,093 feet above sea-level; and during our stay the mercury barometer which we carried up with us registered from 452 to 462 mm. (17·8 to 18·2 inches). The mountain is situated on the Eastern side of the Rocky Mountain range, near Colorado Springs, and within sight of Denver. It stands out prominently, overlooking the prairie, which extends eastwards. The Ute Pass, through which lay the track used by the pioneers of Californian gold mining, winds round its base, and Pike's Peak came to be a famous landmark, as it could be seen from great distances across the dry and almost desert prairie which had to be traversed in the old "prairie schooners." "Pike's Peak or bust" is a well-known American motto. The peak is named after Lieutenant Zebulon M. Pike, who discovered it in 1806, and, after failing in

all attempts to ascend it, is said to have reported that "no human being could ascend to its pinnacle."

Fig. 1 shows the house and tower on the summit, with the terminus of the cog-wheel railway. Mr. J. G. Hiestand, proprietor of the house, placed at our disposal

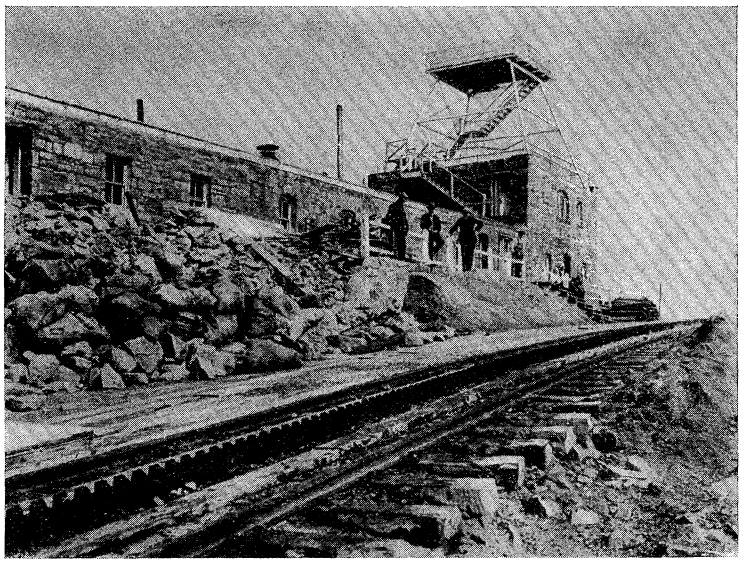

Fig. 1.
The Summit House and terminus of the cog railway.

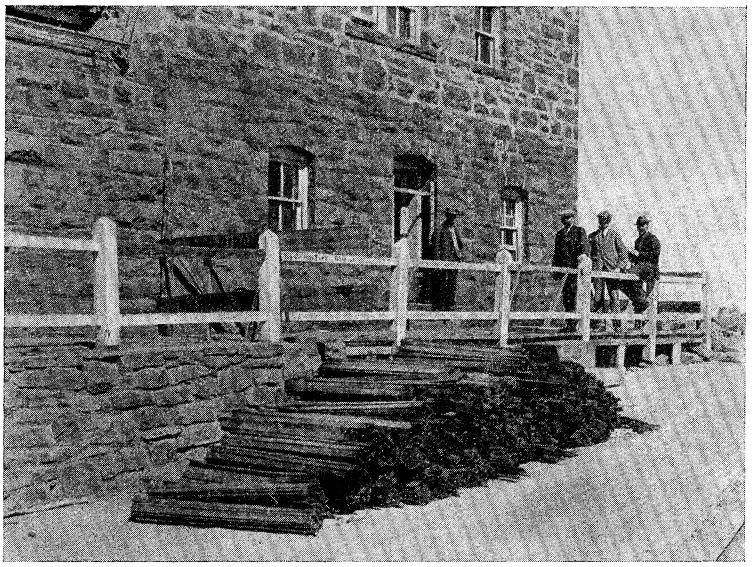

Fig. 2.
Exterior of our laboratory.

four rooms on the ground floor beneath the tower, with a separate private entrance. The largest of these rooms was fitted out with shelves, tables, and electric light to serve for a laboratory. The exterior and interior are shown in figs. 2 and 3.

The whole summit of Pike's Peak is covered with broken granite, through which the track of the cog-wheel railway has been cleared. There is also a rough track formerly used for wheeled vehicles and now employed by pedestrians and riders on donkeys. The gradient on the railway track as it approaches the summit is 1 in 4,

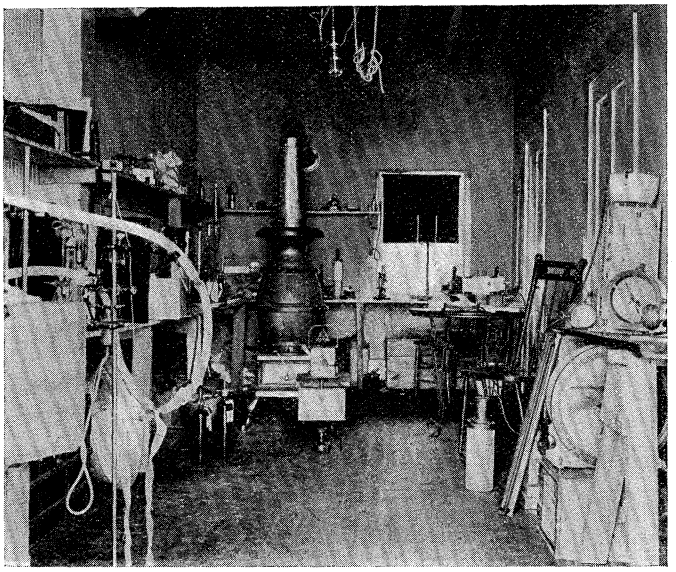

Fig. 3.
Interior of our laboratory.

but at the summit for about 50 yards the track is practically level. Both the level piece and the steep gradient were of great use for experiments, in which the absence of snow was a great advantage.

During the summer two or more car-loads of passengers come up by the railway twice a day, and once a week cars arrive just before sunrise. In addition a number of persons walked up or came on donkeys, arriving at all times of the day and night, and in all varieties of weather. The Summit House is organised as a restaurant, with sleeping accommodation for a few visitors.

After making some preliminary observations in the Biological Laboratory of Colorado College, for which purpose we stayed about five days at Colorado Springs (altitude 6,000 feet), we proceeded to the summit by the cog-wheel railway on July 12, and stayed till August 16. During this period the weather was fine on the whole, but with frequent showers of hail or snow, usually accompanied by thunder-storms—many of them rather violent: electrical disturbances were very prominent. During our stay balls of fire were several times seen in or about the house: the telephone wires were fused, and we frequently observed electrical discharges from our heads or from the hands when held upwards. No injury has been done as yet to any-one in the house by lightning. Except for some permanent patches, snow never lay on the ground for more than a few hours. At night the temperature nearly always

fell to below freezing point. The days were, however, fairly warm, with a shade temperature averaging about 50° F. Our room was comfortably warmed by a stove, and we did not even find it necessary to wear winter clothing.

The *cuisine* was excellent, with an ample supply of fresh meat, vegetables, and fruit; and the discomforts or hardships usually associated with a stay on the summit of a high mountain in other parts of the world were entirely absent. The conditions under which we lived were thus as nearly normal as possible. The experiments kept us well occupied, but time was left for occasional walks on the neighbouring hill-tops.

We wish to take this opportunity of offering our very hearty thanks to Mr. C. W. Sells, President of the Manitou and Pike's Peak Railway, for many facilities freely granted to the expedition; and to Mr. J. G. Hiestand, proprietor of the Summit House, for much kind hospitality and help. We are also indebted to Mr. H. Robison, resident manager at the Summit House, for his constant care during our stay.

On August 16 we descended to Colorado Springs, and stayed there for about a week, making frequent observations at the Biological Laboratory of the College on the changes following the descent. From August 27 to September 6 three of us continued these observations at New Haven in the Physiological Laboratory of Yale Medical School, and some further experiments were made by two of us after reaching Oxford on September 13th. Control experiments were made at Oxford and New Haven both before and after the Expedition.

We are particularly indebted to scientific and other friends at Colorado Springs for their hospitality and help in furthering the objects of the Expedition—in particular to President W. F. Slocum and Prof. W. Strieby, of Colorado College, and to Dr. Gerald Webb. Mr. J. E. Fuller, who was at the time working in Dr. Webb's private laboratory, most kindly volunteered to act as a subject of experiment on the Peak during several days, and in this way enabled us to obtain an extremely important result: he came to the summit knowing from previous experience that he would suffer from mountain sickness.

II. *Symptoms observed on Pike's Peak.*

In describing the abnormal symptoms observed on Pike's Peak we may begin with ourselves. We reached the summit about 11 a.m. on July 12, the journey up from Manitou (a rise of 7,485 feet) occupying $1\frac{1}{2}$ hours. During the journey up we noticed little or no discomfort; but on leaving the train we all became unusually breathless on moving about, unscrewing the cases of apparatus, &c. The ordinary breathing was also noticed to be more or less periodic in Douglas, Haldane, and Henderson, but not in Schneider. In all of us the lips, &c., had become more or less blue, this change in colour being quite marked. The symptoms observed in each of us were as follows :—

DOUGLAS.—Slight headache observed in train. This gradually increased after arrival, but did not prevent work. Took a little supper in spite of some nausea. Breathing more or less periodic. Next morning he awoke early with headache, throbbing of the temporal vessels, nausea, and abdominal discomfort, and vomited twice. He was quite disabled and had to remain in bed most of the morning, eating nothing, and looking blue and ill. Next morning headache and depression still very severe, but became less about midday, and in the afternoon he was able to do an experiment. During next night the headache disappeared completely and did not return. Colour of lips, &c., also became quite normal again, and no further symptoms (except unusual hyperpnœa on exertion) were subsequently noticed.

HALDANE.—On evening of arrival suffered from nausea, could not take food, and had some diarrhœa and abdominal pain, but slept well and was quite fit next day, though he still had some diarrhœa and could not eat much. Breathing often more or less periodic for some days. The hyperpnœa on exertion seemed to diminish after the first day or two, but remained excessive. The colour of lips, &c., soon became very good, and better than usual.

HENDERSON.—Felt some "tightness" in the head on the day of arrival, and developed a marked tendency to periodic breathing. Otherwise was very little affected, and had no nausea, but some diarrhœa. Colour of lips gradually became normal after several days, and breathlessness on exertion also diminished somewhat. The tendency to periodic breathing became gradually much less during the day but continued more or less during sleep. Even at sea-level, however, periodic breathing often occurs in HENDERSON during sleep, and can be very readily induced experimentally during waking hours.

SCHNEIDER.—Soon after arrival began to suffer from headache, accompanied by nausea. No periodic breathing. Headache very severe during the night, next day, and the succeeding night and day, and night. After this the headache disappeared during the day, but reappeared at night until the night of the 18th, when it finally disappeared. The headache was accompanied by throbbing and accelerated pulse, very noticeable at night. On the 18th some periodic breathing was noticed, but it never returned. Colour of lips gradually improved and became normal.

After the first few days we all felt particularly well, slept well and soundly, and had good appetites. Mental work seemed quite as easy as at sea-level, but excessive breathlessness on any considerable exertion remained a prominent symptom. Our weights tended to fall somewhat: DOUGLAS, who weighed (stripped) 140 lbs. before the ascent, lost 6 lbs. on Pike's Peak, mostly in the first three days; HALDANE, who weighed 175 lbs., gradually lost 8 lbs.; HENDERSON, who weighed 155 lbs., gradually lost 6 lbs.; while SCHNEIDER, whose weight was not taken before the ascent, remained about constant at 113½ lbs. from July 16th onwards.

During our stay on the summit several friends or other visitors came up and stayed the night. They all showed more or less blueness of the lips, and most of them

experienced headache, nausea, or actual vomiting by next morning. Similar symptoms were observed during the first day or two in the cases of several workmen who came up for the first time.

Among the numerous visitors who came up by train and stayed only about three-quarters of an hour the most marked, and almost universal symptom was blueness of the lips, cheeks, &c., accompanied by great hyperpnœa on exertion. As a rule there was no marked discomfort, but some persons became very miserable and faint, and actual fainting was observed occasionally, as well as vomiting. One press representative who came to "interview" us became so alarmingly blue and faint that we gave him oxygen, which revived him at once and immediately restored his colour and spirits. He continued all right for a few minutes, and then again became blue and faint, and was again completely revived by the oxygen, after which he hurried into a descending train. In the case of two friends who stayed several hours severe headache developed on the way down and continued till night.

Fig. 4.

The terrace outside the Summit House at sunrise. The remnant who were able to watch the sunrise out of about two hundred tourists who had come up for that purpose.

Among those who walked up, or came on donkeys, the symptoms were much more general and severe. The blueness was more marked, and nausea, vomiting, headache, and fainting were extremely common. Many persons walked or rode up during the night to see the sunrise, especially on Sunday morning, and the scene in the restaurant and on the platform outside can only be likened to that on the deck or in the cabin of a cross-channel steamer during rough weather. The walkers straggled in one by one, looking blue, cold, exhausted and miserable, often hurrying out again to vomit. Some lay on the floor, blue and faint. Others were able to swallow some coffee, but very few had the heart to look at the magnificent sunrise. Fig. 4 shows the remnant who

remained outside at sunrise out of about 200 who had come up on donkeys or walking on a Sunday morning. Most of those who walked were quite inadequately clad and shod, and had come from towns on the plains, so that they were wholly unfit for such a climb, and had evidently started with no idea of the cold, or of the exhaustion and breathlessness caused by a climb of 14,000 feet. They had often taken 10 or 12 hours to get up from Manitou. Among them were many old men and quite young children, besides many women. All seemed equally reckless of the difficulties and hardships. It appeared extraordinary that deaths on the journey or on the summit were practically unknown.* One alarming case of a woman who became unconscious during the ascent occurred during our stay, but she was brought down in a special train and recovered under medical care. We saw several alarming cases of persistent fainting; but all recovered after a time. Bleeding from the nose, &c., has sometimes been described as a symptom of mountain sickness; but we did not observe any case of bleeding.

Among healthy persons it appeared to be invariably the case that after a stay of two or more days on the summit the blueness, headache, nausea, lack of appetite, &c., completely disappeared, while the excessive hyperpnœa on exertion became less. It was thus perfectly clear that acclimatisation to the low pressure occurred to a very marked extent. Mr. Robison, the resident manager of the Summit House, had performed the remarkable feat of walking from Manitou to the summit up the track in 2 hours 31 minutes. The distance is 8·9 miles and the rise 7,485 feet. His weight was 156 lbs., so that in spite of the rarefied atmosphere he had in this ascent on an average ascended 49·6 feet per minute and performed $49{\cdot}6 \times 156 = 7{,}730$ foot pounds of lifting work—a remarkable enough performance even at sea-level. For unacclimatised persons the time needed was usually three or four times as long, and towards the summit progress became extremely slow. Those living on the summit could easily pass all new-comers in ascending the track, and on the last quarter of a mile, where the gradient was 1 in 4, we often found persons who looked so blue and seemed so helpless that in sheer pity we pulled them up to the summit.

On account of the absence of snow we were only slightly troubled by irritation of the eyes due to the excess of actinic rays in the light: nor did we observe this symptom to any marked extent in others. Dryness and cracking of the lips and nose, due to the increased rate of breathing and evaporation in the rarefied atmosphere, were often observed.

III. *Cause of the Symptoms of Mountain Sickness.*

There is not now any room for doubt that the essential cause of all the symptoms described above, and popularly known as "mountain sickness," is lack of oxygen.

* The above sentence was written during our stay on the Peak. Five days after we left it two persons, a printer and his wife, from a town in Texas, perished in a snowstorm during the ascent; they were quite inadequately clad and had lain down exhausted about half a mile from the summit, at the side of the railway track, where their bodies were found next day, covered with snow.

The probability of this explanation was first clearly pointed out by JOURDANET, but it was PAUL BERT* who furnished clear experimental proof that the abnormal symptoms and dangers associated with low barometric pressure depend, not on the diminished mechanical pressure, as was often supposed, but on the diminished partial pressure of oxygen, and consequent imperfect æration of the arterial blood with oxygen. It may be useful to summarise very briefly his main results bearing on this question.

By varying both upwards and downwards the total atmospheric pressure and the respective percentages of oxygen and nitrogen in the atmospheres breathed by animals and men, he found that while the partial pressure of nitrogen might be increased or diminished indefinitely without effect, definite symptoms of want of oxygen began to appear whenever the partial pressure of oxygen was reduced below a certain limit. Thus at ordinary atmospheric pressure a cat died when the proportion of oxygen was reduced to about 4·5 per cent.,† or a partial pressure of 4·5 per cent. of an atmosphere. At a barometric pressure of half an atmosphere, on the other hand, the animal died when the oxygen was reduced to about 9 per cent., which is again 4·5 per cent. of an atmosphere; and at two atmospheres pressure a reduction of the oxygen percentage to 2·25 per cent. was needed. By experiments with oxygen, carbon dioxide, nitrous oxide, &c., he established the general law that the physiological action of a gas depends upon its partial pressure. He further showed that the percentage by volume of oxygen which blood takes up, either in the lungs or outside the body, depends upon the partial pressure of oxygen and is greatly reduced when the reduction in oxygen pressure becomes dangerous. He was the first to obtain approximately correct data as to the dissociation curve of oxyhæmoglobin in blood at the body temperature. It is remarkable that in this respect his data were much more nearly correct than those subsequently obtained by HÜFNER, whose mistaken conclusions, afterwards rectified by ZUNTZ, LOEWY, BOHR, and BARCROFT, made it for long very difficult to form a coherent theory of mountain sickness.

PAUL BERT concluded that all the symptoms of mountain sickness are simply those of want of oxygen; but several subsequent observers have questioned this conclusion, and attributed the symptoms to other causes, in whole or part. Mosso, for instance, has supposed that lack of carbon dioxide ("acapnia") is a cause of many of the symptoms, and KRONECKER has even invoked mechanical factors as a cause. We hardly think it necessary to refer in detail to these theories, which are undoubtedly incorrect. A full and very clear discussion of them by ZUNTZ and his co-workers has recently been published.‡ It will also be seen in the sequel that every new fact recorded by us is in harmony with JOURDANET'S and PAUL BERT'S explanation.

* 'La Pression Barométrique,' 1878.

† The experiments were made in presence of a high percentage of CO_2, and BERT was not aware of the influence of this CO_2 in averting death from want of oxygen.

‡ ZUNTZ, LOEWY, MÜLLER, and CASPARI, 'Höhenklima und Bergwanderungen,' Berlin, 1906.

The symptoms of want of oxygen, as observed on high mountains, are very similar to those produced by want of oxygen in other ways. The similarity to the symptoms of carbon monoxide poisoning is specially striking.* The headache, throbbing, nausea, vomiting, fainting, &c., of mountain sickness are all experienced in carbon monoxide poisoning, all of the symptoms of which have been shown to be due to want of oxygen and nothing else. When only slight and temporary lack of oxygen is produced by carbon monoxide the headache and nausea often come on after the carbon monoxide has mostly disappeared from the blood, *i.e.*, after a practically normal supply of oxygen to the tissues has been re-established. We were interested to find, from the experience of several friends, that severe headache frequently appeared on going down by train after a stay of 3 or 4 hours on the summit of Pike's Peak.

In carbon monoxide poisoning the psychical disturbances produced by want of oxygen are often almost as prominent as in alcoholic poisoning. In high balloon ascents similar disturbances of mental equilibrium and power of judgment seem to occur. It was somewhat difficult to judge to what extent the persons who ascended Pike's Peak were affected psychically, but it seemed to us that in all probability many of them were so affected. The number of people who in one way or another were inclined to be unreasonable seemed, at any rate, to be unusually great, and the duties of those in charge of the Summit House were, in consequence, by no means easy. For this reason a deputy-sheriff was stationed at the Summit House during the summer.

When men or animals are rapidly subjected to atmospheres deficient in oxygen, or at low pressures, marked hyperpnœa is produced, even during rest. The absence of any marked hyperpnœa during rest on high mountains, &c., might, perhaps, suggest that some factor other than want of oxygen is producing the symptoms. It was shown, however, by HALDANE and POULTON† that the marked hyperpnœa of oxygen want is only temporary, and is due to the fact that want of oxygen aids carbon dioxide in exciting the respiratory centre. The effect of this is that for a short time the proportion of carbon dioxide already present in the blood and tissues is more than sufficient to excite the centre normally. When the excess has been got rid of by a temporary hyperpnœa the breathing again becomes quiet; and if the transition to want of oxygen is gradual the temporary marked hyperpnœa is not noticed. Want of oxygen, without the aid of carbon dioxide, does not excite the respiratory centre at all; for YANDELL HENDERSON has shown that after vigorous and prolonged artificial respiration, or hyperpnœa produced by excessive stimulation of afferent nerves, sufficient to remove most of the carbon dioxide from the blood and tissues, animals die from want of oxygen without drawing a single breath.‡

The fact that, besides atmospheric pressure, other factors, such as wind, light,

* The explanation of certain minor peculiarities in the symptoms of carbon monoxide poisoning is discussed by DOUGLAS, HALDANE, and J. B. S. HALDANE in the 'Journ. of Physiol.,' XLIV., p. 293, 1912.

† 'Journ. of Physiol.,' XXXVII., p. 390, 1908.

‡ 'American Journ. of Physiol.,' XXV., pp. 310, 385, 1910.

temperature, muscular exertion, &c., may influence the actual onset of the symptoms of mountain sickness, appears to us to be perfectly intelligible without assuming any other essential cause for these symptoms than want of oxygen. When the symptoms are on the verge of appearing any slight cause may precipitate their actual appearance.

IV. *The Oxygen Pressure of the Arterial Blood on Pike's Peak.*

In giving an account of our experimental investigations it will be convenient to deal first with the partial pressure of oxygen in the arterial blood, as all the symptoms due to diminished barometric pressure depend directly or indirectly upon diminution of arterial oxygen pressure, and consequent imperfect aeration of the arterial blood and deficient saturation of its hæmoglobin with oxygen.

For measuring the partial pressure of oxygen in the arterial blood only two methods have hitherto been employed. One of these is the "aerotonometer" method, first used in a somewhat rudimentary form by PFLÜGER and his pupils, and improved gradually by BOHR, FREDERICQ, and KROGH. In this method a stream of the arterial blood is kept in contact with a limited volume of air, or of a gas-mixture, at the pressure and temperature existing in the lungs, during a period sufficiently long for equilibrium to establish itself between the partial pressures in the gas-mixture and those in the blood, so that from an analysis of this air or gas-mixture the partial pressures of the gases in the blood can easily be calculated. In the apparatus of KROGH only a small bubble of air is placed in the aerotonometer and used for analysis. This greatly adds to the rapidity and accuracy of the experiment.

The other method is the Carbon Monoxide one, employed first by HALDANE and LORRAIN SMITH, and in an improved form by DOUGLAS and HALDANE.* This is the method which we have employed. The following is a short description of it, as applied in its improved form to determinations on Man on Pike's Peak.

A measured volume of CO, sufficient to saturate the subject's hæmoglobin to the extent of about 20 to 25 per cent., is first administered by means of a small apparatus in the course of about 10 minutes. The subject then proceeds to breathe through a mouth-piece and valves into a closed air-space of about 15 litres, arranged on the Regnault-Reiset principle, so that the expired CO_2 is absorbed by potash and the oxygen absorbed is constantly replaced automatically, the result being that the air in the enclosed space remains nearly constant in composition, and is constantly being breathed, over and over again, by the subject. As CO is a physiologically indifferent gas which passes by diffusion into or out of the blood in the lungs, the partial pressure of CO in the air breathed equalises itself with that of the arterial blood in the lung capillaries, and this occurs rapidly as the total volume of air in the apparatus is small. But the partial pressure of CO in the arterial blood depends (1) upon the percentage

* 'Journ. of Physiol.,' XLIV., p. 305, 1912. References to the literature and a detailed discussion of methods will be found in this paper.

saturation of this blood with CO, and (2) upon the partial pressure of oxygen, since oxygen and CO are shared by the hæmoglobin in exact proportion to their relative partial pressures multiplied by a constant. Hence the lower or higher the pressure of oxygen in the arterial blood the lower or higher also will be the pressure of CO in the air breathed, after equilibrium has been established, with a given percentage saturation of the subject's blood with CO.

To determine the actual arterial oxygen pressure a drop of the subject's blood is taken, after the breathing has been continued for 20 minutes or more, and the percentage saturation of this blood with CO determined colorimetrically, in duplicate, with carmine solution. Another small portion of the blood is defibrinated, and 0·05 c.c. spread in a ring on the inside of a saturating vessel, which is then filled with air from the closed air-space, a sample of this air being also taken for analysis. Sufficient CO_2 is then added to make the partial pressure of CO_2 in the saturator equal to that in the alveolar air. The saturator is then placed in a bath at 38°, and rotated for half an hour or more, after the excess of pressure (due to the warming) has been blown off. The percentage saturation with CO of the blood from the saturator is then determined in duplicate, and compared with the percentage saturation of the blood taken direct from the subject. A little consideration will show that if the blood from the saturator is more highly or less highly saturated with CO the oxygen pressure in the arterial blood must be higher or less high than that in the air of the saturator (which is the air which the subject was inspiring); and it is easy, from the results of the two titrations and the determination of the oxygen percentage in the saturator air, to calculate the actual arterial oxygen pressure, since we know that the law of mass action holds good.

For full details of the method, and a discussion of its accuracy, and of that of the aerotonometer method, we must refer to the paper of DOUGLAS and HALDANE. A protocol containing the details of an actual experiment (including also the determination of blood volume, &c., as described in Section IX.) is given at the end of the present section. We may remark that we always added CO_2 to the air of the saturator in order to avoid the corrections discussed at p. 332 of DOUGLAS and HALDANE'S paper*; and we believe that every precaution was taken to ensure accuracy and certainty in each detail of the experiments. The difficulty of keeping the bath at a constant temperature in the absence of gas was overcome by using a "Primus" lamp for heating, with regulation by hand. The oxygen was supplied from an oxylith generator, and was thus absolutely pure. A sample of the alveolar air was taken just before the subject ceased to breathe into the closed space; and samples of the inspired air were also taken at intervals, so that we could be sure of the proper working of the apparatus.

The results of the experiments are given in Table I. It will be seen that there was

* As the oxygen pressures in the arterial blood and in the air of the saturator were high, and nearly the same, these corrections would have been very small in any case.

TABLE I.—Pike's Peak. Arterial Oxygen Tension.

Date.	Subject.	Inspired air. Gases, per cent.						Air introduced into saturator. Gases, per cent.		Alveolar air. Gases, per cent.		Percentage saturation of blood with CO.		O_2 tension of arterial blood in percentage of the existing atmosphere, without allowance for aqueous vapour.	O_2 tension of alveolar air in mm. Hg [at 37° moist].	O_2 tension of arterial blood in m. Hg [at 37° moist].	
		Start.		Middle.		Finish.											
		O_2.	CO_2.	O_2.	CO_2.	O_2.	CO_2.	O_2.	CO_2.	O_2.	CO_2.	*In vivo.*	*In vitro.*				
July 19	C.G.D.	20·43	0·95	20·44	0·87	20·31	0·60	20·05	0·62	13·03	6·91	21·0	22·5	21·9	53·4	89·8	
20	„	18·71	1·65	18·31	1·10	18·93	0·64	18·36	0·74	11·96	6·82	20·5	22·7	20·9	49·0	85·6	
24	„	28·23	2·10	28·21	1·54	28·13	0·95	28·10	0·64	21·13	7·09	19·2	17·5	25·1	88·0	103·6	High O_2 insp.
26	„	32·13	2·25	32·53	0·62	31·75	0·60	31·21	0·42	24·23	7·40	18·15	16·0	26·8	99·3	109·9	High O_2 insp.
Aug. 2	„	21·26	1·63	20·92	2·03	20·83	2·02	20·09	1·68	15·80	6·58	17·5	20·75	24·0	64·6	98·1	Work.
July 21	J.S.H.	22·35	1·45	22·15	1·16	23·18	0·67	23·35	0·43	16·20	6·28	19·35	20·4	24·9	66·8	102·4	
28	„	20·21	2·21	20·41	2·61	20·85	1·70	20·61	1·12	14·81	6·41	19·45	21·0	22·7	60·5	92·8	
Aug. 1	„	15·67	0·51	13·82	0·48	13·25	0·42	12·56	0·39	8·13	4·76	18·3	19·4	13·5	33·2	55·2	Low O_2 insp.
13	„	36·38	1·46	35·29	1·72	36·16	1·38	35·64	1·47	29·20	7·40	19·0	17·3	31·7	120·6	131·0	High O_2 insp.
July 29	Y.H.	20·23	2·12	19·88	2·07	22·13	1·25	20·60	0·99	13·77	6·67	18·0	16·7	18·8	56·9	77·7	
Aug. 9	„	24·33	0·84	23·32	0·72	23·15	0·90	21·78	0·75	16·56	5·86	16·3	18·4	25·3	68·4	104·4	
July 31	E.C.S.	15·77	3·01	16·42	3·00	17·21	1·68	17·48	1·40	10·61	7·61	19·2	21·6	20·3	43·4	83·0	
Aug. 8	„	21·42	1·09	20·64	1·08	20·46	1·07	20·39	0·98	12·70	7·63	18·6	20·8	23·4	52·3	96·4	
Aug. 4	J.E.F.	23·26	1·44	17·30	1·74	21·20 18·63	1·77 1·74*	18·08	1·62	11·16	7·93	12·8	9·5	12·9	45·6	52·7	On arrival.
7	„	18·76	1·90	16·65	2·30	16·13	2·04	16·24	1·57	9·86	7·62	16·75	19·7	19·75	40·7	81·4	

* A fourth inspired air analysis was made in this experiment, as owing to the irregular breathing of the subject the oxygen percentage in this air was varying considerably. The alveolar air should be compared with this fourth sample.

usually about 1 per cent. of CO_2 in the inspired air (and in that introduced into the saturator) at the time when the subject ceased to breathe into the apparatus. This was due to a slight defect in the absorption of CO_2. We did not correct this defect, as its presence made it easier (with the gas-pipette which we were using) to add to the air of the saturator the amount of CO_2 required to make the pressure of CO_2 in the saturator practically equal to that in the alveolar air.

The table gives the results of fifteen experiments on five different subjects—ourselves and Mr. J. E. FULLER. Of these experiments nine may be classified as resting experiments under normal conditions after acclimatisation, the alveolar oxygen pressure being approximately that of normal rest on Pike's Peak, though averaging a little higher. Taking these nine experiments, it will be seen that in every case the arterial is much above the alveolar oxygen pressure. This result is clearly inconsistent with the theory that diffusion alone, apart from active secretion of oxygen inwards, accounts for the passage of oxygen into the blood. The average excess of oxygen pressure in the arterial blood is 35·8 mm. The mean normal resting alveolar oxygen pressure of the five subjects during the period over which the experiments extended was 52·5 mm. Adding 35·8 to this, we reach the result that the mean resting arterial oxygen pressure was 88·3 mm. As the mean alveolar oxygen pressure at or near sea-level is about 100 mm., it appears that the figure for Pike's Peak was only about 12 mm. below normal. The oxygen pressure in pure air warmed to the body-temperature and saturated with moisture was only 85·7 mm., so that the arterial oxygen pressure was slightly above that of the inspired air. At 88 mm. of oxygen pressure the arterial blood would be 95 per cent. saturated, instead of 96 per cent. as at sea level. The perfectly normal red colour of our faces and lips is thus easily intelligible.

Of the other six experiments, three were made with considerably increased percentages of oxygen in the air breathed, our object being to ascertain whether, by increasing the alveolar oxygen pressure, we could abolish the secretory activity of the lungs, and reduce to zero the difference between alveolar and arterial oxygen pressure. In these experiments the average alveolar oxygen pressure was 102·6 mm. or just above normal at about sea-level, and the average arterial oxygen pressure 114·8 mm., or 12·2 mm. higher. The difference was thus reduced to about a third, but not completely abolished. That it should have been abolished completely in the course of about half an hour was, perhaps, hardly to be expected.

In one experiment, as will be seen, the oxygen percentage was reduced, so that the alveolar oxygen pressure was only 33·2 mm. In this experiment the subject was quite comfortable, but there was slight hyperpnœa, as shown by the fact that the alveolar CO_2 percentage had fallen distinctly and the respiratory quotient was high. The colour of the subject's face was also slightly bluish, and he felt somewhat "slack" just after the experiment. The oxygen pressure of the warmed and moistened inspired air was 54·3 mm. (corresponding to a height of about 25,000 feet). The arterial oxygen pressure found was 55·2 mm., or 22 mm. above the alveolar oxygen

pressure. At 55·2 mm. of oxygen pressure the blood would be 85 per cent. saturated, or 11 per cent. less saturated than normal. Assuming that the circulation rate was normal, and allowing for the increased percentage of hæmoglobin in the blood, the venous blood returning to the heart would be about 59 per cent. saturated if we calculate on the probable assumption that under normal resting conditions at sea-level the venous blood is 64 per cent. saturated. But 59 per cent. saturation corresponds to a pressure of 34 mm. of oxygen, which is slightly higher than that in the alveolar air. In this experiment, therefore, the oxygen was apparently passing in *against* diffusion pressure during the whole time of the passage of the blood through the lung capillaries.

In another experiment the subject was working with one arm. The work raised the oxygen intake (which was measured) in the proportion of 1 : 2·1. The work apparatus was the same as that described by DOUGLAS and HALDANE in the paper already referred to, and was loaded with a piece of granite. It will be seen that in spite of the increased intake of oxygen, the arterial was 33·5 mm. above the alveolar oxygen pressure. The lung must thus have been doing about double the amount of secretory work done during rest.

The last experiment, which was on Mr. FULLER, was made within an hour of his reaching the summit of Pike's Peak by the railway. His face had a distinctly bluish colour, and, as already mentioned, he suffered somewhat severely from mountain sickness during the ensuing 24 hours, although it was some hours after the experiment before he developed headache, nausea, and vomiting. It will be seen that his arterial oxygen pressure was 52·7 mm., or only 7 mm. above the alveolar oxygen pressure, although three days later, when he had become acclimatised and felt perfectly well, and his colour was normal, the difference found was 40·7 mm. In consequence of the colour of his face when he first came up we gave him, in the first experiment, less CO than usual.

These results are very striking, and they all point consistently to the conclusion that in acclimatisation to high altitudes the lung acquires a greatly increased power of raising the arterial oxygen pressure by actively secreting oxygen into the blood passing through the lungs. DOUGLAS and HALDANE found that at normal atmospheric pressure during rest the arterial is practically identical with the alveolar oxygen pressure. This is the result demanded by the theory that oxygen is passing into the blood by simple diffusion, and diffuses in at the rate calculated by BOHR and KROGH from measurements of the rate at which carbon monoxide diffuses in. The lower figures usually given by the aerotonometer method were shown to be due to defects inherent in this method; but allowing for these defects, all the experimental results by both methods agree in showing that during rest under normal conditions oxygen passes in by diffusion alone or almost alone. On the other hand, DOUGLAS and HALDANE found that deficiency in the oxygen supply to the tissues, whether this deficiency is produced by a diminished oxygen percentage in the air breathed, or by

CO poisoning, or by muscular work, leads to active secretion of oxygen inwards by the lungs, and consequent raising of the arterial above the alveolar oxygen pressure. In the case, however, of a diminished oxygen percentage in the air breathed the raising of arterial oxygen pressure only amounted to about 9 mm.—an amount about the same as was observed in Mr. FULLER before he became acclimatised.

The figures for the arterial oxygen pressure during rest after acclimatisation on Pike's Peak are entirely inconsistent with the theory that oxygen passes into the blood by diffusion alone, and indicate a secretory activity, presumably in the alveolar epithelium, far greater than that observed on themselves by DOUGLAS and HALDANE when the oxygen percentage was diminished at sea-level. From the experiment on Mr. FULLER, and the fact that it takes two or more days for the blueness of the face to disappear, it is evident that it takes some time for the increased secretory activity to develop. It may be presumed that the secretory power gradually increases with use, just as does muscular power, or as the habitual drinking of large quantities of light beer increases the secretory power of the kidneys.

That want of oxygen is the stimulus to this increased activity is clearly shown by the experiments in which the oxygen percentage of the inspired air was raised. It is true that lowering still further the alveolar oxygen pressure caused a diminution, and not an increase, in the absolute difference between alveolar and arterial oxygen pressure. This, however, is no evidence that secretory effort was less: for diffusion was probably acting against secretion entirely in the latter case, and only in the last stages of the absorption of oxygen in the other determinations. It is probable, also, that, as pointed out by DOUGLAS and HALDANE, the carbon monoxide method gives too low a result when the alveolar oxygen pressure is very low.

The complete absence of any sign of blueness of the face in persons acclimatised on Pike's Peak, as compared with the evident bluish colour in newcomers, lends strong support to the above conclusions. Our alveolar oxygen pressure was about 53 mm., and on saturating samples of the blood of HALDANE and DOUGLAS with alveolar air *in vitro* at body temperature we found that its colour was quite noticeably dark in colour as compared with blood saturated with pure air.

It might, perhaps, be suspected that the improved colour after acclimatisation was due to an alteration in the dissociation curve of the hæmoglobin, with the result that it became saturated at a lower partial pressure of oxygen than is the case with normal blood at sea-level. As will be seen below, the alveolar CO_2 pressure was markedly diminished on Pike's Peak, and the resulting diminution in the CO_2 pressure of the arterial blood would, by itself, alter the dissociation curve in the direction suggested. It was found, however, by BARCROFT* that no such effect was produced on the Peak of Teneriffe. The effect of the deficiency in CO_2 was just balanced by that of acid substances abnormally present in the blood, the result being that the dissociation curve was unaltered.

* BARCROFT, 'Journ. of Physiol.,' XLII., p. 44, 1911.

We have been able to verify BARCROFT'S conclusion. The normal dissociation curves of the blood of DOUGLAS and HALDANE are practically identical.* Fig. 5 shows the curve. At intervals on this curve we have plotted the results of a series of determinations made by the same method on Pike's Peak. The results at Oxford

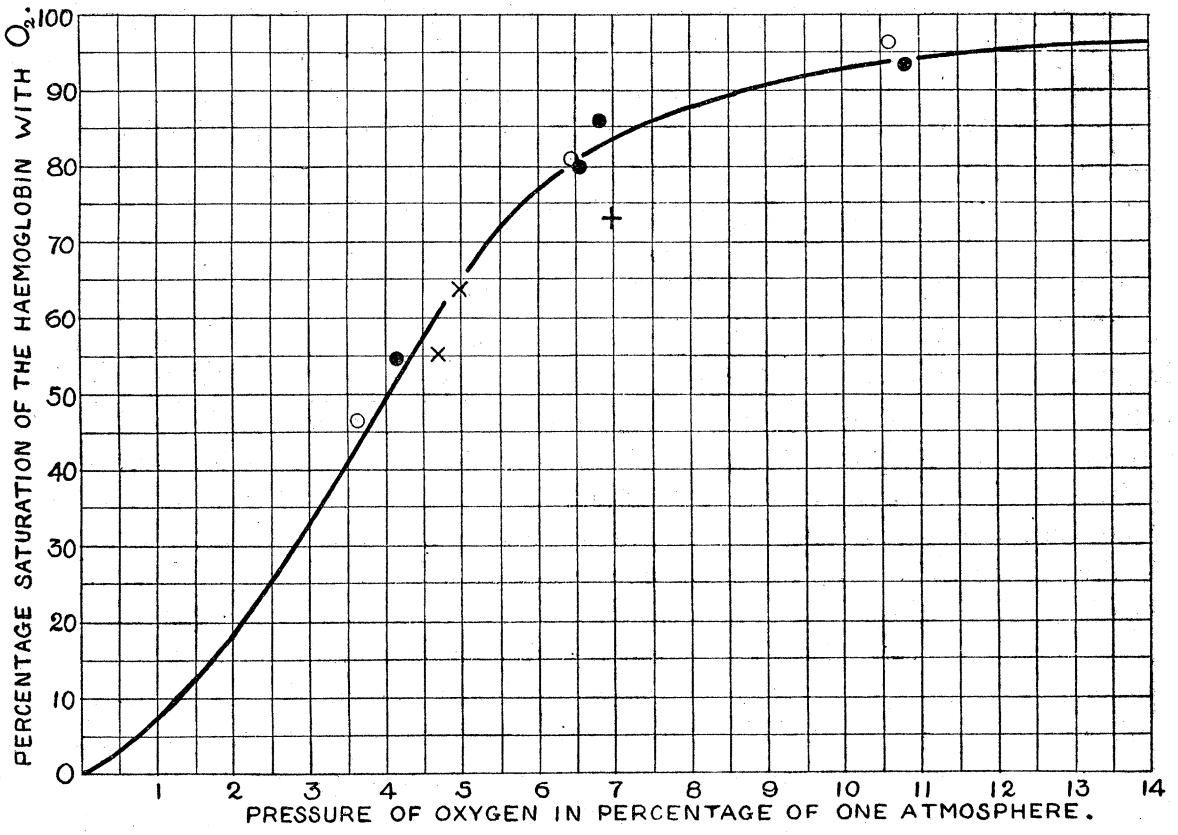

Fig. 5.

The continuous line represents the dissociation curve of oxyhæmoglobin in the blood of DOUGLAS and of HALDANE determined in Oxford in the presence of 40 mm. pressure of CO_2 at 38°.

The determinations made on Pike's Peak at 38° are shown thus:—

○ Blood of DOUGLAS, in the presence of 28 mm. pressure of CO_2.
● ,, HALDANE, ,, ,, ,, ,,
× ,, DOUGLAS, in the presence of 41 mm. pressure of CO_2.
\+ ,, HALDANE, ,, ,, ,, ,,

were obtained in presence of 40 mm. pressure of CO_2. On Pike's Peak our alveolar CO_2 pressure had fallen to about 27 mm., and the determinations were therefore made in presence of 27 mm. of CO_2. It will be seen that the results still fall on the curve, and thus completely confirm BARCROFT'S work. Three results are also shown in which the CO_2 pressure was 40 mm.; and on an average these results fall distinctly to the right of the curve, as might be expected.

* 'Journ. of Physiol.,' XLIV., p. 283, 1912. The apparatus used on Pike's Peak for determining the dissociation curve was the same as in the experiments of DOUGLAS and HALDANE at Oxford.

Further confirmation of the increased secretory activity of the lungs on Pike's Peak is afforded by a comparison of the symptoms experienced with corresponding lowering of the alveolar oxygen pressure on Pike's Peak and near sea-level. In the experiment on HALDANE recorded in Table I., where the alveolar oxygen pressure was lowered to 33 mm., there was only slight blueness with very trifling subjective symptoms. Four experiments at Oxford on HALDANE with the alveolar oxygen pressure reduced to almost exactly the same point (33 to 34 mm.) are recorded by HALDANE and POULTON.* In these the face became very blue, and there was twitching of the muscles and confusion of mind, the symptoms of want of oxygen being so marked that each experiment had to be stopped as the subject seemed on the point of losing consciousness.

During muscular work the intake of oxygen by the lungs is greatly increased, and on Pike's Peak this would involve a corresponding increase of secretory work by the lungs unless the oxygen pressure of the arterial blood were allowed to fall. The experiment during work with one arm (recorded in Table I.) shows that with the oxygen intake doubled there was no appreciable fall of the arterial oxygen pressure. Unfortunately we had no means of making determinations during hard work with numerous muscles, as in walking or climbing; but we made a number of observations on the colour of the lips, tongue, and face during hard work. During spells of experimental walking work on the level, with the oxygen intake increased to about 1725 c.c. per minute, or five times as much as during rest standing, as recorded below, the colour of the lips, etc., seemed to remain perfectly normal, with no blueness. Nor could we detect any very distinct blueness during short walks up the railway track, even when the exertion was pushed to such a point that the panting was almost unbearable. We sometimes thought that slight blueness was present, but at any rate it was so slight that we could hardly be certain of it. It would thus seem that the arterial oxygen pressure could be kept high for a time, in spite of the greatly increased oxygen intake.† After walking for a considerable distance uphill the result was different, however, and very definite blueness, which disappeared very rapidly on resting, was always observed, even though the exertion was not extreme.

DOUGLAS and HALDANE found that muscular work furnishes a powerful stimulus to secretory absorption of oxygen by the lung epithelium. It would seem, therefore, from the above observations that the additional stimulus furnished by muscular work excites at first the necessary increased activity of the lung epithelium. But the blueness after prolonged muscular exertion seems to indicate that after a time the lung epithelium becomes fatigued and ceases to respond adequately. This fatigue of the lung epithelium has probably much to do with the onset of mountain sickness, and may probably occur at much lower altitudes, particularly in untrained persons,

* 'Journ. of Physiol.,' XXXVIII., p. 394, 1908.

† In these short experiments the alveolar oxygen pressure was abnormally raised, as will be explained below, and this must have aided considerably the absorption of oxygen.

since the adequate aeration of the blood during hard muscular work depends in all probability on the activity of the lung epithelium, even at sea-level.

As the theory that oxygen passes into the blood through the lung epithelium by diffusion alone is deeply rooted in the minds of physiologists, it may be well to consider at this point the possibilities of the diffusion theory as applied to the facts observed by us on Pike's Peak.

BOHR* has shown that the rate of diffusion of oxygen from the alveolar air into the blood may be inferred from the rate at which carbon monoxide diffuses in. A. and M. KROGH† have also calculated the rate of diffusion by the same method, and it seems probable, as DOUGLAS and HALDANE have pointed out, that their figures are more nearly correct for the rate of diffusion in man during rest than BOHR's original estimate. According to the revised estimate, about 25 c.c. of oxygen diffuse into the blood per minute for one millimetre of difference in oxygen pressure between the alveolar air and the blood. During rest standing at Pike's Peak DOUGLAS absorbed about 345 c.c. of oxygen per minute. Hence for the absorption of this amount by diffusion a mean pressure difference of about $\frac{345}{25} = 14$ mm. between the oxygen in the alveolar air and in the blood would be needed. We may assume provisionally that the circulation rate (which is discussed below) was unaltered, and that the venous blood returning to the heart contains under normal conditions about two-thirds as much oxygen as the arterial blood, the hæmoglobin being 64 per cent. saturated, as against 96 per cent. in the arterial blood.

Let us first suppose that the blood becomes saturated by diffusion up to an oxygen pressure of 53 mm., which corresponds on the dissociation curve to 84 per cent. saturation of the hæmoglobin. As the hæmoglobin percentage was increased by a seventh or more (as shown later) the arterial blood would then contain as much oxygen as usual, and if it lost as much oxygen as usual the venous blood would also return with as much oxygen as usual, but would only be 56 per cent. saturated, corresponding to an oxygen pressure of 33 millimetres (after the extra CO_2 in the venous blood had been got rid of). There would thus be an initial diffusion pressure of $53-33 = 20$ mm. available for driving oxygen inwards. If this pressure were available during the whole period occupied by the blood in passing through the alveolar capillaries it is evident that $20 \times 25 = 500$ c.c. of oxygen might be absorbed per minute. But the available diffusion pressure diminishes constantly as the blood becomes more and more saturated in the alveolar capillaries, and if this be allowed for and the result calculated for successive fractions of the time in the manner explained by BOHR and by DOUGLAS and HALDANE it will be found that the arterial blood would not be saturated to 53 mm. of oxygen pressure. The oxygen pressure of both arterial and venous blood would thus have to drop appreciably before the required oxygen could be absorbed, and the arterial blood would be

* 'Skand. Archiv für Physiol.,' XXII., p. 261, 1909; 'Zentralb. für Physiol.,' XXIII., p. 374, 1909.

† 'Skand. Archiv für Physiol.,' XXIII., p. 236, 1911.

still more dusky in colour than blood saturated at the alveolar oxygen pressure. Moreover, the CO method of determining the arterial oxygen pressure would for the reasons explained by DOUGLAS and HALDANE (p. 341 of their paper) give a result below the true arterial oxygen pressure, low as the latter would actually be. The actual result was much above the alveolar oxygen pressure, however.

It is possible that an adaptive change occurs by which the rate of diffusion through the alveolar walls is increased at high altitudes; but even so, the red colour of the lips, etc., would not be explained.

Let us now take the case of oxygen absorption during work. Numerous determinations of this were made with the Douglas respiration apparatus on Pike's Peak, as described in a subsequent section. The amount of oxygen absorbed during continuous walking at 4·3 miles per hour on the level rose to an average of 1725 c.c. per minute, as shown below. According to BOHR'S and KROGH'S measurements, the rate of diffusion of oxygen inwards is increased during the hyperpnœa of muscular work to about 38 c.c. per minute and per millimetre of diffusion pressure. To absorb 1725 c.c. of oxygen per minute a mean diffusion pressure of $\frac{1725}{38} = 45{\cdot}3$ mm. would thus be needed. The alveolar oxygen pressure, as measured during the walking, averaged 53·4 mm. Had the venous blood been absolutely free from oxygen, and had the arterial blood been saturated to a pressure of only about 15 mm., the oxygen might, therefore, have passed in by diffusion, since the required 45·3 mm. of mean pressure difference would have existed. But arterial blood saturated to 15 mm. is only 18 per cent. saturated with oxygen and is almost black in colour, while the colour of the subject was absolutely normal. There was also no sign, direct or indirect, of want of oxygen in any part of the body, and the oxygen pressure in the venous blood can hardly have been below 20 mm., or the arterial oxygen pressure below 60 mm.

It thus appears that, apart altogether from the evidence furnished by our determinations of the actual arterial oxygen pressure, the diffusion theory entirely fails to explain the facts observed on Pike's Peak, and comes nowhere near explaining them, unless, indeed, some adaptive change occurs by which the rate of diffusion is enormously increased. Increase in the circulation rate, if it existed, would not help, for such an increase would raise the oxygen pressure in the venous blood, and so diminish the available diffusion pressure. The same remark applies to increase in the hæmoglobin percentage.

It is well known that men can live and work at higher altitudes than that of Pike's Peak. In his recent explorations in the Himalayas the Duc d'Abruzzi and his companions climbed to 24,580 feet, the barometric pressure being 312 mm. At this point the explorers felt no discomfort during rest, and do not seem to have experienced any difficulty in performing the work required in climbing. The oxygen pressure of the inspired air, saturated at body temperature with moisture, was $(312-47) \times \frac{20{\cdot}9}{100} = 55{\cdot}4$. Judging from the curve published by Miss FITZGERALD in a succeeding paper, the alveolar CO_2 pressure would be about 21 mm., and the alveolar oxygen about

55·4 − 25·4 = 30·0 mm. Blood saturated with alveolar air at this pressure is very dark in colour and not quite half saturated with oxygen, the percentage saturation corresponding to what is found in the arterial blood of animals at the point of death from asphyxia. On the diffusion theory the arterial blood would be at a considerably lower saturation even during rest, and work such as that of cutting steps with an ice-axe, or climbing, would apparently be wholly impossible.

The difficulties of the diffusion theory appear to become greater and greater as the altitude increases; but in the absence of more definite physiological observations on mountains at great altitudes we need hardly carry the argument into further detail. Recent advances in knowledge as to the blood-gases and the physiology of respiration seem, in fact, to have been altogether fatal to the simple diffusion theory hitherto adopted by the majority of physiologists. The indirect evidence points as clearly to this conclusion as the direct evidence furnished by our determinations of arterial oxygen pressure on Pike's Peak.

Protocol of an Experiment on the Arterial Oxygen Tension and Blood Volume. Pike's Peak. July 20, 1911.

Subject, Douglas. Bar., 457 mm.

9.23–9.34½ a.m. 301 c.c. of CO of 96·8 per cent. purity by analysis, at 14·5°, and under a pressure of 65 cm. of water (= 179·5 c.c. dry, at 0° and 760 mm.) administered to subject, who continued to breathe into the small apparatus till 9.38½.

9.38½. Began breathing into large respiration apparatus.

9.43½. First sample of inspired air.

9.53½. Second sample of inspired air.

10.03½. Third sample of inspired air.

10.04½. Sample of alveolar air.

10.07. Samples of blood from fingers for direct titration.

10.07½. Stopped and apparatus closed.

10.08. Sample of blood taken and defibrinated for saturator. A sample of air from the large respiration apparatus was then taken, ·05 c.c. of the defibrinated blood spread inside the saturator, and the latter filled with air from the large respiration apparatus, corked, and 25 c.c. of CO_2 added to it bringing the percentage of CO_2 in the saturator up to about 6·6 per cent. The saturator was then rotated in the water bath at 38°, and after a few minutes the excess of pressure due to the rise of temperature was blown off so as to reduce the pressure inside the saturator to atmospheric pressure. The rotation of the saturator in the bath was continued for a further 35 minutes.

Results of Analyses.

	O_2 per cent.	CO_2 per cent.
First sample of inspired air	18·71	1·65
Second sample of inspired air	18·31	1·10
Third sample of inspired air	18·93	0·64
Alveolar air	11·96	6·82
Air from large respiration apparatus	18·36	0·74

Percentage Saturation of the Hæmoglobin with CO.

Blood direct from fingers.	Sample 1	20·6
	Sample 2	20·4
	Mean . . .	20·5
Blood from saturator.	Sample 1	22·8
	Sample 2	22·6
	Mean . . .	22·7

O_2 pressure of arterial blood (not corrected for moisture)

$$= 18{\cdot}36 \times \frac{22{\cdot}7}{77{\cdot}3} \times \frac{79{\cdot}5}{20{\cdot}5} = 20{\cdot}9 \text{ per cent. of existing atmosphere.}$$

O_2 pressure of arterial blood (corrected for moisture)

$$= \frac{20{\cdot}9}{100} \times (457 - 47) = 85{\cdot}6 \text{ mm.}$$

Calculation of Total Oxygen Capacity and Blood Volume.

CO administered = 179·5 c.c. at S.T.P.

Percentage saturation of hæmoglobin with CO in the samples direct from the fingers = 20·5.

Total oxygen capacity $= \frac{179{\cdot}5 \times 100}{20{\cdot}5} = 875$ c.c.

Hæmoglobin percentage = 113.

$\therefore$ percentage oxygen capacity $= 113 \times \frac{18{\cdot}5}{100} = 20{\cdot}9.$

Blood volume $= \frac{875 \times 100}{20{\cdot}9} = 4{,}190$ cc.

V. *The Respiration.*

One of the most striking symptoms experienced at low atmospheric pressures is the excessive hyperpnœa which accompanies muscular exertion. This hyperpnœa is familiar to all mountaineers, and our own experience of it was similar to that of other observers. That it is dependent in some way on lack of oxygen hardly any physiologist can now doubt; but we have endeavoured to study both the hyperpnœa on exertion and the ordinary breathing during rest more closely than has yet been done.

Under normal conditions, and near sea-level, the volume of fresh air taken into the lungs per minute is so regulated as to keep the partial pressure of carbon dioxide in the alveolar air practically constant (at about 40 mm. for adult men) for each individual.* In other words, the alveolar ventilation (measured by *volume*, and at the pressure, temperature and saturation with moisture, existing in the lungs at the time) varies as the *mass* of carbon dioxide given off. Even during muscular work, or when the

* HALDANE and PRIESTLEY, 'Journ. of Physiol.,' XXXII., p. 225, 1905.

percentage of carbon dioxide in the inspired air is increased to as much as 4 or 5 per cent., this rule holds good approximately, and HALDANE and PRIESTLEY found that when hyperpnœa was produced by breathing air containing percentages up to 6·6 per cent. of carbon dioxide, the partial pressure of carbon dioxide in the alveolar air increased from the normal of about 40 mm. of mercury by only about 1·9 mm. for each 100 per cent. of increase over the resting alveolar ventilation.*

Let us consider what would happen if the same alveolar CO_2 pressure were maintained at the barometric pressure (about 457 mm.) existing on Pike's Peak. Inasmuch as deficiency of oxygen in the alveolar air runs parallel to excess of CO_2, but is about a fourth greater in consequence of the respiratory quotient being below unity, the partial pressure of oxygen in the alveolar air would be about $40 \times \frac{5}{4} = 50$ mm. lower than in the inspired air saturated with moisture at the body temperature. As the pressure of aqueous vapour at 37° is 47 mm., the pressure of oxygen in pure air at 457 mm. saturated at 37° is $\frac{20{\cdot}93}{100} \times (457-47) = 85{\cdot}8$ mm. of mercury, and this minus 50 mm. = 35·8 mm. An oxygen pressure of 35·8 mm. is the same as when the (dry) alveolar air contains only 5·0 per cent. of oxygen at normal atmospheric pressure; and it is known that marked symptoms of want of oxygen are ordinarily produced under such conditions.

It is already known, however, that want of oxygen, whether produced by low atmospheric pressure or by other means, causes an increase in the volume of air

* In a recent paper ('Journ. of Physiol.,' XLII., p. 337, 1911) LINDHARD concludes, from experiments on three persons, that (1) the sensibility of the respiratory centre to changes in the alveolar CO_2 pressure is normally far less than HALDANE and PRIESTLEY find; and (2) that the excitability of the centre by CO_2 is governed by the alveolar oxygen pressure, in such a way that an increase or diminution of the normal alveolar oxygen pressure makes the centre more, or less, excitable to a given increase above normal in the alveolar CO_2 pressure. He regards HALDANE and PRIESTLEY'S results as probably due to the fact that the oxygen percentage in the air which they inspired while making their experiments was somewhat diminished owing to vitiation with expired air. The same line of reasoning and experiment has been further developed in a still more recent paper by HASSELBALCH and LINDHARD ('Skand. Archiv für Physiol.,' XXV., p. 361, 1912).

We wish to point out that although the oxygen percentage of the inspired air was diminished in HALDANE and PRIESTLEY'S experiments the oxygen of the alveolar air (which is what matters) was not diminished but slightly increased above normal. The analyses are given in their paper. LINDHARD'S conclusions run directly contrary to numerous other experimental results previously obtained. The method which he used for obtaining samples of the alveolar air seems to us a very doubtful one, and his normal values for CO_2 are most suspiciously low. We are also doubtful as to whether he allowed sufficient time to elapse before the samples were taken when mixtures containing CO_2 were breathed from a spirometer. We have, however, re-investigated the matter, using the same method as wasemployed by HALDANE and PRIESTLEY, the subject being enclosed in an air-tight chamber of 70 cubic feet capacity, filled with the gas-mixture, and plenty of time being allowed to elapse before the samples of inspired and alveolar air were taken. The results, which were obtained on DOUGLAS and HALDANE, and will be given in full elsewhere, agreed closely with those of HALDANE and PRIESTLEY. It was also found that it made not the slightest difference whether the inspired air contained 18 per cent. or 60 per cent. of oxygen. We, therefore, cannot accept LINDHARD'S conclusions as applicable to our experiments

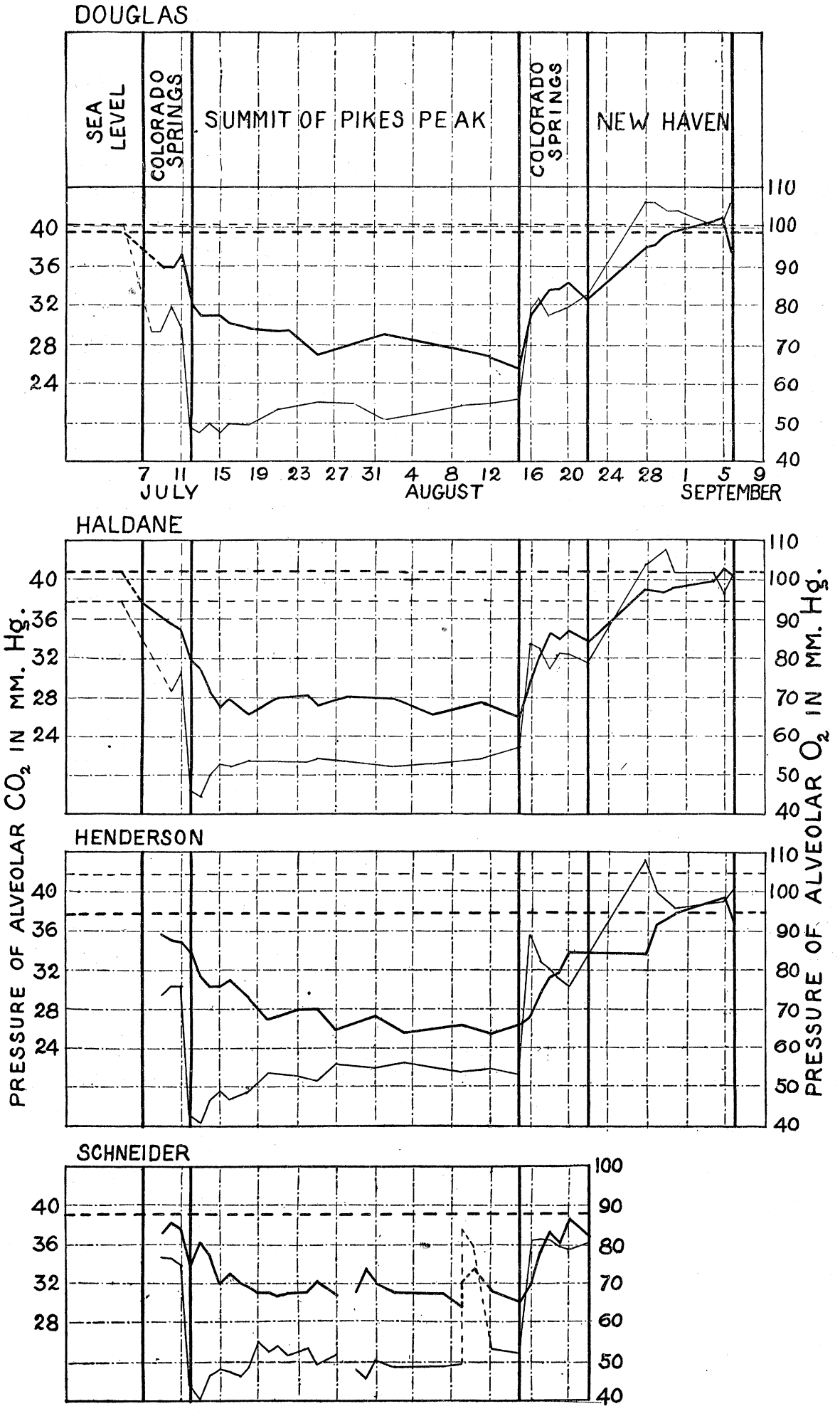

Fig. 6.

Thick line = alveolar CO_2 pressure. Thin line = alveolar O_2 pressure.

The horizontal interrupted lines represent the mean normal alveolar CO_2 and oxygen pressures at sea-level (*i.e.*, Oxford and New Haven).

Abscissæ plotted to the same scale in each case. SCHNEIDER spent the nights of July 28 and August 9 in Colorado Springs.

His second determinations on August 9 and those on August 10 were made in Colorado Springs.

breathed, with consequent lowering of the partial pressure of carbon dioxide in the alveolar air. The extent of this lowering with different diminutions of atmospheric pressure and various durations of exposure has been directly measured by BOYCOTT and HALDANE* in a steel chamber, by OGIER WARD† on Monte Rosa, and by DOUGLAS‡ on the Peak of Teneriffe. Indirect estimates of the lowering have also been made with great care by ZUNTZ, LOEWY, DURIG, and others, though these estimates are only approximate.

We made a series of observations on our own alveolar air under resting conditions during, and before and after, our stay at Colorado Springs, and on Pike's Peak. The direct method of HALDANE and PRIESTLEY was used in obtaining the alveolar air, and the samples were analysed in the apparatus described by HALDANE in 'Methods of Air Analysis,' p. 47, 1912. Two samples, one at the end of inspiration and one at the end of expiration, were always taken, each result being the mean of the two determinations. The following tables (II. to V.) give the results of these determinations for each of us. Fig. 6 shows the same results plotted graphically.

TABLE II.—DOUGLAS.

Date.	Percentage of gases in dry alveolar air.		Partial pressure of gases in mm. Hg in alveolar air at 37° saturated with moisture.		Barometer in mm. Hg.	Alveolar respiratory quotient.	
	CO_2	O_2	CO_2	O_2			
Nov. 1908 to Feb. 1909	—	—	39·75	—	—	—	Oxford.
Feb. 1910 to March 1910	5·72	13·84	40·8	98·7	751	·800	Oxford.
1911.							
April 1	5·49	14·25	39·0	101·3	758	·781	Oxford.
5	5·68	14·01	40·6	100·1	762	·779	
8	5·57	—	40·0	—	766	—	
9	5·50	—	39·6	—	767	—	
10	5·62	—	40·2	—	761	—	
13	5·51	14·26	39·8	102·9	769	·784	
May 2	5·56	13·81	39·4	98·0	756	·735	
5	5·44	14·13	38·8	100·9	761	·755	
10	5·28	14·35	37·5	101·9	757	·759	
18	5·63	14·26	40·1	101·5	759	·806	

* 'Journ. of Physiol.,' XXXVIII., p. 355, 1908.

† *Ibid.*, XXXVIII., p. 378, 1908.

‡ *Ibid.*, XL., p. 472, 1910.

TABLE II. (continued).

Date.		Percentage of gases in dry alveolar air.		Partial pressure of gases in mm. Hg in alveolar air at 37° saturated with moisture.		Barometer in mm. Hg.	Alveolar respiratory quotient.	
		CO_2	O_2	CO_2	O_2			
May	25	5·53	14·22	39·3	101·1	758	·775	
	31	5·57	—	39·5	—	757	—	
June	1	5·55	14·21	39·6	101·5	761	·784	
	7	5·44	13·85	39·3	100·1	770	·720	
	17	5·56	14·06	39·2	99·1	752	·767	
	22	5·88	13·57	41·7	96·1	756	·755	
		5·55	14·08	39·6	100·4	761	·767	Mean for Oxford, April–June, 1911.
July	8	6·59	12·98	37·1	73·0	610	·789	Colorado Springs.
	9	6·33	12·84	36·0	73·0	616	·735	
	10	6·28	13·95	35·9	79·6	618	·871	
	11	6·54	12·94	37·3	73·8	617	·778	
July	12	7·80	—	32·2	—	460	—	Summit of Pike's Peak 40 minutes after arrival.
	12	7·76	11·77	32·1	48·6	460	·811	4 hours after arrival.
	13	7·52	11·38	31·1	47·1	461	·742	
	14	7·46	11·96	31·0	49·6	462	·793	
	15	7·41	11·26	30·7	46·6	461	·719	9.30 a.m.
	15	7·57	11·48	31·3	47·4	460	·757	8.15 p.m.
	16	7·29	11·91	30·2	49·4	461	·766	
	18	7·21	11·98	29·6	49·0	457	·760	
	21	7·14	12·93	29·3	53·1	458	·863	
	22	7·19	—	29·4	—	457	—	
	25	6·75	13·35	27·9	55·2	460	·860	
	29	6·53	13·27	26·9	54·7	459	·815	
Aug.	1	7·10	12·33	29·0	50·4	456	·786	
	9	6·63	13·08	27·4	54·0	460	·807	
	12	6·45	13·26	26·5	54·5	458	·803	
	15	6·21	13·43	25·6	55·5	460	·787	
Aug.	16	5·48	13·82	31·1	78·5	616	·721	Colorado Springs on return 2½ hours after arrival.
	17	5·68	14·35	32·4	81·8	617	·828	11.15 a.m.
	17	5·53	14·03	31·5	80·0	617	·756	5.15 p.m.
	18	5·89	13·51	33·5	77·0	617	·748	
	19	5·87	13·73	33·4	78·2	617	·772	
	20	5·97	13·84	34·1	79·1	618	·805	Evening of 20th and most of 21st at Cripple Creek, altitude 9,000 feet.
	22	5·70	14·36	32·6	82·0	618	·833	

TABLE II. (continued).

Date.	Percentage of gases in dry alveolar air.		Partial pressure of gases in mm. Hg in alveolar air at 37° saturated with moisture.		Barometer in mm. Hg.	Alveolar respiratory quotient.	
	CO_2	O_2	CO_2	O_2			
Aug. 28	5·26	14·76	37·8	106·0	765	·815	New Haven.
29	5·32	14·79	38·2	106·0	764	·831	
30	5·42	14·44	39·2	104·3	770	·795	
31	5·52	14·48	39·6	104·0	765	·819	
Sept. 4	5·60	13·95	40·4	100·6	768	·758	
5	5·66	13·97	40·8	100·5	767	·770	
6	5·26	14·94	37·4	106·2	758	·845	

TABLE III.—HALDANE.

Date.	Percentage of gases in dry alveolar air.		Partial pressure of gases in mm. Hg in alveolar air at 37° saturated with moisture.		Barometer in mm. Hg.	Alveolar respiratory quotient.	
	CO_2	O_2	CO_2	O_2			
1911.							
April 1	5·79	13·28	41·1	93·9	758	·732	Oxford.
5	5·64	13·32	40·3	95·3	762	·690	
May 27	5·75	13·36	41·0	95·2	760	·710	
June 19	5·64	13·37	39·6	93·8	749	·695	
22	5·85	13·06	41·5	92·6	756	·692	
	5·73	13·28	40·7	94·2	757	·704	Mean for Oxford, April–June, 1911.
July 7	6·66	—	37·6	—	611	—	Colorado Springs.
10	6·22	12·60	35·5	71·4	618	·695	
11	6·10	13·23	34·8	75·4	617	·746	
July 12	7·65	—	31·6	—	460	—	Summit of Pike's Peak 1 hour after arrival.
12	7·70	10·94	31·8	45·2	460	·724	$4\frac{1}{2}$ hours after arrival.
13	7·44	10·60	30·8	43·9	461	·668	
14	6·90	11·94	28·6	49·6	462	·719	
15	6·48	12·54	26·8	52·0	461	·725	
16	6·69	12·53	27·7	51·9	461	·751	

TABLE III. (continued).

Date.	Percentage of gases in dry alveolar air.		Partial pressure of gases in mm. Hg in alveolar air at 37° saturated with moisture.		Barometer in mm. Hg.	Alveolar respiratory quotient.	
	CO_2	O_2	CO_2	O_2			
July 18	6·37	12·92	26·1	53·0	457	·750	
21	6·73	12·90	27·7	53·0	458	·800	
24	6·78	12·67	28·0	52·9	460	·780	
25	6·65	13·00	27·1	53·7	460	·801	
28	6·80	12·90	27·9	52·9	457	·810	
Aug. 2	6·82	12·72	27·7	51·6	453	·791	
6	6·38	12·78	26·0	52·1	455	·736	
11	6·62	12·92	27·3	53·2	459	·786	
15	6·23	13·65	25·7	56·4	460	·820	
Aug. 16	5·20	14·57	29·5	82·8	616	·775	Colorado Springs on return, 2 hours after arrival.
17	5·62	14·34	32·0	82·7	617	·816	11.30 a.m.
17	5·58	14·20	31·8	80·9	617	·789	5.30 p.m.
18	6·00	13·46	34·2	76·7	617	·760	
19	5·91	14·14	33·7	80·6	617	·837	
20	6·05	14·08	34·5	80·3	618	·851	Night of 20th and most of 21st at Cripple Creek, altitude about 9,000 feet.
22	5·88	13·66	33·6	78·0	618	·765	
Aug. 28	5·41	14·35	38·8	103·0	765	·780	New Haven.
30	5·33	14·73	38·5	106·7	770	·823	
31	5·43	14·07	39·0	101·0	765	·746	
Sept. 4	5·51	14·05	39·7	101·3	768	·756	
5	5·70	13·28	41·0	95·6	767	·694	
6	5·66	14·14	40·3	100·5	758	·790	

TABLE IV.—HENDERSON.

Date.	Percentage of gases in dry alveolar air.		Partial pressure of gases in mm. Hg in alveolar air at 37° saturated with moisture.		Barometer in mm. Hg.	Alveolar respiratory quotient.	
	CO_2	O_2	CO_2	O_2			
1911. June 10	5·49	—	39·0	—	758	—	New Haven.
July 9	6·26	12·83	35·5	73·0	616	·725	Colorado Springs.
10	6·13	13·18	35·0	75·3	618	·765	
11	6·11	13·26	34·8	75·6	617	·752	

TABLE IV. (continued).

Date.	Percentage of gases in dry alveolar air.		Partial pressure of gases in mm. Hg in alveolar air at 37° saturated with moisture.		Barometer in mm. Hg.	Alveolar respiratory quotient.	
	CO_2	O_2	CO_2	O_2			
July 12	8·08	—	33·4	—	460	—	Pike's Peak Summit just after arrival. Inspiration value only.
12	8·22	10·31	34·0	42·7	460	·727	$3\frac{3}{4}$ hours after arrival.
13	7·59	9·85	31·4	40·7	461	·630	
14	7·27	11·25	30·2	46·8	462	·701	
15	7·33	11·81	30·3	48·9	461	·760	
16	7·44	11·22	30·8	46·5	461	·718	
18	7·11	11·82	29·1	48·5	457	·734	
20	6·54	12·98	26·8	53·2	457	·782	
23	6·76	12·85	27·8	52·4	458	·798	
25	6·73	12·44	27·8	51·4	460	·748	
27	6·23	13·60	25·7	55·6	456	·813	
31	6·65	13·29	27·2	54·4	456	·837	
Aug. 3	6·26	13·72	25·5	55·8	454	·806	
9	6·37	12·94	26·3	53·4	460	·757	
12	6·18	13·19	25·4	54·2	458	·755	
15	6·37	12·81	26·3	52·9	460	·741	
Aug. 16	4·70	15·51	26·7	88·3	616	·836	Colorado Springs on return $2\frac{1}{2}$ hours after arrival.
17	5·14	14·35	29·5	81·8	617	·737	
18	5·48	14·05	31·2	80·1	617	·755	
19	5·53	13·60	31·6	77·6	617	·708	
20	5·88	13·17	33·5	75·3	618	·708	
Aug. 28	4·65	14·98	33·4	107·5	765	·733	New Haven.
29	5·07	13·88	36·4	99·5	764	·665	
31	5·27	13·24	37·8	95·1	765	·628	
Sept. 5	5·44	13·49	39·2	97·0	767	·678	
6	5·15	14·15	36·6	100·6	758	·710	
Oct. 3	5·47	14·06	39·5	101·6	770	·751	
4	5·51	13·94	39·7	100·4	767	·743	
5	5·50	14·10	39·3	100·1	761	·760	
6	5·38	14·24	38·7	102·5	767	·760	
1912.							
Jan. 6	5·17	15·22	37·4	110·2	771	·877	
8	4·98	15·20	36·1	110·2	772	·835	
9	5·15	14·47	37·1	104·2	767	·760	
10	5·07	14·55	36·5	104·6	766	·754	
13	5·02	14·95	36·5	108·7	774	·796	
15	5·20	14·93	36·5	104·9	750	·831	
	5·25	14·57	37·7	104·7	767	·787	Mean for New Haven. Oct. 1911 and Jan. 1912.

TABLE V.—SCHNEIDER.

Date.	Percentage of gases in dry alveolar air.		Partial pressure of gases in mm. Hg in alveolar air at 37° saturated with moisture.		Barometer in mm. Hg.	Alveolar respiratory quotient.	
	CO_2	O_2	CO_2	O_2			
1911.							
May 7	5·40	—	38·9	—	767	—	New Haven.
7	5·17	—	37·2	—	767	—	
7	5·50	—	39·6	—	767	—	
8	5·44	—	39·1	—	765	—	
9	5·91	—	42·1	—	759	—	
9	5·48	—	39·0	—	759	—	
10	5·30	—	37·7	—	759	—	
	5·46	—	39·1	—	763	—	Mean for New Haven.
July 9	6·55	13·77	37·3	78·3	616	·890	Colorado Springs, 1 week after return from near sea level.
9	6·46	13·06	36·7	74·3	616	·780	
10	6·66	13·31	38·1	76·0	618	·842	
11	6·58	13·01	37·5	74·2	617	·791	
July 12	8·12	—	33·5	—	460	—	Pike's Peak summit just after arrival.
12	8·27	10·63	34·2	43·9	460	·760	$3\frac{1}{4}$ hours after arrival.
13	8·73	9·71	36·1	40·2	461	·733	
14	8·34	11·20	34·6	46·5	462	·824	
15	7·70	11·53	31·9	47·7	461	·778	
16	7·94	11·44	32·8	47·3	461	·798	
17	7·76	11·15	32·0	46·1	460	·750	
18	7·69	11·77	31·5	48·2	457	·802	
19	7·55	13·28	30·9	54·4	457	·979	
20	7·50	12·72	30·8	52·2	457	·889	
21	7·44	13·10	30·6	53·8	458	·934	
22	7·52	12·48	30·8	51·2	457	·861	
24	7·50	13·23	31·0	54·6	460	·963	8.40 a.m.
24	7·20	12·42	29·7	51·3	460	·809	5 p.m.
25	7·79	11·82	32·2	48·8	460	·822	
27	7·50	12·51	30·7	51·2	456	·862	In Colorado Springs, night of 28th.
29	7·54	11·56	31·1	47·7	460	·762	Just after return from Colorado Springs.
30	8·13	11·04	33·4	45·4	458	·782	
31	7·83	12·26	32·0	50·1	456	·878	
Aug. 2	7·62	11·83	31·0	48·1	454	·801	
7	7·47	11·73	30·8	48·3	459	·770	
9	7·14	11·87	29·5	49·0	460	·744	Descended to Colorado Springs, arriving there at 2.30 p.m. Returned on 10th.

TABLE V. (continued).

Date.	Percentage of gases in dry alveolar air.		Partial pressure of gases in mm. Hg in alveolar air at 37° saturated with moisture.		Barometer in mm. Hg.	Alveolar respiratory quotient.	
	CO_2	O_2	CO_2	O_2			
Aug. 9	5·34	14·63	30·3	83·1	615	·811	3 p.m. } Colorado
9	5·65	14·49	32·1	82·6	615	·846	6 p.m. } Springs.
10	5·89	13·94	33·5	79·2	615	·806	7.30 a.m. }
12	7·57	12·84	31·2	52·9	459	·917	Pike's Peak summit.
15	7·20	12·42	29·7	51·3	460	·810	
16	7·36	12·59	30·4	52·0	460	·853	7.50 a.m.
Aug. 16	5·64	14·17	32·1	80·6	616	·929	3.45 p.m. Colorado Springs on return. 2¼ hours after arrival.
17	6·20	14·05	35·3	80·1	617	·875	9.25 a.m.
17	6·09	14·32	34·7	81·6	617	·899	3.30 p.m.
18	6·49	14·10	37·0	80·4	617	·935	
19	6·32	14·04	36·0	79·0	617	·895	
20	6·75	13·67	38·5	78·1	618	·909	Evening of 20th, and most of 21st at Cripple Creek, altitude 9000 ft.
22	6·43	13·97	36·7	79·8	618	·903	

It will be seen from these tables and fig. 6 that on going from about sea-level to Colorado Springs, with a fall of barometric pressure of about 145 mm. from normal, the alveolar carbon dioxide pressure fell by about 4 mm. on an average during our stay, and that on Pike's Peak, with a further fall of about 160 mm. in barometric pressure, the alveolar carbon dioxide pressure fell about 10 mm. further on an average, the full extent of the fall taking about a fortnight to develop, and thereafter remained practically steady or fell very slightly. On returning to Colorado Springs and thereafter to sea-level at New Haven there was a corresponding rise to the former value at that barometric pressure, and this took about the same time to develop completely. These results resemble on the whole those already recorded by WARD and DOUGLAS, and by HALDANE and BOYCOTT in long experiments in the steel chamber; but the slowness with which the change becomes complete is first shown clearly in the Pike's Peak experiments.

Parallel with the fall of about 13 mm. in alveolar CO_2 pressure there was of course a rise in alveolar oxygen pressure of about $13 \times \frac{5}{4} = 16{\cdot}2$ mm., so that the alveolar oxygen pressure was about 52 mm. instead of 35·8 mm.

To explain the fall in alveolar CO_2 pressure at low barometric pressures BOYCOTT and HALDANE put forward the theory that lactic acid is formed in the tissues in

consequence of lack of oxygen, and thus comes to be present in abnormal amount in the blood. The respiratory centre is partly excited by the lactic acid, so that with a given production of carbonic acid the centre works more vigorously, and the exciting threshold of alveolar carbon dioxide pressure falls correspondingly. This hypothesis will be discussed in detail later.

It may be asked what evidence there is that at low atmospheric pressures or when low oxygen percentages are breathed, it is still carbon dioxide, and not want of oxygen, which immediately governs the respiratory movements. The evidence* is the

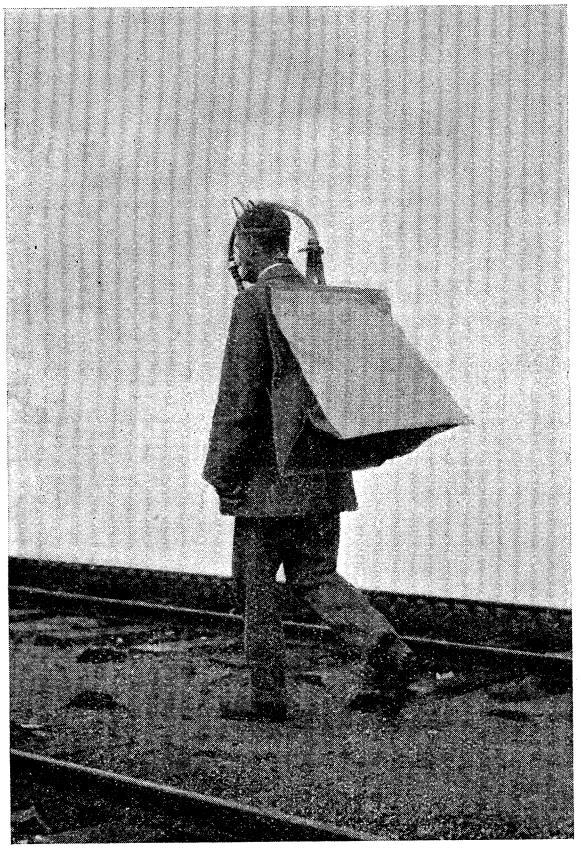

Fig. 7.

Determination of the total respiratory exchange whilst walking on the flat.

same as that which proves that carbon dioxide is the immediate governing factor at normal atmospheric pressures. Forced breathing, which lowers the carbon dioxide pressure of the alveolar air and blood, caused apnœa just as certainly on Pike's Peak or the Peak of Teneriffe as at sea-level, although during the apnœa the alveolar oxygen pressure fell to a good deal below the ordinary level; and, as already mentioned, HENDERSON† has shown that by sufficiently vigorous artificial respiration so much carbon dioxide is removed from the blood of an animal that the subsequent

* See HALDANE and POULTON, 'Journ. of Physiol.,' XXXVIII., p. 390, 1908.

† 'American Journ. of Physiol.,' XXV., pp. 310, 385, 1910.

apnœa lasts until death from want of oxygen occurs. On the other hand, any rise in the existing alveolar carbon dioxide pressure causes panting, whether the atmospheric pressure be low or high, while a rise in the alveolar oxygen pressure has little or no immediate effect after acclimatisation to a low pressure.

As the partial pressure of carbon dioxide in the alveolar air was about a third less (about 27 mm. as compared with 40 mm.) on Pike's Peak than at sea-level, it is evident that the alveolar ventilation during rest was, for an equal production of carbon dioxide, 50 per cent. greater on Pike's Peak.

To determine the actual volume of air breathed, and at the same time to measure the total respiratory exchange, we made a series of experiments by the "bag" method recently described by DOUGLAS.*

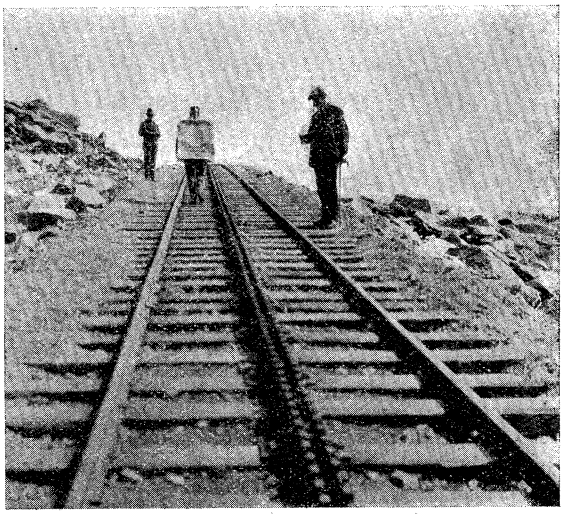

Fig. 8.

The highest portion of the 1 in 4 grade on the cog railway: an experiment on the total respiratory exchange in progress.

In this method of determining respiratory exchange the whole of the expired air is collected during a given short period in a vulcanised india-rubber bag (protected by stout twill) carried on the back of the subject of the experiment. The expired air is allowed to pass to the outside until at a given moment, after the conditions of respiration have become constant, a tap is turned so as to direct the expired air into the bag. When the bag is nearly full the tap is again turned, so as to close the bag and direct the expired air to the outside. The exact interval between opening and closing the tap is determined with a stop-watch, and the volume of air collected in the bag during this interval is accurately measured with a wet gas-meter, temperature and pressure being at the same time noted. A sample of the air from the bag is also

* 'Journ. of Physiol.,' XLII., p. 17, 1911. The apparatus is supplied by Messrs. Siebe, Gorman & Co., Westminster Bridge Road, London, S.E.

collected over mercury during the process of measurement, after the air in the bag has been thoroughly mixed up. With the vulcanised rubber bags employed there was no sensible alteration in composition of the air in the bag during half an hour; but the samples were taken within a few minutes of filling the bag.

The advantages of this method are that it is very simple and easily adapted to experiments on the effects of muscular work, and that it avoids many sources of error and uncertainty associated with the more complicated methods used by previous observers. Figs. 7 and 8 show the apparatus in use during experiments on the cog-wheel railway track.

Table VI. embodies average results, as regards the breathing, of an extensive series of experiments made by DOUGLAS on himself at Oxford and on Pike's Peak. The results of the individual experiments are contained in Tables X. and XVII. The first two columns of Table VI. show the actual volumes of air breathed (at 37° and existing barometric pressure, and saturated with moisture) and amount of CO_2 (at 0° and 760 mm., dry) given off. The third and fourth columns show the relations between volumes breathed and CO_2 given off. It will be seen that the volume breathed per cubic centimetre of CO_2 given off was about 27 per cent. greater on Pike's Peak during rest in bed, 31 per cent. greater during rest standing, 50 per cent. greater during walking on the level at rates up to $4\frac{1}{2}$ miles an hour, and nearly 100 per cent. greater in more severe exertion.

To understand the exact physiological significance of these figures it is necessary to take into consideration the influence of the so-called "dead space" in breathing. At the end of each expiration the respiratory air-passages, together with the very short connection between the mouth and inspiratory valve, are filled with alveolar air. This air has to travel back to the alveoli before any fresh air reaches the lungs, and the space filled by it is thus a "dead" space, so far as the alveolar ventilation is concerned. To calculate the alveolar ventilation we must therefore allow for this dead space; and to make proper allowance we must evidently know the volume of air inspired per breath and the volume of the dead space itself.

It was pointed out by HALDANE and PRIESTLEY that the dead space must vary according to the varying degree of contraction of the bronchi, and Siebeck* has more recently brought forward experimental evidence as to this variability. It is evident that if we know the average composition of the alveolar air and expired air, and also the volume of air breathed at each expiration we can calculate the volume of the effective dead space. Supposing, for instance, that the alveolar air is known to contain 5·6 per cent. of CO_2, the expired air contains 3·5 per cent., and the volume of air (at 37° moist) expired per breath is 600 c.c., then the effective dead space is evidently $600-(600\times\frac{3\cdot5}{5\cdot6}) = 225$ c.c. If the breathing is through valves this includes the dead space between the valves and the mouth.

* 'Skand. Archiv für Physiol.,' LV., p. 81, 1911.

The bag method gave us the average composition of the expired air and the volume of air per breath (see Tables X.–XVII.). The percentage of CO_2 in the alveolar air was determined separately, during both rest and work. Results during work are given

TABLE VI.

	Litres of air (at 37°, saturated, and existing barometric pressure) breathed per minute.	C.c. of CO_2 (at 0° and 760 mm. dry) given off per minute.	Volume of air breathed per c.c. of CO_2 given off.		Volume of alveolar ventilation per c.c. of CO_2 given off.	
			In c.c.	Ratio.	In c.c.	Ratio.
Pike's Peak, rest in bed.	10·21	206	49·5	1·27	30·1*	1·45
Oxford, rest in bed	7·67	197	39·1	1·00	20·8	1·00
Pike's Peak, rest standing	14·89	288	51·8	1·31	32·4	1·47
Oxford, rest standing	10·40	264	39·5	1·00	22·0	1·00
Pike's Peak, walking 2 miles per hour .	27·9	666	41·9	1·49	30·5*	1·49
Oxford, 2 miles per hour on grass . .	18·6	662	28·1	1·00	20·5	1·00
Oxford, 2 miles per hour in laboratory.	16·3	561	29·0	1·03	21·5	1·00
Pike's Peak, 3 miles per hour. . . .	38·8	922	42·1	1·56	30·5*	1·50
Oxford, 3 miles per hour on grass . .	24·8	922	26·9	1·00	20·4	1·00
Oxford, 3 miles per hour in laboratory.	20·9	737	28·4	1·05	20·6	1·01
Pike's Peak, 4 miles per hour	57·0	1439	39·6	1·46	32·0	1·62
Oxford, 4 miles per hour on grass . .	37·3	1398	26·7	1·00	19·8	1·00
Oxford, 4 miles per hour in laboratory.	29·0	1057	27·4	1·02	20·0	1·01
Pike's Peak, $4\frac{1}{4}$ miles per hour . . .	71·3	1725	41·0	1·57	—	—
Oxford, $4\frac{1}{2}$ miles per hour on grass . .	46·5	1788	26·1	1·00	19·9	1·00
Oxford, $4\frac{1}{2}$ miles per hour in laboratory	34·2	1251	27·3	1·05	19·7	0·99
Pike's Peak, 5 miles per hour. . . .	110·2	2208	50·0	1·96	—	—
Pike's Peak, up 25 per cent. grade . .	109·7	2025	54·2	2·16	—	—
Oxford, 5 miles per hour on grass . .	60·9	2386	25·5	1·00	20·2	1·00
Oxford, 5 miles per hour in laboratory.	51·3	2000	25·7	1·01	19·7	0·98

below. The dead space, determined by this method, was found to vary enormously. It was greatly increased during work, this fact indicating that during natural hyperpnœa the bronchi dilate greatly, as might be expected. Deducting the external dead space (exactly 53 c.c.) between the mouth and the valves, the effective dead space in

* These data are approximations. We made no direct analyses of the alveolar air.

DOUGLAS was found to vary from 160 c.c. during rest in bed at sea-level to 565 c.c. during walking at $4\frac{1}{2}$ miles per hour at sea level. It was considerably greater during rest standing than during rest in bed, and greater during rest, at any rate when standing, on Pike's Peak than at sea level. From these results it is quite clear that the method of calculating the composition of the alveolar air from that of the expired air on the assumption that the dead space has a certain fixed value gives most uncertain results; and these results become doubly uncertain when the same dead space is assumed for every individual. The subject will be dealt with more fully by two of us in a separate paper,* and is only referred to here in order to explain the basis of our calculations of alveolar ventilation and the want of exact agreement between our own direct determinations of the composition of the alveolar air and the indirect estimations by the older method used by a number of other investigators.

The fifth and sixth columns of the table show the calculated alveolar ventilation per c.c. of CO_2 (at 0° and 760 mm.) given off, the calculations being made by multiplying the corresponding values in the third column by the percentage of CO_2 in the expired air and dividing by the percentage in the alveolar air. It will be seen that the alveolar ventilation so calculated, is about steady, whether on Pike's Peak or at Oxford, but is about 50 per cent greater at Pike's Peak, whether during rest or during muscular exertion up to walking at $4\frac{1}{2}$ miles an hour. This result corresponds very satisfactorily with the observation that the exciting threshold of alveolar CO_2 pressure was just about 50 per cent. higher at Oxford than on Pike's Peak. The reason for the volume of air breathed per minute during rest in bed being only 25 per cent. higher on Pike's Peak was that the volume of air per breath was about 30 per cent. greater on Pike's Peak, and that on account of the dead space this extra 30 per cent. in depth increased the alveolar ventilation by about 50 per cent. During muscular work, on the other hand, there was very little relative difference, at Pike's Peak and at Oxford, in the volume of air per breath. Hence the increase in volume of air breathed per minute corresponded pretty closely with the increase in alveolar ventilation.

The Table shows that with still harder work, such as walking on the level at 5 miles an hour, or ascending the railway track at 2 miles an hour, the air breathed was about 100 per cent. greater on Pike's Peak than at Oxford. The explanation of this will be discussed presently. The alveolar ventilation could not be calculated, as the exact composition of the alveolar air was uncertain.

A difference of 50 per cent. in the alveolar ventilation, or 30 per cent. in the air breathed per minute, is not noticeable subjectively during rest. A similar increase in the breathing is produced by the presence of 1·4 per cent. of CO_2 in the inspired air, and is not noticed during rest. During hard work, on the other hand, an increase of 50 per cent. in the alveolar ventilation is very noticeable, since panting becomes excessive with a good deal less muscular work. During hard work the *depth* of breathing is about maximal in any case; hence the increased alveolar ventilation

* DOUGLAS and HALDANE, 'Journ. of Physiol.,' XLV., p. 235, 1912.

implies a full corresponding increase in the frequency of the breathing, with corresponding increased sense of effort and diminished power of co-ordinating the respiratory movements with any kind of muscular work. In the hard work of hewing coal or hammering a drill a miner may, for instance, be hampered because he cannot co-ordinate his breathing with the slow strokes of his hammer; and air containing 1·4 per cent. of CO_2 seriously affects his efficiency. In going up the track at Pike's Peak, unless the rate of progression was extremely slow, the hyperpnœa was apt to become so overpowering that it was even impossible to take a sample of alveolar air. To think of anything else but breathing, or to interrupt the breathing for even a moment, was quite out of the question. At the end of a short effort of this kind one could only stand in a stooping position and breathe for dear life.

On examining the respiratory quotients, as calculated from the composition of the alveolar air in Tables II. to IV., it will be noticed that the quotients are usually below 0·8, and occasionally below even 0·7. These values are evidently not true respiratory quotients, as they are too low. Thus for DOUGLAS the true respiratory quotient, as given by the bag experiments on Pike's Peak, averaged 0·833, whereas the alveolar quotients averaged only ·791. From numerous experiments, which will be described more fully elsewhere, we have convinced ourselves that the ratio of deficiency of oxygen to excess of CO_2 is higher in the alveolar than in the expired air. The cause of this phenomenon is doubtless the fact that in the smaller bronchioles and so-called "respiratory bronchioles" the conditions for giving off of CO_2 are, on account of its greater solubility, more favourable than for the absorption of oxygen when these parts are filled with pure air at each inspiration. The want of correspondence between the true and the "alveolar" respiratory quotient must, of course, add to the other sources of error, already mentioned, in the method of calculating the alveolar oxygen percentage from the composition of the expired air.

Experiments on the alveolar air during and after exertion were made as follows. Portions of the cog railway track were selected, and during and after the hyperpnœa produced by walking along or up the track for varying periods and on varying gradients samples of the alveolar air were collected and analysed. In some experiments the samples were taken straight into the gas analysis apparatus, which was placed either on a piece of rock at the side of the track or in the laboratory at the top. In other experiments the samples were collected in exhausted gas-sampling tubes, the wide-bored flexible pipe from which the samples were taken being carried round the neck.

During hard muscular work the breathing was too rapid to make it possible to take separate samples just after inspiration and just after expiration, so each experiment represents only a single determination.

The results of these experiments varied somewhat in different individuals, and are therefore quoted in detail. In the first group the exercise was of short duration, but was pushed so as to produce extreme hyperpnœa. The results were as follows:—

TABLE VII.—Alveolar Air after Maximal Exertion of Short Duration up 25 per cent. Grade.

All values "inspiration" except where stated.

	CO_2, pressure in mm. Hg.	O_2, pressure in mm. Hg.	R.Q.	
		July 15. DOUGLAS, up for about 45″.		
9.30 a.m.	30·7	46·6	·719	Normal mean inspiration and expiration.
2.20 p.m.	23·3	68·0	1·342	Immediately after stop.
	26·4	59·5	·962	7¼′ after stop.
	26·5	52·4	·727	19¼′ „ „
	28·1	51·1	·745	33′ „ „
	28·2	50·7	·740	54′ „ „
	28·6	49·3	·726	70′ „ „
		July 25. DOUGLAS, up for 45″.		
	27·9	55·2	·860	Normal mean before experiment.
	24·5	67·1	1·346	Immediately after stop.
	23·5	58·9	·817	10′ after stop.
	25·8	58·2	·889	19′ „ „
	25·3	55·5	·776	27′ „ „
	27·6	52·5	·770	38′ „ „
	27·5	53·4	·794	50′ „ „
		August 9. DOUGLAS, 425 yards up track into house in 4′ 55″.		
	27·4	54·0	·807	Mean normal expiration and inspiration.
	27·3	53·7	·794	Inspiration only, just before experiment.
	19·1	68·0	1·039	Immediately after stop.
	22·8	59·2	·794	8′ after stop.
	24·4	56·0	·758	16½′ „ „
	24·6	55·0	·736	25½′ „ „
	27·1	52·2	·744	35′ „ „
	27·7	51·9	·755	45′ „ „
	27·1	52·7	·758	60′ „ „
	26·7	52·9	·749	80′ „ „
	27·1	51·9	·735	100′ „ „
	26·0	54·5	·766	120′ „ „
	26·7	51·2	·709	142′ „ „
	26·0	53·8	·750	157′ „ „
	26·3	52·5	·727	171′ „ „
	26·9	52·3	·738	Mean expiration and inspiration.
	27·9	53·1	·800	231′ after stop, lunch since last two. Mean inspiration and expiration.
	28·2	53·5	·809	266′ after stop, mean inspiration and expiration.

TABLE VII. (continued).

	CO_2, pressure in mm. Hg.	O_2, pressure in mm. Hg.	R.Q.	
				July 15. HALDANE, up for 1′ 57″.
	25·4	54·9	·756	Immediately before experiment, inspiration only.
	26·4	52·4	·723	
	20·4	69·0	1·199	Immediately after stop.
	23·8	58·8	·817	9′ after stop.
	24·3	55·0	·720	22′ „ „
	25·4	51·3	·665	45′ „ „
				July 25. HALDANE, up for 62″.
8.45 a.m.	27·1	53·7	·801	Normal mean inspiration and expiration.
10.35 a.m.	20·6	69·7	1·210	Immediately after stop.
	22·8	61·3	·872	9′ after stop.
	22·0	57·1	·696	19′ „ „
	23·8	56·7	·752	30′ „ „
	24·3	55·7	·744	46′ „ „
	24·9	55·5	·760	60′ „ „
				August 6. HALDANE, up about 210 yards of track into house.
	26·0	52·1	·736	Normal mean inspiration and expiration.
	25·7	51·5	·707	Inspiration value only, just before experiment.
	18·4	69·1	1·155	1′ after stop.
	21·1	64·2	·986	10′ „ „
	21·1	60·8	·820	20′ „ „
	22·4	56·1	·715	30′ „ „
	23·8	54·6	·721	40′ „ „
	26·1	49·9	·682	55′ „ „
	26·1	49·5	·674	70′ „ „
				July 25. SCHNEIDER, up for 55″.
	32·17	—	—	Normal mean inspiration and expiration.
	31·7	—	—	Inspiration only, just before experiment.
	32·2	—	—	Immediately after stop.
	26·5	—	—	6′ after stop.
	24·8	—	—	11′ „ „
	24·5	—	—	17′ „ „
	25·9	—	—	25′ „ „
	25·8	—	—	35′ „ „
	27·3	—	—	50′ „ „
	29·5	—	—	65′ „ „
	29·4	—	—	100′ „ „

TABLE VII. (continued).

	CO_2, pressure in mm. Hg.	O_2, pressure in mm. Hg.	R.Q.	
				July 25. HENDERSON, up for 80″.
	27·8	—	—	Normal mean inspiration and expiration.
	28·6	—	—	Inspiration only, just before experiment.
	25·1	—	—	Immediately after stop.
	23·8	—	—	7′ after stop.
	25·2	—	—	15′ ,, ,,
	27·0	—	—	30′ ,, ,,
				August 7. SCHNEIDER, up 167 yards in 45″ to laboratory.
	30·4	48·4	·761	Inspiration only, just before experiment.
	27·5	64·1	1·322	Immediately on return.
	21·8	57·5	·712	15′ after stop.
	22·9	57·3	·746	25′ ,, ,,
	26·9	51·1	·720	35′ ,, ,,
	27·3	51·8	·750	50′ ,, ,,
	28·1	53·3	·819	65′ ,, ,,
	27·7	52·9	·793	80′ ,, ,,
	29·3	50·3	·774	100′ ,, ,,
	29·8	48·2	·740	120′ ,, ,,
				August 5. FULLER, morning after arrival, up 122 yards in 60″.
	27·5	51·2	·755	Inspiration only, just before experiment.
	35·8	51·7	1·069	Immediately after stop.
	23·8	57·4	·809	10′ after stop.
	28·2	39·2	·547	21′ ,, ,,
	27·0	50·5	·722	37′ ,, ,,
	28·4	47·0	·685	50′ ,, ,,
	28·2	47·4	·687	65′ ,, ,,
	28·4	45·8	·660	80′ ,, ,,
	28·9	50·6	·785	100′ ,, ,,
				August 6. FULLER, up 167 yards into laboratory in 45″.
	29·2	47·7	·728	Inspiration only.
	35·7	54·6	1·210	Immediately after stop.
	22·3	62·5	·963	8′ after stop.
	21·8	57·8	·744	18′ ,, ,,
	23·4	54·5	·708	28′ ,, ,,
	25·7	50·6	·689	46′ ,, ,,
	26·7	50·2	·711	60′ ,, ,,
	25:7	53·5	·763	80′ ,, ,,
	25·6	53·2	·750	105′ ,, ,,

Several points appear very clearly from these experiments: in the first place it is evident that just at the end of the exertion, and when the hyperpnœa was very extreme (since the work was pushed to the point at which the hyperpnœa was as great as could be tolerated), the alveolar carbon dioxide pressure fell, except in the case of FULLER, to below what it was before the experiment. This fall was very marked in DOUGLAS and HALDANE; less so in SCHNEIDER. In FULLER, on the other hand, the alveolar CO_2 pressure rose on the exertion, just as normally happens near sea-level. Along with the drop in alveolar CO_2 pressure in the first four subjects there was a much greater rise (about 15 mm.) in the alveolar oxygen pressure, and consequently a very marked rise in the alveolar respiratory quotient (*i.e.*, the ratio by volume of CO_2 given off to oxygen absorbed in the lung alveoli). It will be noticed also that in all the subjects the alveolar CO_2 pressure was very low for some time after the exertion, and usually took about 45 to 60 minutes to return to normal; also that the alveolar respiratory quotient, which was extremely high during and just after the exertion, diminished rapidly afterwards, and within about 10 minutes fell to below normal, and remained more or less below normal for more than an hour.

The high respiratory quotient during or just after very severe exertion is also present at sea-level, together with the subsequent fall in alveolar CO_2 pressure and in respiratory quotient. DOUGLAS and HALDANE* have interpreted these phenomena as follows. During sudden and severe muscular exertion the circulation through the active muscles is insufficient to supply them with all the oxygen they require. In consequence of this some lactic acid is formed, as in other conditions when the oxygen supply is insufficient. This acid passes into the blood-stream, and helps the carbon dioxide to excite the respiratory centre. In consequence, a lesser partial pressure of CO_2 is required to excite the respiratory centre to a given amount. During or just after the exertion the effect on the alveolar air of this lactic acid is masked, as a large excess of CO_2 has to be got rid of, and the consequent hyperpnœa implies a considerable rise in the alveolar CO_2 pressure. In spite of the lactic acid, this rise is still present to a greater or less extent, and amounted to several millimetres of mercury in the case of DOUGLAS and others near sea-level. When, however, the excessive production of CO_2 has disappeared the effect of the lactic acid is unmasked, and for about an hour after the exertion the alveolar CO_2 pressure is abnormally low, as the lactic acid takes some time to disappear. That an excess of lactic acid actually remains in the blood for about this time was directly shown by RYFFEL,† and BOYCOTT and CHISOLM‡ found the alkalinity of the blood diminished during a corresponding period. The high respiratory quotient during or just after muscular exertion is a further consequence of the formation of lactic acid, since the increased ventilation due to the action of the lactic acid on the centre washes out pre-formed CO_2 from the body, and

* 'Journ. of Physiol.,' XXXVIII., p. 420, 1909.

† *Ibid.*, XXXIX., p. 29, 1910.

‡ 'Bio-chemical Journal,' V., p. 23, 1910.

brings the general level of CO_2 pressure in the body down lower than would otherwise be the case. It is probable also that the completion of this washing-out process is one, at any rate, of the causes of "second wind." The lowered respiratory quotient some time after excessive muscular work represents the process of recovery during which CO_2 is being stored up again in the tissues to re-establish a normal level of CO_2 pressure when the lactic acid disappears. This point will be again referred to below in the section on the Respiratory Exchange.

The effects of excessive work on Pike's Peak differed from those at sea-level in this respect—that, except in FULLER, the alveolar CO_2 pressure *fell* during and just after muscular exertion, the fall amounting sometimes to one-third. This fall can, we think, best be explained as follows. During hard work at low atmospheric pressure the aeration of the arterial blood with oxygen becomes incomplete, as neither by diffusion nor by active secretion can sufficient oxygen pass through the lung epithelium to aerate the arterial blood as thoroughly as during rest. As a consequence of this deficient aeration with oxygen the respiratory centre is excited to increased activity in consequence of products of deficient oxidation being carried past the lungs, or formed in the centre itself, just as occurs when air deficient in oxygen is breathed during rest. This effect on the centre is superimposed on that due to the lactic acid from the muscles, and in spite of the greatly increased production of CO_2 in the body the breathing is so much increased that the alveolar CO_2 pressure actually falls. The rise in respiratory quotient during work, and the subsequent fall, are of course accentuated by this cause. The difference present in different individuals as regards their reaction to this want of oxygen are such as might be expected from what is already known as to the effects of want of oxygen on the breathing. Some persons will turn blue in the face, and even lose consciousness, in consequence of deficient oxygen without showing any marked hyperpnœa, while others (including DOUGLAS, HALDANE, and HENDERSON) show marked hyperpnœa with want of oxygen before the face becomes at all markedly blue. During the hyperpnœa resulting from short periods of muscular work it was difficult to be sure of blueness of the face, although we thought that the lips became redder a minute or two after the exertion had ceased. When, however, the exertion was continued for a considerable time, as in the next series of experiments, blueness during the exertion was quite evident, and the lips turned redder very shortly after stopping to rest. During the long exertion the excess of the pre-formed CO_2 had been blown off. As a consequence the respiratory quotient had fallen to normal, and the alveolar oxygen pressure was about 10 mm. lower than in short experiments. The appearance of the blueness after long continued exertion may have been due entirely to the alveolar oxygen pressure being about 10 mm. lower than with short exertions; but we are inclined to think that fatigue of the alveolar epithelium was also a potent factor. In unacclimatised persons walking up the Peak the blueness was often extreme.

The following table shows the results of alveolar air analyses with long continued

exertion in walking up the track. The exertion was of course not so severe as in the preceding experiments :—

TABLE VIII.—Alveolar Air during and after long continued severe Muscular Exertion up 25 per cent. Grade.

	CO_2, pressure in mm. Hg.	O_2, pressure in mm. Hg.	R.Q.	
		July 31. HENDERSON, up 1·77 miles (1640 ft. rise) in 55′.		
9 a.m.	27·2	54·4	·837	Normal mean inspiration and expiration.
4.40 p.m.	21·2	58·1	·720	39′ from start, walking.
	19·1	63·6	·833	39¾′ „ „ ¾′ rest.
	23·4	58·0	·808	50′ „ „ walking.
	26·2	63·3	1·227	51′ „ „ 1′ rest, slight apnœa.
	26·1	49·1	·664	7′ from stop, apnœa.
	21·7	57·8	·733	25′ „ „ after breathing period.
	25·8	45·3	·580	40′ „ „ quiet breathing.
	24·8	45·5	·560	60′ „ „ „ „
		August 4. HENDERSON, up 1 mile (1200 feet rise) as fast as possible in 27′.		
8.55 a.m.	25·2	52·2	·701	Inspiration only.
9.33 a.m.	21·1	68·5	1·000	3′ after start.
	21·9	65·7	·912	5′ „ „
	20·8	62·8	·823	20′ „ „
	22·7	58·3	·801	25′ „ „
	22·8	52·0	·624	¾′ after stop.
	25·1	52·5	·702	15′ „ „
	25·8	52·0	·675	30′ „ „
	25·6	52·8	·740	50′ „ „
	26·6	53·0	·780	75′ „ „
	23·7	52·9	·678	100′ „ „
	26·5	46·6	·632	130′ „ „
	24·6	52·7	·703	240′ „ „ and 30′ after lunch.
		August 2. SCHNEIDER, up 1·77 miles (1640 feet rise) in 43′.		
	31·0	48·1	·801	Normal mean, inspiration and expiration.
	30·4	48·4	·787	Inspiration only, just before experiment.
	22·5	60·3	·879	5′ from start.
	24·8	57·8	·883	10′ „ „
	24·7	57·3	·855	20′ „ „
Walking faster	23·1	60·4	·911	36′ „ „
	22·1	61·5	·911	41′ „ „
	23·7	57·1	·805	7′ after stop.
	25·5	51·9	·719	20′ „ „
	26·7	49·4	·696	40′ „ „
	29·1	44·7	·688	60′ „ „
	27·8	49·9	·743	100′ „ „ after lunch.

TABLE VIII. (continued).

	CO_2, pressure in mm. Hg.	O_2, pressure in mm. Hg.	R.Q.	
August 3. SCHNEIDER, up ½ mile in 13′.				
	28·9	50·7	·799	Inspiration only, just before experiment.
	21·7	63·3	·983	2′ from start.
	21·5	63·4	·980	5′ ,, ,,
	20·3	64·1	·952	8′ ,, ,,
	21·0	64·1	·990	1′ after stop.
	20·4	62·4	·866	12′ ,, ,,
	24·5	55·3	·780	25′ ,, ,,
	26·0	53·9	·794	40′ ,, ,,
	28·1	47·9	·705	60′ ,, ,,

It will be seen from this table that during and just after the long-continued powerful exertion the alveolar CO_2 pressure is much below normal, just as with the shorter periods of great exertion; but that after the first few minutes of exertion the respiratory quotient falls to about the normal value, the excess of preformed CO_2 in the body having been blown off by the hyperpnœa. On resting the respiratory quotient falls below normal, while the alveolar CO_2 pressure gradually rises again to a normal value. In the case of Y.H. the observations were complicated by the fact that after the exertion there was a great tendency to periodic breathing, which made the results somewhat irregular. The periodic breathing will be discussed later.

A further series of observations on the alveolar air was made during the quite moderate exertion of walking on the level at about four miles an hour. This exertion produced no real respiratory distress, although, as will be shown below, it increased the respiratory exchange to about six times its amount during rest in bed. The results are shown in Table IX.

TABLE IX.—Alveolar Air during and after Moderate Exercise on the Level.

	CO_2, pressure in mm. Hg.	O_2, pressure in mm. Hg.	R.Q.	
August 9. DOUGLAS, walking at 4 miles per hour for 9′.				
	28·0	54·1	·834	Inspiration only, just before experiment.
	29·4	52·0	·817	Immediately after stop.
	29·5	53·1	·852	9′ after stop.
	28·3	53·0	·806	18′ ,, ,,
	28·4	52·3	·792	30′ ,, ,,

TABLE IX. (continued).

	CO_2, pressure in mm. Hg.	O_2, pressure in mm. Hg.	R.Q.	
August 12. DOUGLAS, walking at 4 miles per hour.				
	26·7	53·7	·785	Inspiration only, just before experiment.
	26·0	54·6	·784	5′ after start.
	27·1	52·0	·752	10′ „ „
August 12. HENDERSON, walking at 4 miles per hour.				
	25·4	54·2	·755	Normal mean inspiration and expiration.
	24·4	55·9	·765	Inspiration only, just before experiment.
	26·6	53·9	·784	8′ from start.
	24·8	57·3	·821	15′ „ „
August 14. HENDERSON, walking at 4 miles per hour.				
	27·2	52·2	·740	Inspiration only, just before experiment.
	26·9	56·9	·864	10′ from start.
	26·8	59·2	·955	15′ after stop.
August 12. SCHNEIDER, walking at 4 miles per hour.				
	31·2	52·9	·917	Normal mean inspiration and expiration.
	30·9	53·4	·921	Inspiration only, just before experiment.
	29·2	55·2	·922	5′ from start.
	29·5	55·9	·960	10′ „ „
August 12. HALDANE, walking at 4 miles per hour.				
	26·0	53·8	·759	Inspiration only, just before experiment.
	21·6	63·9	·954	5′ from start.
	26·0	57·9	·887	8′ „ „
August 14. HALDANE, walking at 4 miles per hour.				
	25·0	54·7	·731	Inspiration only, just before experiment.
	21·0	63·0	·847	5′ from start.
	22·0	61·5	·834	8′ „ „

It will be seen that in DOUGLAS, HENDERSON, and SCHNEIDER, there was little or no change in the alveolar CO_2 pressure during the exertion, or after it. The exertion was insufficient to produce shortage of oxygen in either the contracting muscles or the respiratory centre. Consequently the alveolar CO_2 pressure remained about

normal. Only in the case of HALDANE was there an appreciable fall in the alveolar CO_2 pressure, the rate of walking having been somewhat too fast in his case to allow of a completely normal oxygen supply to the body.

From the foregoing sets of experiments it is clear that the excessive hyperpnœa on exertion at high altitudes is due firstly to the fact that the normal level of alveolar CO_2 pressure is greatly lowered. On Pike's Peak this lowering implied an increase of about 50 per cent. in the volume of air breathed per unit mass of CO_2 produced in the body. During hard muscular work the alveolar CO_2 pressure is still further lowered, however, in consequence of deficient aeration of the arterial blood with oxygen. The net result on Pike's Peak was that during fairly hard work the alveolar CO_2 pressure was about 20 mm. of mercury, instead of about 45 mm. with corresponding work at sea-level. In other words the lung ventilation required to be about $2\frac{1}{4}$ times as great for a given elimination of CO_2. This is not all, however, for the rapid lowering of the CO_2 pressure during the work necessitated the washing out of a large quantity of pre-formed CO_2 from the body. During this process, as has been shown, the respiratory quotient rises to 1·2 or 1·3. This implies a further temporary increase of about 30 per cent. in the lung-ventilation per unit of work done, or of oxygen absorbed, so that for the time the hyperpnœa is probably about three times greater than would be the case with a corresponding exertion at sea-level. The extreme and urgent hyperpnœa produced by such an exertion as walking up the cog-railway track at even two miles an hour is thus readily intelligible. Such an exertion at sea-level would cause no respiratory inconvenience, and very little disturbance of the respiratory quotient.

One of us (SCHNEIDER) had occasion to descend on July 28 for 24 hours to Colorado Springs. Next day, just before ascending, he walked up the cog railroad track from Manitou to the next station, the gradient being nearly the same as near the top. Walking at the same rate as in the experiments near the top he experienced nothing like the same hyperpnœa. He was able to walk for about a mile at a rate of 4·4 miles an hour on a gradient of about 1 in 5—a rate quite out of the question near the summit. His resting alveolar CO_2 pressure, determined just before starting from Manitou on a subsequent visit of 24 hours to Colorado Springs, was only about 3 to 4 mm. higher than on the summit, so that the greatly diminished hyperpnœa could not be attributed to a mere alteration in the resting alveolar CO_2 pressure, and must have been caused mainly by a direct influence of the greatly increased alveolar oxygen pressure. This observation therefore confirms the interpretation given above of the more or less immediate influence of want of oxygen on the hyperpnœa experienced at the summit during any considerable exertion.

With regard to the influence of acclimatisation on the hyperpnœa of muscular exertion, we unfortunately made no definite measurements. Excessive hyperpnœa on exertion persisted in all of us up to the end of our stay; but we noted that the hyperpnœa on slight exertion became less after the first day or two, and that walking

up-hill became progressively easier. We also seemed to be much less affected by muscular exertion than the people who came up, and used to pull some of the more helpless ones up the last steep part of the track.

VI. *Periodic Breathing.*

The fact that at high altitudes the breathing tends to become periodic or of the "Cheyne-Stokes" type was discovered by Mosso, who made many valuable observations on the subject, and published a number of tracings.* Unfortunately, he was led to very mistaken conclusions as to the cause of nearly all of the peculiar respiratory phenomena met with at high altitudes.

Periodic breathing appeared at one time or another in all of us. In HENDERSON it was constantly present during sleep to the end of our stay, and often during the waking hours, particularly in the first days. In HALDANE it was often present, and in DOUGLAS not so often, during the day for the first few days; in SCHNEIDER it was only once observed, six days after our arrival. Except in HENDERSON, it was not observed during sleep. On the whole, its appearance became much less frequent as we became acclimatised. Curiously enough, it re-appeared in DOUGLAS, who had been free from it for weeks, on the last morning of our stay, after the exertion of moving some heavy packing-cases.

The type of periodic breathing differed in the different persons. We made a number of records with a Marey stethograph attached to a slow-running Mackenzie polygraph, and some of these records are reproduced. In HENDERSON (figs. 9, 10, No. 3,

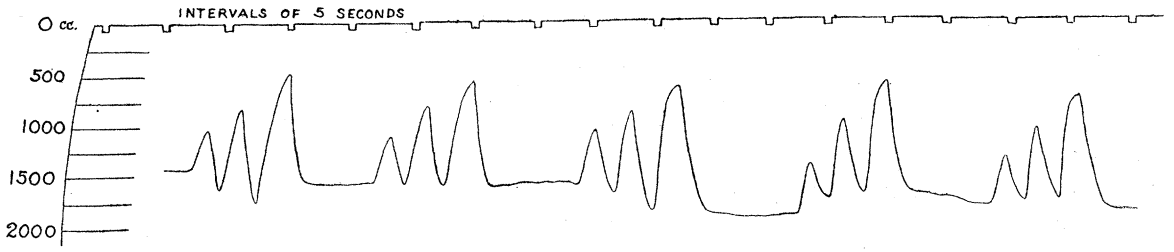

Fig. 9.

HENDERSON, August 13. Quantitative record of the respiration during periodic breathing. Inspiration upwards.

and 13), the type was quite distinctive, the breaths occurring in groups of three or four, each succeeding breath being deeper than the preceding one, and the last being very deep. Fig. 9 is a quantitative record of this breathing, the tracing being made, not in the ordinary way with the Marey stethograph, but with an arrangement giving a movement of the tracing-pen quantitatively proportional to the air breathed.

* MOSSO, 'Life of Man on the High Alps,' London, 1898, chap. 3.

In HALDANE (figs. 10, No. 2 and No. 4, and 13, No. 1) each group consisted of three or four more or less equal breaths; while in DOUGLAS (figs. 10, No. 1, and 13, No. 2) the depth of the successive breaths tended to "wax and wane" in accordance with

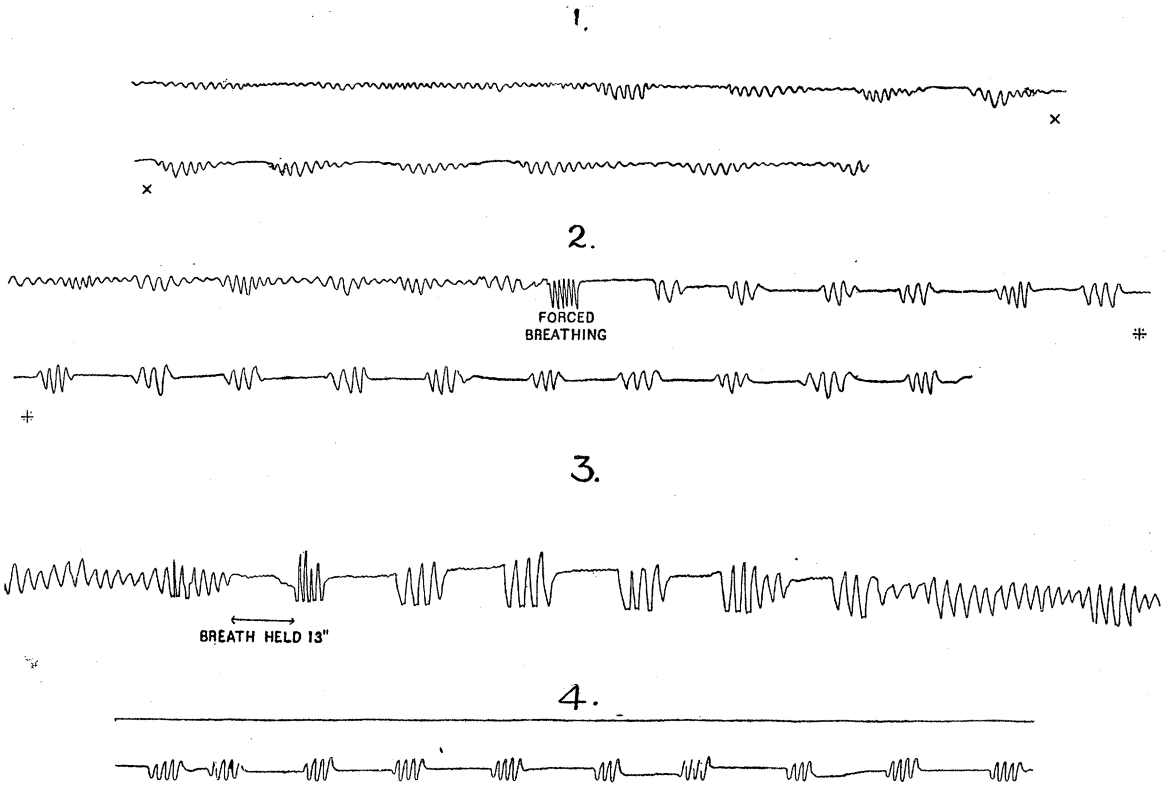

Fig. 10.

Tracing 1. DOUGLAS, July 12. Evening of arrival on Pike's Peak. Natural periodic breathing.

Tracing 2. HALDANE, July 12. Evening of arrival on Pike's Peak. Natural periodic breathing passing into typical Cheyne-Stokes breathing after making six forced breaths.

Tracing 3. HENDERSON, July 12. Evening of arrival on Pike's Peak. Natural breathing slightly periodic and passing into well-marked periodic breathing after holding the breath to the breaking point (13 seconds).

Tracing 4. HALDANE, July 15. Natural periodic breathing.

The tracings should be read from left to right and from above downwards.

Fig. 11.

FULLER, August 4. Tracing of natural respiration whilst sitting quiet two hours after arrival on Pike's Peak. Periodicity only shown by the occurrence of gasps at intervals. Inspiration downwards. Time in seconds.

the classical descriptions of Cheyne-Stokes breathing. In FULLER a single deep breath occurred at periodic intervals (fig. 11). It was noticed in DOUGLAS, HENDERSON, and HALDANE that the periodic breathing tended to occur after some muscular exertion. In HENDERSON this was very marked, and the breathing was

often more or less periodic even during the exertion of walking. At any time periodic breathing could be started by a few forced breaths (fig. 10, No. 2) or by holding the breath for a few seconds (fig. 10, No. 3).

Mosso concluded that the periodic breathing is an effect, not of want of oxygen, but of "acapnia" or deficiency of CO_2, produced as a direct physical effect of the diminution of atmospheric pressure.* This acapnia tends to cause a diminution in the breathing, since the normal stimulus of CO_2 in the respiratory centre is diminished. The diminution may show itself, either by a general diminution in the depth or frequency of the respirations, or in periodic diminutions. Periodic breathing is, according to this explanation, simply one of the means by which the respiratory centre diminishes the lung ventilation. Mosso furnished apparent experimental proof that periodic breathing at high altitudes is not abolished by breathing oxygen in place of atmospheric air. He also published tracings and other measurements to show that the volume of air is, or may be, diminished at low atmospheric pressures. These tracings are not quantitative records of the air breathed; and such measurements as were made of the actual volume of air breathed were vitiated by the fact that the rate of respiratory exchange was not taken account of in making the comparison. As shown in the preceding section, and in a succeeding paper by Miss FitzGerald, the alveolar CO_2 pressure is always diminished at high altitudes. In other words, the volume of alveolar ventilation per unit mass of CO_2 produced is always increased. If the volume of air breathed is reduced to standard pressure and temperature there is, of course, a diminution in the air breathed†; but the volume reduced in this way has no physiological significance in view of what is now known as to the relation between respiratory movements and partial pressure of CO_2 in the alveolar air and arterial blood.

Other writers have so far accepted Mosso's explanation as to regard periodic breathing as an effect of diminished excitability of the respiratory centre, though why this, if it existed, should produce periodic breathing is not at all clear. In any case, there is no indication of diminished excitability of the centre at high altitudes.

It was discovered by Pembrey‡ in 1905 that ordinary Cheyne-Stokes breathing, as observed in clinical cases, can be abolished by the administration of pure oxygen. Douglas and Haldane§ showed in 1909 that temporary periodic breathing can easily be produced in most normal persons, and at normal atmospheric pressure, as a consequence of forced breathing of air, or by breathing air through soda-lime and a long tube, or other simple methods by which the alveolar CO_2 pressure is temporarily

* That no such physical effect is produced was shown clearly by Boycott and Haldane, who found that when the alveolar oxygen pressure was prevented from falling mere reduction of atmospheric pressure had absolutely no influence on the alveolar CO_2 pressure ('Journ. of Physiol.,' XXXVII., p. 363, 1908).

† On Pike's Peak this diminution was about 14 per cent.

‡ 'Journ. of Physiol,' XXXIII.; 'Proc. Phys. Soc.,' p. 18, 1905; 'Medico-Chirurgical Transactions,' XL., p. 49, 1907.

§ 'Journ. of Physiol.,' XXXVIII., p. 401; and XXXVIII., p. 420, 1909.

reduced. They showed by analysis of the alveolar air and various control experiments that the onset of each period of breathing is due, not simply to rise of the alveolar CO_2 pressure, but to diminished alveolar oxygen pressure in addition; and that the cessation of each period depends similarly on rise in the alveolar oxygen pressure. HENDERSON has further shown that there are variations in the gas content of the arterial blood which correspond with this conclusion.* Want of oxygen is thus a necessary condition to the production of the periodic breathing, which is essentially due to the fact that the excitation, in so far as produced by the want of oxygen, occurs very rapidly and ceases very rapidly. The centre thus responds like an engine provided with a very sensitive governor but no fly-wheel, and thus acts periodically. The normal stimulus of CO_2 *per se*, on the other hand, acts and ceases much more gradually, with the consequence that normal breathing is quite regular, like the working of an engine with a heavy fly-wheel.

The very rapid effect produced by want of oxygen in helping to excite the respiratory centre must be carefully distinguished from the comparatively slow, gradual, and long-lasting effect due to an alteration in the alkalinity of the blood. DOUGLAS and HALDANE suggested that the rapid effect is due to production of lactic acid in the cells of the centre itself, and that the equally sudden disappearance of the effect when the alveolar oxygen pressure rises is due to very rapid oxidation or assimilation of this intra-cellular lactic acid, although lactic acid which has passed into the blood takes a considerable time to disappear. Perhaps it is more probable that some other substance than lactic acid is responsible—for instance, some readily oxidisable substance escaping complete oxidation in the lungs or formed in the centre itself. Or oxygen-want may simply act directly in helping to excite the centre. This latter explanation is the simplest, and is quite a possible one so long as we do not assume that oxygen-want *per se*, and without the aid of CO_2, is an adequate stimulus to the centre.

In a subsequent paper DOUGLAS† showed that at the low atmospheric pressure met with on the Peak of Teneriffe the periodic breathing which follows forced breathing lasts much longer, and may continue for more than fifteen minutes after forced breathing for one minute. He also proved by numerous experiments that the commencement and cessation of the periods of breathing depend on variations in the oxygen pressure of the alveolar air, just as at sea-level, and that these variations, as might be expected, remain within the critical limits for a much longer time than when the oxygen pressure of the inspired air is normal. Even at Colorado Springs we found that forced breathing gave much more prolonged periodic breathing than at Oxford. With a sufficient lowering of the barometric pressure a point must evidently be reached where the smallest lowering of alveolar oxygen pressure will initiate periodic breathing, or where this form of breathing will become permanent.

It would thus seem almost certain that the spontaneous periodic breathing met

* 'American Journ. of Physiol.,' XXV., pp. 310, 385, 1910.

† 'Journ. of Physiol.,' XL., p. 454, 1910.

with at high altitudes depends upon want of oxygen acting as a factor in rapidly exciting the respiratory centre. Against this conclusion, however, there stands the apparent observation made by Mosso on Monte Rosa, that the administration of oxygen did not stop or modify the periodic breathing.*

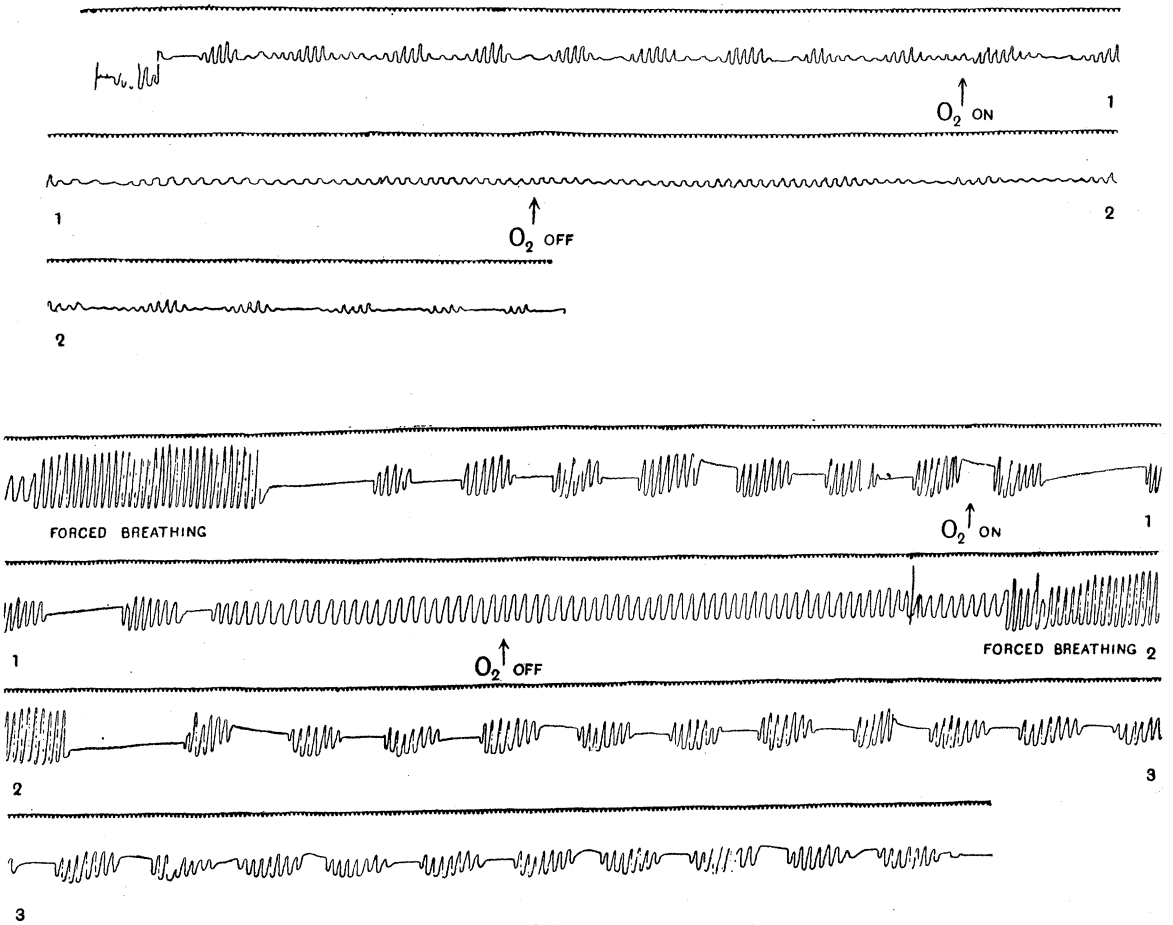

Fig. 12.

Upper tracing. July 16, HALDANE. Natural periodic breathing abolished by administration of oxygen. Reappearance of periodic breathing on withdrawing the oxygen. Subject breathing through valves throughout.

Lower tracing. July 20, DOUGLAS. Periodic breathing induced by making thirty forced breaths. Periodicity abolished by administration of oxygen. Repetition of the forced breathing followed by periodic breathing.

Time tracings in seconds. Inspiration downwards. The tracings should be read from left to right and from above downwards.

Mosso's experiment consisted in administering oxygen through a funnel held close to the face during sleep. This method of administering oxygen was a very uncertain one, and it seemed very doubtful whether much of the oxygen was really inhaled during

* MOSSO, "La respiration périodique (phénomène de CHEYNE-STOKES) telle qu'elle se produit chez l'homme sur les Alpes par l'effet de l'acapnie," 'Travaux du laboratoire scientifique du Monte Rosa,' vol. II., 1907.

the experiment. In attempting to administer CO_2 by this method one of us found that hardly any of the gas was inhaled. As already mentioned, we frequently observed in one or other of ourselves persistent periodic breathing during waking hours, so that it was easy to ascertain the effects of breathing oxygen.

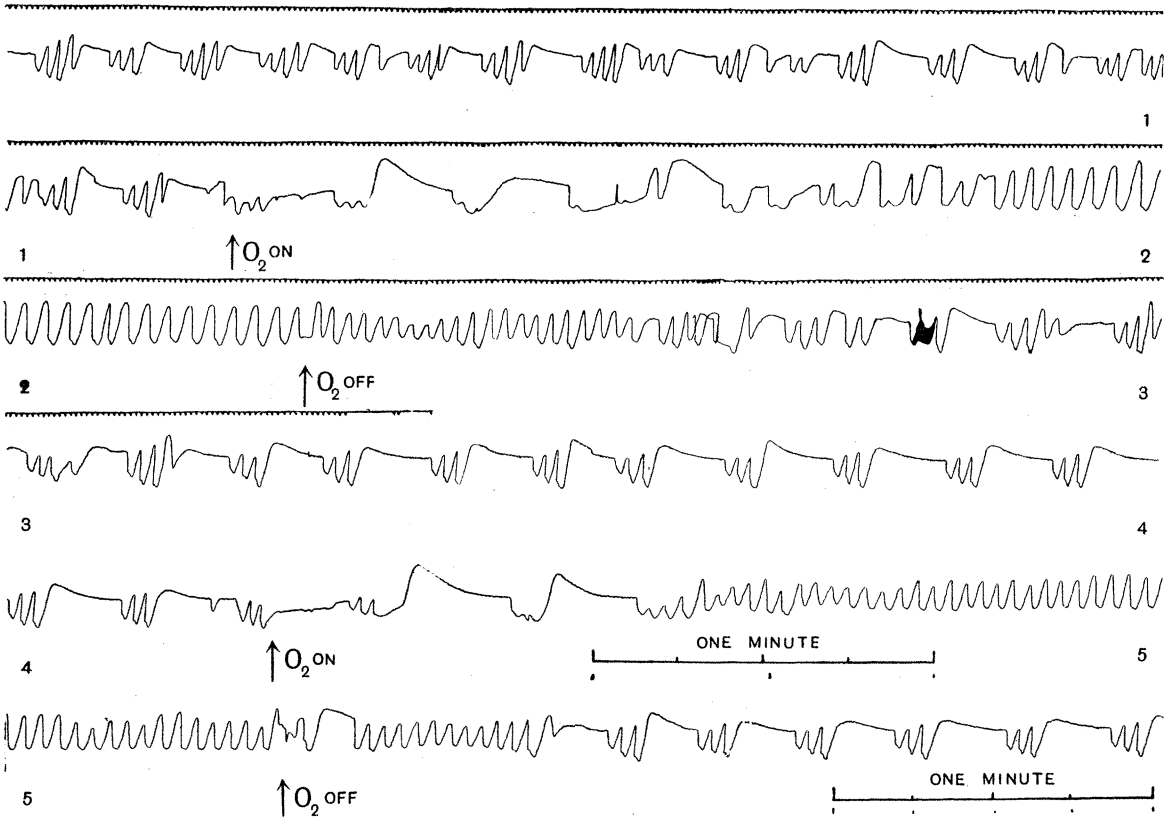

Fig. 13.

July 27, HENDERSON. Natural periodic breathing on the return from climbing a height of 1200 feet in 25 minutes. Periodicity abolished by the administration of oxygen. Time tracing in seconds. Inspiration downwards.

The immediate effect of the oxygen was to cause a very irregular type of breathing with great prolongation of the individual breaths accompanied by great subjective discomfort, which passed off rapidly. This effect has been noticed in other cases where the subject has been exposed to great want of oxygen just previous to the administration of pure oxygen.

The tracing should be read from above downwards, and from left to right.

The subject of the experiment breathed through a short mouth-piece connected with inspiratory and expiratory valves. The inspiratory valve was connected with a piece of wide-bore tubing leading to a large three-way tap, which could be opened so as to connect either with a bag of oxygen or with the outside air. The breathing was recorded by means of a modified Marey stethograph. Figs. 12 and 13 are tracings of spontaneous periodic breathing, showing the effects of breathing oxygen. At the points indicated the tap was turned, so that either air or oxygen was breathed. The

oxygen was pure, being produced directly from an oxylith generator; but little or none of the oxygen would reach the lung alveoli at the first breath, owing to the dead space in the connections.

From these tracings it is perfectly clear that oxygen abolished the periodic breathing, which returned again soon after air was breathed. It will be seen that the first effect of the oxygen was to prolong the succeeding period of apnœa, but that at least one other period of breathing, and subsequent apnœa, followed before the breathing became regular. It might, perhaps, have been expected that the oxygen would simply produce a long apnœa, followed by regular breathing. This would doubtless have been the case if the oxygen inspired at first had been sufficient to raise the alveolar oxygen pressure higher; but as a matter of fact it would take a number of breaths thoroughly to wash out the alveoli with oxygen, and the first two or three breaths would only raise the oxygen pressure sufficiently to prolong the subsequent apnœa. The numerous analyses of alveolar air by DOUGLAS and by DOUGLAS and HALDANE, after taking in a breath or two of oxygen, illustrate this point. Similarly, it took a considerable time after the breathing of air was re-established before the periodic breathing returned.

We are now in a position to discuss the periodic breathing and other allied phenomena observed on Pike's Peak. It will be seen from Tables II.–V. and fig. 6 that on ascending Pike's Peak the alveolar oxygen pressure fell from about 100 mm. at sea-level to about 50 mm. At this alveolar oxygen pressure want of oxygen plays, under ordinary circumstances, a part in exciting the respiratory centre in most persons; and it is only what might be expected, in view of the investigations of DOUGLAS and HALDANE on artificially produced periodic breathing, that a tendency to periodic breathing would be produced; for with any pause in the breathing the alveolar oxygen pressure would fall sufficiently to lower the exciting threshold value of the alveolar CO_2 pressure, and so produce a sudden excessive excitation of the respiratory centre; and this excitation would disappear with equal suddenness when the excessive breathing raised the alveolar oxygen pressure above the existing normal. Conditions similar to those existing after forced breathing at sea-level would, in fact, exist permanently in the lungs. In the case of the after-effect of forced breathing the abnormal condition is brought about by temporary deficiency in the carbon dioxide discharge; while at high altitudes deficiency in the oxygen pressure of the inspired air brings about a similar abnormal relation between the pressures of oxygen and CO_2 in the alveolar air.

Even when the breathing was quite regular on Pike's Peak, periodic breathing was easily started either by holding the breath for a few seconds or by deep inspirations (figs. 10 and 12). Mosso has already published tracings showing that a single deep inspiration will initiate periodic breathing at high altitudes.

The tendency to disappearance of periodic breathing when acclimatisation was established is also intelligible, as the rise in arterial oxygen pressure would make it

less easy for shortage of oxygen to affect the respiratory centre. It is also easy to understand the sudden and overwhelming hyperpnœa caused by any unusual muscular exertion, for under such circumstances, as we have already seen, the blood becomes imperfectly aerated with oxygen. As a consequence of this the exciting threshold of CO_2 pressure is suddenly lowered and intense hyperpnœa is produced. If the oxygen supply catches up and overtakes the demand an equally sudden apnœa, or partial apnœa results; and with this violent game of battledore-and-shuttlecock going on in their respiratory centres many unfortunate persons ascended the last part of the track on Pike's Peak. As illustrating what was apt to happen we may quote the following notes from our journal:—

> "July 22. SCHNEIDER and HENDERSON walked down cog railway about a mile (vertical distance about 1000 feet). Returned in 30 minutes. Up the last 200 yards of track (25 per cent. grade) they walked faster. SCHNEIDER led, but HENDERSON, who was lagging, made an extra effort, caught up, and had a few seconds of vigorous hyperpnœa. He then had a fine supply of 'second wind,' and went with long steps up the remainder of the slope, leaving SCHNEIDER some way behind. He was then nearly knocked out, however,—great respiratory distress, nearly vomited, turned an ashy grey colour, knees wobbled. He managed to reach the laboratory however. After the violent hypernœa there was a period of irregular apnœas and deep gasps, then Cheyne-Stokes breathing. Oxygen caused at first apnœa, then regular deep breathing, very comforting and agreeable to the subject. On stopping the oxygen Cheyne-Stokes breathing returned."

The greater tendency to periodic breathing *after* an exertion was probably due to a temporary fatigue of the lung epithelium, and consequent lowering of *arterial* oxygen pressure. After an exertion the *alveolar* oxygen pressure was usually rather high for some time, so that a lowering of this could not have been the cause.

Closely connected with periodic breathing is the fact that any temporary holding of the breath caused hyperpnœa immediately. This was very evident during the first days on Pike's Peak, and caused us a good deal of inconvenience in such operations as reading gas burettes, shaving, &c. At ordinary barometric pressures one is accustomed to hold the breath during various short exertions, and to make it synchronise with other exertions, such as that of walking. The partial loss of this power was a distinct trouble.

We were all able to hold the breath at sea-level for about 40 seconds by voluntary effort. After the first 48 hours on Pike's Peak, HENDERSON, DOUGLAS, and HALDANE could not hold longer than 15 to 18 seconds, though SCHNEIDER could hold for 40 seconds. On our descent to Manitou, HENDERSON and HALDANE found, much to their surprise, that they could still hold no longer than on the summit. At Colorado Springs during the next days they could hold, as could DOUGLAS, for about 30 seconds.

The reason why they could not hold longer at Manitou just after the descent is not clear; but of course their arterial oxygen pressure was unknown, although their alveolar oxygen pressure was certainly much higher than on Pike's Peak. At sea-level it is possible to hold the breath much longer if the lungs are filled with oxygen, as was shown by HILL and FLACK, and confirmed by DOUGLAS and HALDANE.*

As regards the varying susceptibilities of different persons to periodic breathing, we think that it is probably connected with varying susceptibilities in the respiratory centre to want of oxygen. This varying susceptibility seems to be a very marked phenomenon. Thus the respiratory centres of both BOYCOTT and POULTON were found to respond much less readily to want of oxygen than those of HALDANE, DOUGLAS, and WARD. BOYCOTT'S alveolar CO_2 pressure remained steady in the steel chambers of the Lister Institute at diminished pressures which had markedly lowered HALDANE'S alveolar CO_2 pressure. At lower pressures BOYCOTT simply became bluer and bluer, and rapidly developed acute symptoms of mountain sickness. In an experiment with RYFFEL† he remained for four hours at a pressure of 450–460 mm., the same pressure as on Pike's Peak. At the end of the experiment he "was cyanosed and suffered from violent headache and nausea." With a rapidly falling alveolar oxygen pressure some persons simply become blue and lose consciousness, without the respiratory centre making any evident response. Of ourselves HENDERSON'S respiratory centre seems to have been most responsive, and SCHNEIDER'S least so, to want of oxygen in the alveolar air. HENDERSON suffered least, and SCHNEIDER most, from headache, &c., preliminary to acclimatisation; and HENDERSON showed most, and SCHNEIDER least, tendency to periodic breathing. SCHNEIDER could also hold his breath longest, and his alveolar CO_2 pressure was highest just after powerful exertions. The marked individual differences which are observed in the response of the respiratory centre to changes in the alveolar air are very probably due at least partly to differences in the freedom of the blood-supply to the centre and in the manner in which this supply is regulated by the arterioles.

We may mention at this point an observation first made incidentally on himself by HENDERSON. He had occasion to fill some sampling vessels with air, and was doing so by rapidly squeezing a small india-rubber bag provided with valves to direct the air. He found that on continuing this exertion for a short time he became very hyperpnœic, although the exertion was a very slight one as compared, for instance, with that of walking. The hyperpnœa lowered his alveolar CO_2 pressure to 19·6 mm., with the very high alveolar respiratory quotient of 1·28. He was thus rapidly washing out CO_2 from his blood. The effect on SCHNEIDER was similar; but in DOUGLAS and HALDANE it was much less. At sea-level (New Haven) this marked effect could no longer be obtained, though it was partly present at Colorado Springs. The most probable explanation is that products of imperfect oxidation in the

* 'Journ. of Physiol.,' XXXVIII., p. 424, 1909.

† *Ibid.*, XXXIX., p. 29, 1910.

fatigued flexor muscles of the fingers escaped oxidation in the lungs in consequence of the lowered alveolar oxygen pressure on Pike's Peak, and were thus enabled to act on the respiratory centre. This explanation is in harmony with our general conclusions (stated in Section X.) as to the physiological action of low atmospheric pressures. The matter is at present being investigated further by one of us, as the phenomena are evidently of great interest.

VII. *The Total Respiratory Exchange.*

It would seem perhaps unnecessary for us to have taken up this subject in detail on the present expedition after the classical researches of DURIG and of ZUNTZ and their colleagues, undertaken in the different expeditions to Monte Rosa and Teneriffe during the last few years.* After consideration it became, however, evident that we should require data on this point in our own case, as the information which had been previously obtained would not in all cases satisfy our requirements. The points on which we required definite information were, in the first place, measurements of the total ventilation of the lungs, which we might compare with the behaviour of the alveolar air, so as to obtain a more precise idea of the various factors concerned in adjusting this ventilation under the altered conditions of life (this has been already dealt with in Section V.); in the second place we required information on the actual oxygen consumption under different conditions of rest and activity in order to investigate the factors determining the passage of gases through the alveolar walls; in the third place we desired to know to what extent the atmospheric deficiency of oxygen influenced the character of the metabolic processes after complete acclimatization to the high altitude.

The method which we adopted has been already described in Section V. The sample of air which was taken off from the bag in which the expired air had been collected was analysed, and the total volumes of oxygen consumed and of carbonic acid produced during the experiment were then readily calculated. All the values obtained were calculated as for one minute. The time during which the sample of expired air was being collected varied from about $6\frac{1}{2}$ minutes in the experiments made during rest in bed to a little over one minute in the most strenuous exertions on the top of the Peak; the actual volume of air collected varying between 40 and 95 litres when measured at the temperature of the meter, and as a general rule being over 50 litres. The shortness of some of the experimental periods may at first sight appear to detract from exactness in the results, but we would point out that the period was curtailed in proportion as the work got more severe, and it is precisely in

* DURIG and ZUNTZ, 'Arch. f. (Anat. u.) Physiol.,' Suppl., 1904, p. 417; ZUNTZ, LOEWY, MÜLLER, and CASPARI, 'Höhenklima und Bergwanderungen,' Berlin, 1906; DURIG, KOLMER, RAINER, REICHEL, and CASPARI, 'Denkschr. d. Math. Naturwiss. Kl. der K. Akad. d. Wissensch. Wien.,' 1909, vol. LXXXVI.; DURIG, V. SCHRÖTTER, and ZUNTZ, 'Biochem. Zschr.,' XXXIX., p. 435, 1912.

the last condition that the respiration is least susceptible to accidental alteration. Neither do we think that samples of expired air so small as 40 litres (corresponding to the total volume expired during a period of 6 or $6\frac{1}{2}$ minutes when at rest in bed) lead to a fallacious result. A few direct observations made on this point before leaving England showed that doubling the length of the experimental period made no difference to the results. The simple apparatus which we employed had the great advantage that the experiments could be entirely completed by the subject himself without external assistance—an advantage which became really significant on the summit of the Peak when we were all working under high pressure. The resistance of the valves and tubing was extremely slight under all ordinary conditions of muscular exertion, but became evident in the most violent exertions on the Peak, for the apparatus had not been designed to allow of the perfectly free passage of air through it at a rate of nearly 100 litres a minute.

We had only been able to make a series of control observations on one of us (DOUGLAS) before the start of the expedition, and these were made at Oxford. In Colorado Springs we came to the conclusion that it would probably fulfil our purpose best if we made numerous observations on the same subject rather than a limited number of observations on all the members of the expedition. All the experiments in America, as well as the second series of control experiments in Oxford, were therefore made on DOUGLAS.

In the experiments which we are about to describe we were particularly anxious to obtain information on the total respiratory exchange under the various conditions associated with normal waking life, and we have not, therefore, pursued in great detail the respiratory exchange during complete rest which has been an outstanding feature in the work of other observers. The experiments bearing on this point are contained in Table X., the first series being made on Pike's Peak, and the second four months later in Oxford.

In each series the experiments were made immediately after waking in the morning before the subject rose. The apparatus was arranged the evening before the experiment by the side of the bed so that the experiment could be commenced with the least possible movement on the part of the subject, and a period of five minutes was allowed to elapse after commencing to breathe through the valves before the sample was taken. It will be noted that the individual results do not vary much from one another and that the average respiratory exchange is almost the same in the two cases, though the series on Pike's Peak gives slightly the greater value (248 c.c. oxygen and 206 c.c. CO_2 on Pike's Peak as opposed to 237 c.c. oxygen and 197 c.c. CO_2 in Oxford).

For the purpose of comparison in the series of experiments on the effects of muscular work we took a different unit of rest, namely, standing still whilst keeping the muscles as slack as was consistent with the retention of the erect posture. The subject remained in this position for a period of five or ten minutes after previously

TABLE X.—Respiratory Exchange at Rest in Bed, immediately after Waking in the Morning.

	Date.	Barometer in mm. Hg.	Breaths per minute.	At 37°, moist and prevailing barometer.		At 0° and 760 mm.		Respiratory quotient.	C.c. expired air at 37°, moist and prevailing barometer per 1 c.c. of CO_2 at S.T.P. produced.
				Litres breathed per minute.	C.c. per breath.	C.c. O_2 absorbed per minute.	C.c. CO_2 produced per minute.		
Pike's Peak.	1911.								
	Aug. 3 . . .	454	16·5	10·04	609	242	208	·860	48·3
	4 . . .	457	17·3	10·08	583	251	210	·837	48·0
	5 . . .	456	16·0	9·97	623	256	201	·785	49·6
	7 . . .	459	18·0	10·36	576	240	206	·858	50·3
	8 . . .	458	17·7	10·36	586	247	203	·822	51·0
	9 . . .	460	18·0	10·42	580	250	209	·836	49·9
	Mean . . .	457	17·3	10·21	593	248	206	·833	49·5
Oxford.	1911.								
	Dec. 6 . . .	761	16·5	7·85	476	251	209	·833	37·6
	7 . . .	749	16·7	7·42	445	234	186	·795	39·9
	8 . . .	745	17·6	7·37	419	226	186	·823	39·6
	10 . . .	734	16·3	7·87	483	234	203	·867	38·8
	11 . . .	739	17·2	8·14	473	252	208	·826	39·1
	12 . . .	751	16·5	7·39	448	225	187	·831	39·5
	Mean . . .	747	16·8	7·67	457	237	197	·829	39·1

performing the slight work associated with the ordinary laboratory routine before commencing to take the sample of expired air; the collection of the sample took $3\frac{1}{2}$–$6\frac{1}{2}$ minutes, during which time 60–100 breaths were taken. The full results of these experiments are given in Tables XI. and XII. It was found to be quite easy to get consistent results for the total respiratory exchange after standing at rest for the periods noted, the longer preliminary period giving values which were on the average lower than those obtained with the shorter preliminary period, but only by an insignificant amount. The average figures obtained for the respiratory exchange per minute in the three series of results at standing rest were about 40 per cent. higher than those at complete rest in bed. The first series in Oxford in the months preceding the expedition gave 333 c.c. oxygen and 272 c.c. CO_2; second series in Oxford some months after the return, 330 c.c. O_2 and 266 c.c. CO_2; experiments on Pike's Peak, 345 c.c. O_2 and 285 c.c. CO_2. The two series in Oxford therefore agree

TABLE XI.—Respiratory Exchange whilst Standing Still in the Erect Posture.

	Date.	Barometer in mm. Hg.	Breaths per minute.	At 37° moist and prevailing barometer.		At 0° and 760 mm.		Respiratory quotient.	C.c. expired air at 37°, moist and prevailing barometer per 1 c.c. of CO_2 at S.T.P. produced.
				Litres breathed per minute.	C.c. per breath.	C.c. O_2 absorbed per minute.	C.c. CO_2 produced per minute.		
Oxford Series 1.	1911.								
	Feb. 7 . . .	773	—	10·80	—	336	271	·807	39·9
	14 . . .	771	—	9·85	—	320	254	·795	38·8
	March 22 . . .	757	—	9·35	—	343	297	·866	31·5
	24 . . .	759	—	11·83	—	336	290	·863	40·8
	31 . . .	755	—	8·80	—	329	275	·836	32·0
	April 2 . . .	757	—	9·72	—	316	254	·804	38·3
	15 . . .	763	—	10·71	—	365	288	·790	37·2
	May 2 . . .	755	—	11·30	—	350	305	·871	37·1
	June 5 . . .	766	15·8	9·73	616	312	237	·760	41·1
	6 . . .	770	20·7	11·48	554	319	250	·784	45·9
	Mean . . .	763	18·3	10·36	585	333	272	·818	38·3
Oxford Series 2.	1911.								
	Dec. 12 . . .	751	18·2	10·30	566	323	262	·811	39·3
	13 . . .	744	18·0	10·31	573	310	251	·810	41·1
	13 . . .	744	19·2	10·69	556	328	267	·814	40·0
	14 . . .	751	18·8	11·40	606	335	296	·884	38·5
	1912.								
	Feb. 12 . . .	745	19·0	10·79	568	337	258	·766	41·8
	15 . . .	762	19·0	10·42	549	310	252	·813	41·4
	19 . . .	745	18·0	10·77	599	339	284	·838	37·9
	19 . . .	743	16·4	10·14	619	332	256	·771	39·7
	20 . . .	747	18·2	10·10	555	321	257	·801	39·3
	21 . . .	756	15·7	9·84	627	322	258	·801	38·1
	21 . . .	757	17·0	10·60	624	349	278	·796	38·1
	24 . . .	758	17·8	10·08	566	307	241	·785	41·8
	24 . . .	758	17·2	10·58	615	356	277	·778	38·2
	26 . . .	760	16·4	10·29	626	337	266	·789	38·7
	27 . . .	761	17·9	9·94	555	298	242	·812	41·1
	March 19 . . .	740	15·1	10·48	694	339	278	·820	37·7
	21 . . .	733	15·7	10·89	694	342	279	·816	39·0
	22 . . .	740	14·7	10·12	689	346	276	·798	36·7
	23 . . .	748	14·7	9·98	679	333	269	·808	37·1
	24 . . .	750	14·5	9·99	689	333	273	·820	36·6
	25 . . .	760	15·9	10·39	653	327	265	·810	39·2
	Mean . . .	750	17·0	10·39	614	330	266	·807	39·1
Mean of all experiments where data are complete		752	17·1	10·40	612	328	264	·804	39·5

TABLE XII.—Respiratory Exchange whilst Standing Still in the Erect Position.

	Date.	Barometer in mm. Hg.	Breaths per minute.	At 37° moist and prevailing barometer.		At 0° and 760 mm.		Respiratory quotient.	C.c. expired air at 37°, moist and prevailing barometer per 1 c.c. of CO_2 at S.T.P. produced.
				Litres breathed per minute.	C.c. per breath.	C.c. O_2 absorbed per minute.	C.c. CO_2 produced per minute.		
Pike's Peak.	1911.								
	July 14 . . .	461	—	12·89	—	339	251	·740	51·4
	16 . . .	461	16·0	12·64	790	339	278	·820	45·5
	18 . . .	457	22·0	14·58	662	340	284	·835	51·3
	19 . . .	457	22·9	15·69	685	351	305	·869	51·4
	22 . . .	457	17·0	15·04	885	355	314	·885	47·9
	22 . . .	457	19·4	15·64	806	366	309	·844	50·6
	29 . . .	460	18·3	14·48	791	344	287	·835	50·5
	31 . . .	456	17·1	13·55	792	327	266	·814	51·0
	Aug. 7 . . .	459	21·0	15·29	728	352	290	·824	52·7
	7 . . .	459	22·2	14·76	665	343	280	·816	52·7
	8 . . .	460	22·6	15·32	678	347	282	·813	54·4
	8 . . .	460	23·9	15·84	663	345	282	·818	56·2
	9 . . .	460	24·6	14·94	608	324	272	·840	55·0
	12 . . .	459	23·3	15·23	654	346	288	·832	52·9
	14 . . .	462	20·3	15·48	762	360	290	·806	53·4
	Mean . . .	459	20·8	14·76	726	345	285	·826	51·8
Mean of all experiments where data are complete		459	20·8	14·89	726	346	288	·832	51·8

with one another very closely, while the series on Pike's Peak gives a slightly higher value for the total respiratory exchange, just as in the experiments at complete rest.

In all these experiments at complete rest lying down, or at standing rest, the respiratory quotient falls within the normal limits, only five values being below 0·78, and one of these occurs in the first experiment made on Pike's Peak on July 14th, when the exceptionally low respiratory quotient of 0·74 was obtained. DOUGLAS was at this time just reviving after mountain sickness, and had taken practically no food for a couple of days; the low respiratory quotient owes its explanation, therefore, to semi-starvation. The average respiratory quotient of each series is very nearly identical, though the Pike's Peak series give slightly the higher value. This difference may perhaps be due to differences in the diet, as DOUGLAS had the impression that his food on the summit contained a larger proportion of carbohydrate than he was accustomed to in Oxford.

As has been explained in a previous section (p. 225), the respiratory quotient, which under normal circumstances affords an index of the relative amounts of the different food substances undergoing combustion in the body, may be, so to speak, artificially disturbed if the oxygen supply to the muscles is materially interfered with owing to

TABLE XIII.—Respiratory Exchange whilst Walking at 2 miles an hour.

	Date.	Barometer in mm. Hg.	Pace in miles per hour.	Breaths per minute.	At 37° moist and prevailing barometer.		At 0° and 760 mm.		Respiratory quotient.	C.c. expired air at 37°, moist and prevailing barometer per 1 c.c. of CO_2 at S.T.P. produced.
					Litres breathed per minute.	C.c. per breath.	C.c. O_2 absorbed per minute.	C.c. CO_2 produced per minute.		
Oxford, in laboratory.	1911.									
	March 31 . . .	755	1·97	—	15·1	—	621	502	·808	30·1
	April 2 . . .	757	1·94	—	14·7	—	615	523	·850	28·1
	June 6 . . .	770	2·02	14·0	15·4	1099	670	546	·815	28·1
	1912.									
	March 19 . . .	740	2·02	12·2	17·2	1410	675	574	·850	30·0
	23 . . .	748	2·01	11·8	16·3	1380	659	563	·855	28·9
	Mean . . .	754	1·99	—	15·7	—	648	542	·836	29·0
Mean of all experiments where data are complete		753	2·02	12·7	16·3	1296	668	561	·840	29·0
Pike's Peak.	1911.									
	Aug. 7 . . .	459	1·97	20·8	27·9	1340	811	685	·844	40·8
	7 . . .	459	2·05	22·5	27·6	1226	770	648	·842	42·6
	8 . . .	458	1·93	21·5	27·7	1289	782	670	·856	41·3
	8 . . .	458	2·03	22·6	28·4	1257	777	660	·850	43·0
	Mean . . .	459	2·00	21·9	27·9	1278	785	666	·848	41·9
Oxford, grass track.	1911.									
	Dec. 12 . . .	751	1·98	16·2	19·4	1197	777	669	·861	29·0
	13 . . .	744	2·04	16·4	19·8	1206	810	693	·856	28·6
	1912.									
	Feb. 15 . . .	762	1·98	12·2	16·8	1377	752	625	·831	26·9
	20 . . .	747	2·05	14·1	18·4	1305	779	660	·847	27·9
	Mean . . .	751	2·01	14·7	18·6	1271	780	662	·849	28·1

the action of such incompletely oxidized metabolites as lactic acid on the respiratory centre. Deficient oxidation in the muscles can be brought about by excessive muscular work with or without an abnormally low pressure of oxygen in the air breathed, but

TABLE XIV.—Respiratory Exchange whilst Walking at 3 miles an hour.

	Date.	Barometer in mm. Hg.	Pace in miles per hour.	Breaths per minute.	At 37° moist and prevailing barometer.		At 0° and 760 mm.		Respiratory quotient.	C.c. expired air at 37°, moist and prevailing barometer per 1 c.c. of CO_2 at S.T.P. produced.
					Litres breathed per minute.	C.c. per breath.	C.c. O_2 absorbed per minute.	C.c. CO_2 produced per minute.		
Oxford, in laboratory.	1911.									
	March 22 . . .	757	3·09	—	20·6	—	909	762	·839	27·0
	24 . . .	759	3·00	—	22·2	—	894	793	·887	28·0
	May 2 . . .	755	2·88	—	19·1	—	865	715	·827	26·7
	June 5 . . .	766	2·99	17·2	18·6	1081	844	656	·777	28·4
	1912.									
	March 21 . . .	733	3·09	13·8	23·0	1666	953	800	·840	28·8
	22 . . .	740	3·05	13·6	21·1	1552	925	756	·818	27·9
	Mean . . .	752	3·02	—	20·8	—	898	747	·831	27·8
Mean of all experiments where data are complete		746	3·04	14·9	20·9	1433	907	737	·812	28·4
Pike's Peak.	1911.									
	Aug. 7 . . .	459	2·95	21·5	36·6	1701	996	905	·909	40·4
	7 . . .	459	2·98	23·9	39·3	1644	1080	963	·892	40·8
	8 . . .	460	2·89	25·5	39·8	1560	1009	911	·903	43·7
	8 . . .	460	3·04	26·7	39·4	1476	1052	910	·865	43·3
	Mean . . .	460	2·97	24·4	38·8	1595	1034	922	·892	42·1
Oxford, grass track.	1911.									
	Dec. 13 . . .	744	3·13	17·8	24·8	1393	1079	922	·855	26·9
	14 . . .	751	3·11	17·3	25·7	1486	1070	963	·900	26·7
	1912.									
	Feb. 19 . . .	745	2·95	14·6	23·3	1596	1047	900	·860	25·9
	20 . . .	747	3·15	15·2	25·3	1665	1064	903	·848	28·0
	Mean . . .	747	3·09	16·2	24·8	1535	1065	922	·866	26·9

TABLE XV.—Respiratory Exchange whilst Walking at 4 miles an hour.

	Date.	Barometer in mm. Hg.	Pace in miles per hour.	Breaths per minute.	At 37° moist and prevailing barometer.		At 0° and 760 mm.		Respiratory quotient.	C.c. expired air at 37°, moist and prevailing barometer per 1 c.c. of CO_2 at S.T.P. produced.
					Litres breathed per minute.	C.c. per breath.	C.c. O_2 absorbed per minute.	C.c. CO_2 produced per minute.		
Oxford, in laboratory.	1911.									
	April 2 . . .	757	3·83	—	26·5	—	1127	1011	·898	26·2
	15 . . .	763	4·01	—	27·1	—	1232	1000	·812	27·1
	May 2 . . .	755	3·97	—	28·2	—	1203	1058	·879	26·7
	1912.									
	March 19 . . .	740	4·02	14·6	31·0	2120	1201	1102	·917	28·1
	23 . . .	748	3·94	14·2	27·0	1900	1162	1012	·871	26·7
	Mean . . .	753	3·95	—	28·0	—	1185	1037	·875	27·0
Mean of all experiments where data are complete		744	3·98	14·4	29·0	2010	1182	1057	·894	27·4
Pike's Peak.	1911.									
	July 16 . . .	461	4·09	22·0	53·1	2410	1509	1400	·928	38·0
	16 . . .	461	4·15	23·5	51·6	2200	1480	1328	·897	38·9
	22 . . .	457	4·04	22·1	58·9	2660	1605	1520	·948	38·7
	22 . . .	457	4·09	25·6	62·5	2440	1669	1595	·956	39·2
	29 . . .	460	3·93	23·8	54·7	2300	1494	1373	·919	39·8
	29 . . .	460	3·83	28·5	63·1	2220	1598	1512	·947	41·7
	31 . . .	456	4·03	23·4	55·0	2350	1521	1343	·883	40·9
	Aug. 9 . . .	460	4·09	—	61·4	—	1581	1432	·906	42·8
	Mean . . .	459	4·03	—	57·5	—	1557	1438	·923	40·0
Mean of all experiments where data are complete		459	4·02	24·1	57·0	2369	1554	1439	·925	39·6
Oxford, grass track.	1911.									
	Dec. 12 . . .	751	3·93	21·9	39·0	1781	1590	1399	·880	27·9
	13 . . .	744	4·09	20·8	42·3	2030	1727	1562	·906	27·0
	1912.									
	Feb. 12 . . .	745	3·93	17·3	33·9	1960	1540	1289	·836	26·3
	19 . . .	743	4·16	17·4	39·2	2250	1585	1475	·931	26·6
	21 . . .	756	4·13	15·1	36·2	2400	1650	1377	·835	26·3
	21 . . .	756	3·97	16·9	33·2	1965	1476	1283	·870	25·9
	Mean . . .	749	4·04	18·2	37·3	2064	1595	1398	·876	26·7

TABLE XVI.—Respiratory Exchange whilst Walking at $4\frac{1}{2}$ miles an hour.

	Date.	Barometer in mm. Hg.	Pace in miles per hour.	Breaths per minute.	At 37° moist and prevailing barometer.		At 0° and 760 mm.		Respiratory quotient.	C.c. expired air at 37°, moist and prevailing barometer per 1 c.c. of CO_2 at S.T.P. produced.
					Litres breathed per minute.	C.c. per breath.	C.c. O_2 absorbed per minute.	C.c. CO_2 produced per minute.		
Oxford, in laboratory.	1911.									
	Feb. 7 . . .	773	4·47	—	42·3	—	1550	1417	·914	29·9
	14 . . .	771	4·54	—	47·5	—	1530	1380	·904	34·4
	June 6 . . .	770	4·51	20·0	33·4	1670	1449	1196	·826	27·9
	1912.									
	March 21 . . .	733	4·52	—	34·7	—	1493	1282	·859	27·1
	22 . . .	740	4·53	14·3	34·9	2440	1537	1305	·850	26·7
	Mean . . .	757	4·51	—	38·6	—	1512	1316	·871	29·2
Mean of all experiments where data are complete		755	4·52	17·2	34·2	2055	1493	1251	·838	27·3
Pike's Peak.	1911.									
	July 14 . . .	461	4·33	—	54·4	—	1681	1348	·801	40·4
	19 . . .	457	4·20	29·6	71·3	2410	1769	1716	·970	41·6
	Mean . . .	459	4·27	—	62·9	—	1725	1532	·886	41·0
Oxford, grass track.	1911.									
	Dec. 14 . . .	751	4·51	20·3	49·8	2450	2137	1960	·917	25·4
	1912.									
	Feb. 19 . . .	745	4·49	15·5	40·4	2610	1848	1590	·861	25·4
	21 . . .	757	4·71	17·2	48·7	2830	2110	1906	·903	25·6
	24 . . .	758	4·71	20·2	46·7	2310	1973	1732	·878	27·0
	27 . . .	761	4·60	19·5	47·1	2420	1956	1751	·896	26·9
	Mean . . .	754	4·60	18·5	46·5	2524	2005	1788	·891	26·1

the disturbance of the respiratory quotient is only transitory, for if the work can be continued at a steady pace for long enough the respiratory quotient gradually resumes its proper metabolic value. As one of the main points in these experiments was to try and determine to what extent the low alveolar oxygen pressures prevailing on Pike's Peak influenced oxidation processes in the muscles, the behaviour of the respiratory

TABLE XVII.

	Date.	Barometer in mm. Hg.	Pace in miles per hour.	Breaths per minute.	At 37° moist and prevailing barometer.		At 0° and 760 mm.		Respiratory quotient.	C.c. expired air at 37°, moist and prevailing barometer per 1 c.c. of CO_2 at S.T.P. produced.
					Litres breathed per minute.	C.c. per breath.	C.c. O_2 absorbed per minute.	C.c. CO_2 produced per minute.		
Respiratory Exchange whilst Walking at 5 miles an hour.										
Oxford, in laboratory.	1912. March 24. . .	750	5·02	16·6	48·7	2930	2100	1960	·933	24·9
	25. . .	760	5·14	20·0	53·8	2690	2150	2040	·949	26·4
	Mean. . .	755	5·08	18·3	51·3	2810	2125	2000	·941	25·7
Pike's Peak.	1911. Aug. 12. . .	459	4·95	33·9	111·3	3280	2195	2295	1·045	48·5
	14. . .	462	4·95	37·8	109·1	2890	2030	2120	1·044	51·5
	Mean. . .	461	4·95	35·9	110·2	3085	2113	2208	1·045	50·0
Oxford, grass track.	1911. Dec. 13. . .	744	4·87	—	55·7	—	2200	2100	·955	26·5
	1912. Feb. 24. . .	758	5·17	20·5	62·2	3030	2605	2460	·945	25·3
	24. . .	758	5·05	16·4	55·1	3360	2460	2285	·928	24·1
	26. . .	760	5·11	18·7	58·9	3150	2475	2305	·932	25·6
	26. . .	760	5·20	22·2	67·5	3040	2630	2495	·948	27·1
	Mean. . .	756	5·08	—	59·9	—	2474	2329	·942	25·7
Mean of all experiments where data are complete		759	5·13	19·5	60·9	3145	2543	2386	·938	25·5
PIKE'S PEAK. Respiratory Exchange whilst Walking up Grade of 1 in 4.										
	1911. July 27. . .	456	2·02	—	107·1	—	2060	2450	1·190	43·7
	Aug. 14. . .	462	2·26	47·8	109·7	2295	1820	2025	1·113	54·2
	Mean. . .	459	2·14	—	108·4	—	1940	2238	1·152	49·0

quotient for some time after passing from a state of rest into activity was an obvious point to study.

We adopted as our standard form of muscular exercise walking at a steady pace on the flat, and for convenience chose paces as near as possible to 2, 3, 4, $4\frac{1}{2}$, and 5 miles an hour in different series of experiments. In order to take account of variations of the respiratory quotient at rest we commenced the experiments on muscular work by determining the total respiratory exchange whilst standing in the manner described above. Directly after the contents of the gas-bag had been measured, and a sample reserved for subsequent analysis, the exercise was commenced, and after a preliminary period whose length differed in different experiments the expired air was diverted into the bag. So soon as this was full the experiment was stopped, the contents of the bag measured, and a sample reserved as before for subsequent analysis. In a number of cases a second exercise experiment was made immediately afterwards, and unless the pace was the same as in the experiment immediately preceding it was at a faster rate. In no case did the experiment at the faster rate or of the longer duration precede that at the slower rate or of shorter duration. One initial experiment at standing rest was allowed to suffice for pairs of work experiments conducted in this way, otherwise a fresh standing rest experiment was made. With the exception of the paired experiments an interval of not less than two hours was allowed to intervene between experiments conducted on the same day.

Tables XIII., XIV., XV., XVI., and XVII. show the main results of all the work experiments, together with the average results for each series. It will be seen that the oxygen consumption during walking at 5 miles per hour runs up to 2,600 c.c. per minute, as compared with 248 c.c. during rest in bed; while the volume of air breathed per minute runs up to 110 litres during walking at 5 miles an hour on Pike's Peak, as compared with 7·67 litres during rest in bed at Oxford.

Our first series of control experiments on the effects of muscular work was made in Oxford in the months preceding the expedition. The exercise was taken in a large room in the laboratory whose perimeter measured 51 yards. The results of these experiments are given in Table XVIII. This table also contains the results of another series of similar experiments made in the laboratory some months after the return of the expedition. The table is so arranged that it is possible to refer the work experiments to their appropriate standing rest experiments by reading the table horizontally. Experiments at the same pace when bracketed together are to be referred to the same standing rest experiment. In addition to the figures of the total respiratory exchange and the respiratory quotient, the table also shows the time which elapsed after the commencement of the experiment before beginning to collect the sample of expired air (preliminary period), as well as the oxygen consumption required for the motion of one kilo of the body weight through one metre of horizontal distance. In order to obtain the last figure we have subtracted the oxygen consumption per minute at standing rest from that found during the exercise, and have then divided

TABLE XVIII.

OXFORD. Respiratory Exchange whilst Walking on the Flat (in Laboratory) at Different Paces.

Date.	Standing rest.				2 miles an hour.					3 miles an hour.					4 miles an hour.					4½ miles an hour.					5 miles an hour.				
	Preliminary period in minutes.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	Preliminary period in minutes.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per kilo per meter horizontal movement.	Preliminary period in minutes.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per kilo per meter horizontal movement.	Preliminary period in minutes.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per kilo per meter horizontal movement.	Preliminary period in minutes.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per kilo per meter horizontal movement.	Preliminary period in minutes.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per kilo per meter horizontal movement.
1911.																													
Feb. 7 . . .	5	336	271	·807																5	1550	1417	·914	·138					
14 . . .	5	320	254	·795																5	1530	1380	·904	·136					
March 22 . . .	5	343	297	·866						5	909	762	·839	·093															
24 . . .	5	336	290	·863						5	894	793	·887	·094															
31 . . .	10	329	275	·836	10	621	502	·808	·076																				
April 2 . . .	10	316	254	·804	10	615	523	·850	·078						10	1127	1011	·898	·107										
15 . . .	10	365	288	·790											15	1232	1000	·812	·109										
May 2 . . .	5	350	305	·871						5	865	715	·827	·091	5	1203	1058	·879	·108										
June 5 . . .	15	312	237	·760						15	844	656	·777	·095															
6 . . .	15	319	250	·784	15	670	546	·815	·093											35	1449	1196	·826	·133					
1912.																													
March 19 . . .	10	339	278	·820	5	675	574	·850	·085						5	1201	1102	·917	·111										
21 . . .	10	342	279	·816						10	953	800	·840	·101						10	1493	1282	·859	·131					
22 . . .	10	346	276	·798						5	9 5	756	·818	·096						5	1537	1305	·850	·133					
23 . . .	10	333	269	·808	10	659	563	·855	·083						10	1162	1012	·871	·107										
24 . . .	10	333	273	·820																					5	2100	1960	·933	·179
25 . . .	10	327	265	·810																					10	2150	2040	·949	·182

the result by the body weight* in kilos (which for this purpose includes the weight of the clothes and of the apparatus) and by the number of metres traversed in one minute. We chose to subtract the oxygen consumption during standing rest rather than that during complete rest so as to obtain an expression of the oxygen consumption

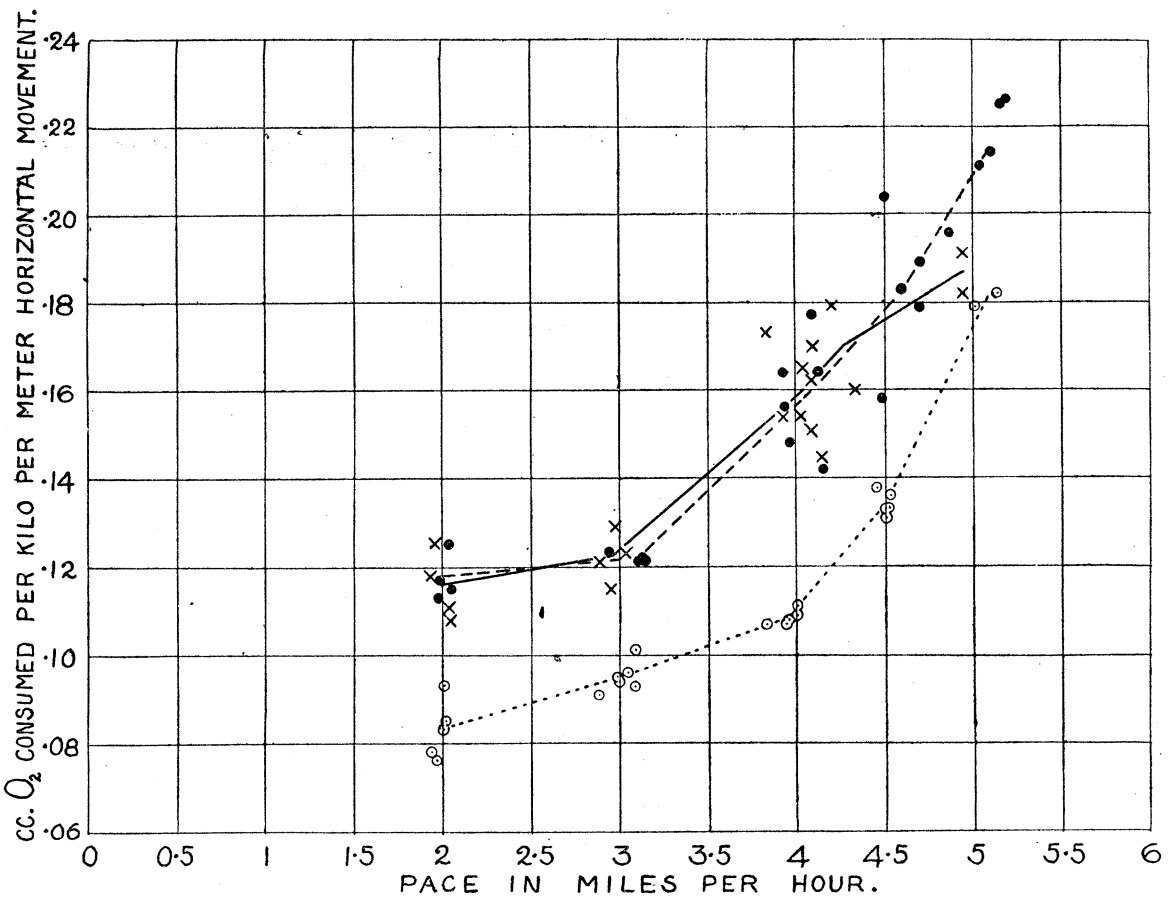

Fig. 14.

× Experiments on Pike's Peak.
● Experiments in Oxford, grass track.
⊙ Experiments in Oxford, laboratory.

The curves join the mean values for the groups of experiments shown in Tables XVIII.–XX.; the continuous line refers to Pike's Peak, the interrupted line to Oxford, grass track, and the dotted line to Oxford, laboratory.

required for progression in the forward direction alone, assuming that that involved in retaining the body in the upright posture was the same in the two cases. The figures for the oxygen consumption per kilo per metre horizontal movement in these experiments are also plotted as the lower curve in fig. 14.

When we reached the summit of Pike's Peak we found that there was only one

* DOUGLAS'S stripped weight showed hardly any variation from 140 lbs. during the experiments in Oxford, or from 134 lbs. on Pike's Peak.

place that would serve as a track for our exercise experiments. This is shown in fig. 7, and consisted of a fifty yards stretch by the side of the railway which was practically level. The subject was obliged to walk backwards and forwards over this short track instead of walking round a circular track as in the laboratory. This difference made it impossible to walk on the summit at paces which should compare directly with those of the laboratory experiments, and on our return we therefore made a second series of control experiments in Oxford on a track in a meadow, taking care that the track should resemble as closely as possible both in regard to length and roughness of surface the track on the summit. The rates of walking on the summit and on the grass track in Oxford include the turns at each end of the track, for the track was traversed either three or four times during the collection of the expired air sample, and the real speed was therefore higher than is indicated by the figures.

Tables XIX. and XX. contain the results of the experiments made on the summit and on the grass track in Oxford, and the figures for the oxygen consumption required to move one kilo body weight one metre horizontally are also plotted as the two upper curves in fig. 14. The different experiments at each pace in the three series give reasonably concordant values for the total respiratory exchange, the consumption per kilo per metre horizontal movement showing the best agreement in the series in the laboratory in Oxford, as may be readily seen in the curves, owing doubtless to the greater ease with which the pace could be kept uniform on the circular track and the absence of any slight disturbing factors such as wind. The series at Pike's Peak gives values that are very nearly identical throughout with those obtained on the grass track in Oxford, though considerably higher than those obtained in the laboratory. From what has been said above it will be evident that higher values were in any case bound to be obtained on the fifty-yard straight track than on the circular track in the laboratory. With this distinction the three series show a number of common features. The oxygen consumed per kilo body weight per metre horizontal movement shows an increasing value as the pace is increased (in a manner closely resembling the figures published by Durig), *i.e.*, the efficiency with which the movement is performed becomes progressively less. The curves show that the loss of efficiency for any given pace is practically identical in the experiments on Pike's Peak and on the grass track in Oxford, save that the loss was less on Pike's Peak at the pace of five miles an hour. The loss of efficiency in these two series was roughly of the same order of magnitude as in the experiments in the laboratory in Oxford. The length of time during which the exercise was kept up seemed to be without appreciable effect upon the efficiency, though here it must be remembered that the exercise was well within the powers of the subject and did not cause fatigue. The respiratory quotient rose during the work distinctly above the value given just previously during standing rest, and the rise became more marked as the pace was increased, values as high as 0·95 being reached at a pace of five miles an hour in Oxford, and greater than unity at the same pace on Pike's Peak. The degree by which the respiratory quotient

Table XIX.

Pike's Peak. Respiratory Exchange whilst Walking on the Flat at Different Paces.

Date.	Standing rest.				2 miles an hour.					3 miles an hour.					4 miles an hour.					4·2–4·3 miles an hour.					5 miles an hour.					Up 1 in 4 grade at 2–2¼ miles an hour.			
	Preliminary period in minutes.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	Preliminary period in minutes.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per kilo per meter horizontal movement.	Preliminary period in minutes.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per kilo per meter horizontal movement.	Preliminary period in minutes.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per kilo per meter horizontal movement.	Preliminary period in minutes.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per kilo per meter horizontal movement.	Preliminary period in minutes.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per kilo per meter horizontal movement.	Preliminary period in minutes.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.
1911. July 14	5	339	251	·740																5	1681	1348	·801	·160									
16	5	339	278	·820											2	1509	1400	·928	·151														
16															5	1480	1328	·897	·145														
19	10	351	305	·869																15	1769	1716	·970	·179									
22	5	355	314	·885											2	1605	1520	·948	·165														
22	5	366	309	·844											15	1669	1595	·956	·170														
27																														2	2060	2450	1·190
29	5	344	287	·835											5	1494	1373	·919	·154														
29															15	1598	1512	·947	·173														
31	10	327	266	·814											30	1521	1343	·883	·154														
Aug. 7	10	352	290	·824						5	996	905	·909	·115																			
7										11½	1080	963	·892	·129																			
7	10	343	280	·816	5	811	685	·844	·125																								
7					20	770	648	·842	·108																								
8	10	347	282	·813	5	782	670	·856	·118																								
8					15*	777	660	·850	·111																								
8	10	345	282	·818						5	1009	911	·903	·121																			
										20	1052	910	·865	·123																			
9	10	324	272	·840											30	1581	1432	·906	·162														
12	5	346	288	·832																					10	2195	2295	1·045	·191				
14																									2	2030	2120	1·044	[·182]				
14	5	360	290	·806																										2	1820	2025	1·113

Table XX.

Oxford. Respiratory Exchange whilst Walking on the Flat (Grass Track) at Different Paces.

Date.	Standing rest.				2 miles an hour.					3 miles an hour.					4 miles an hour.					4½ miles an hour.					5 miles an hour.				
	Preliminary period in minutes.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	Preliminary period in minutes.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per kilo per meter horizontal movement.	Preliminary period in minutes.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per kilo per meter horizontal movement.	Preliminary period in minutes.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per kilo per meter horizontal movement.	Preliminary period in minutes.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per kilo per meter horizontal movement.	Preliminary period in minutes.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per kilo per meter horizontal movement.
1911.																													
Dec. 12. . .	10	323	262	·811	5	777	669	·861	·117						5	1590	1399	·880	·164										
13. . .	10	310	251	·810	10	810	693	·856	·125						10	1727	1562	·906	·177										
13. . .	10	328	267	·814						5	1079	922	·855	·122											5	2200	2100	·955	·196
14. . .	10	335	296	·884						10	1070	963	·900	·121						10	2137	1960	·917	·204					
1912.																													
Feb. 12. . .	10	337	258	·766											10	1540	1289	·836	·156										
15. . .	10	310	252	·813	5	752	625	·831	·113																				
19. . .	10	339	284	·838						10	1047	900	·860	·123						5	1848	1590	·861	·158					
19. . .	10	332	256	·771											20	1585	1475	·931	·142										
20. . .	10	321	257	·801	20	779	660	·847	·115	20	1064	903	·848	·121															
21. . .	10	322	258	·801											{ 2	1650	1377	·835	·164										
															{ 20	1476	1283	·870	·148										
21. . .	10	349	278	·796																5	2110	1906	·903	·189					
24. . .	10	307	241	·785																2¼	1973	1732	·878	·179	5	2605	2460	·945	·225
24. . .	10	356	277	·778																					2	2460	2285	·928	·211
26. . .	10	337	266	·789																					{ 2	2475	2305	·932	·214
26. . .																									{ 10	2630	2495	·948	·226
27. . .	10	298	242	·812																20	1956	1751	·896	·183					

rose for any given pace except the last was not widely different in the three series, and the duration of the exercise did not exert any marked effect on it.

The earlier results of ZUNTZ and DURIG and their colleagues are alike in showing that the respiratory exchange at high altitudes is increased above that at sea-level both during rest and during work by an amount that is too great to be explained by the muscular exertion entailed by the extra hyperpnœa. Our own experiments agree in some measure with this, for both at rest in bed and at standing rest the oxygen consumption per minute was higher on Pike's Peak than in Oxford, though the difference was but small, namely 11 c.c. and 16 c.c. Such a difference as this could very well be explained by the hyperpnœa according to the observations of ZUNTZ and of REACH and RODER* upon this point. Our experiments made during work do not throw any additional light upon this point. As has been noted above, the oxygen consumption during the work was practically identical whether the experiments were done on Pike's Peak or on the grass track in Oxford. We endeavoured to ensure that the two tracks were identical, but we cannot guarantee that they were, though we feel sure that any difference between them was only slight. The higher value obtained when walking at five miles an hour appears to us to indicate that the grass track really required the expenditure of more energy, *i.e.*, was not quite so level as the track we used on Pike's Peak. We should certainly expect that if precisely similar exercise were taken in the two cases the Pike's Peak value would be higher, if only on account of the extra hyperpnœa involved; but apart from this we do not see any reason why in the one case we have investigated the metabolism should have been greater at the high altitude than at sea-level. There was no material difference of external temperature in the two cases, no abnormalities of climate, and no personal discomfort; while, as we have indicated in an earlier section, the deficiency of oxygen had been largely compensated for by changes in the lungs and blood.

Though we cannot speak more precisely than this upon the actual amount of energy required for performing a given piece of work at a high altitude as compared with sea-level, our results enable us to compare the type of the metabolism at the two places under conditions of the same character when the oxygen consumption was practically identical, if we contrast the Pike's Peak experiments with those on the grass track in Oxford. Our index for this purpose is furnished by the respiratory quotient, which in our experiments rose invariably during the work. Taking first of all exercise up to the pace of $4\frac{1}{2}$ miles an hour, it will be noted that the actual value of the respiratory quotient tends to be higher at any given pace on Pike's Peak than in Oxford, but if the respiratory quotient during the exercise is compared with that obtained in the standing rest experiment done immediately beforehand in each instance, it will be found that the degree by which the respiratory quotient rose is much the same in each series, since the initial respiratory quotients on the Peak are on the whole higher than in Oxford. This fact, coupled with the lack of variation in

* *Cf* REACH and RÖDER, 'Biochem. Zschr.,' XXII., p. 471, 1909.

the respiratory quotients in the two series on prolonging the exercise, leads us to believe that, whatever the cause at work may be, it was precisely the same in the two cases. The point that we have to decide is, whether the rise is due to an alteration in the proportions of the different materials being oxidised in the body, or whether it is merely the expression of an excessive hyperpnœa caused by the production of some metabolite which does not occur in resting metabolism and stimulates the respiratory centre. The last explanation will certainly serve in part* to explain the very abnormal respiratory quotients which were obtained on Pike's Peak when walking at five miles an hour on the flat or at two miles an hour up the 1 in 4 gradient (the results of these last experiments are given in Table XVII.). During the exercise in these circumstances the respiratory quotient rose above unity, and on the cessation of the exertion fell back below its normal value. The behaviour of the respiratory exchange after ceasing the exercise is shown more clearly in Table XXI.

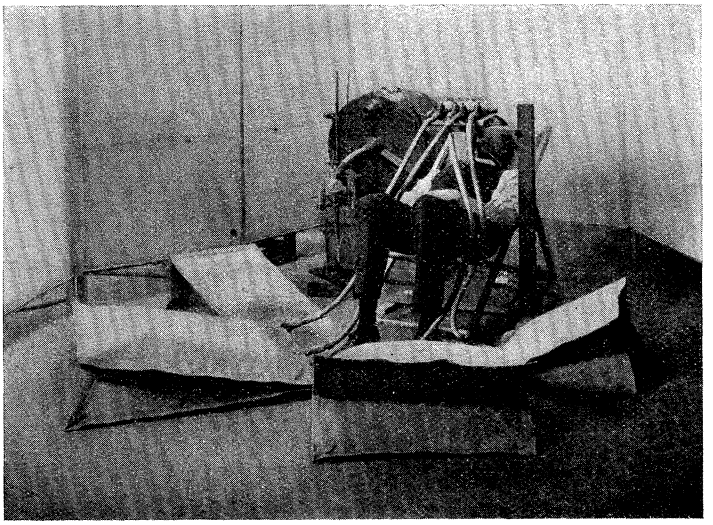

Fig. 15.

Arrangement of apparatus for determining the total respiratory exchange at different intervals after the cessation of muscular work.

The preceding exercise in these experiments consisted of ascending the last quarter of a mile of the 1 in 4 gradient of the railway in five minutes, and as this rate is nearly half as fast again as in the experiments given in Table XVII., the respiratory exchange during the exercise must have been considerably higher and the respiratory quotient also probably higher than is there shown. Immediately after the stop the subject sat down and commenced to breathe through valves connected with a large five-way tap which enabled the expired air to pass freely out to air or to be diverted into each of four bags to succession. The general arrangement of the apparatus is indicated in fig. 15. The air expired over a period of two minutes was collected in

* We attribute a part of the rise of the respiratory quotient under these circumstances to the changes in metabolism which will be considered in discussing the influence of moderate exertion on the respiratory quotient.

TABLE XXI.

PIKE'S PEAK. Respiratory Exchange at Different Intervals after Stopping a Violent Muscular Exertion (Walking $\frac{1}{4}$ mile of 1 in 4 Grade).

	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.
After 10′ sitting rest before exertion	339	266	·785	298	244	·819	308	253	·821	310	262	·845	347	293	·845	360	303	·841	310	257	·829
Minutes after the stop.																					
1 + 2	974	986	1·011																		
3 + 4	459	496	1·080	570	663	1·163															
5 + 6	350	341	·975																		
7 + 8	390	356	·913	395	379	·960	408	362	·887												
11 + 12				368	315	·856															
15 + 16				356	293	·823	366	285	·778	330	256	·776									
23 + 24							328	245	·747												
31 + 32							296	221	·747	298	216	·725									
47 + 48										298	216	·725	330	252	·764	322	234	·726	321	228	·711
63 + 64										294	228	·776	341	265	·777	331	242	·731	325	242	·745
79 + 80													332	272	·820	317	234	·738	319	241	·756
95 + 96													328	276	·841	315	231	·733	332	255	·768

PIKE'S PEAK. Respiratory Exchange at Different Intervals after Stop of Walk on Flat at Rate of 4 miles an hour.

	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.	C.c. O_2 per minute.	C.c. CO_2 per minute.	R.Q.
After 10′ sitting rest before exertion.	355	312	·879	358	300	·838
Minutes after the stop.						
1 + 2	620	533	·860	532	437	·822
3 + 4	364	318	·874			
5 + 6	348	312	·896			
7 + 8	323	291	·901	377	311	·825
13 + 14				337	296	·878
19 + 20				337	285	·846
1½ hours later						·832

each bag, and in the different experiments different periods were allowed to elapse before taking the first sample of expired air and between the different samples. After collecting the samples the contents of the bags were measured and analysed, and the respiratory exchange per minute calculated for each period. A period of about 20 seconds elapsed after stopping the exercise before the first sample of expired air could be collected, owing to the time required for getting into position before the valves, and this is not included in the figures showing the times at which the samples were taken. The experiments were made on different days and were in each instance preceded by a determination of the respiratory exchange after sitting quiet for ten minutes, with a view to establishing the normal respiratory quotient.*

It will be noted with what rapidity the oxygen consumption, which must have been more than 2200 c.c. per minute during the exertion, falls back towards the resting value, though it does not actually reach this value until almost half an hour has elapsed. The respiratory quotient is well above unity immediately after the stop, and gradually falls until the normal value is again reached about a quarter of an hour after the stop; the quotient still continues to fall, to reach its lowest value half an hour to three-quarters of an hour after the stop, and then gradually increases again, though in only one of the experiments does it succeed in attaining the normal value again by the time that ninety-six minutes had elapsed since the stop of the exercise. It will also be seen that the variations in the respiratory quotient are due rather to alterations in the amount of carbonic acid put out than to variations in the amount of oxygen taken in, especially if one judges from the later periods when the oxygen consumption is not very different from what it was before the experiment.

The simplest explanation of these variations is that which has been advanced in Section V., where the alveolar air changes after exercise are dealt with (p. 225), and follows along the lines suggested previously by the work of GEPPERT and ZUNTZ,† LOEWY,‡ and DOUGLAS and HALDANE.§ The severity of the work is such that the muscular activity outruns the oxygen supply, and insufficiently oxidised metabolites such as lactic acid are put out from the active muscles. The lactic acid aids the CO_2 to stimulate the respiratory centre, and the hyperpnœa, being from the point of view of CO_2 alone excessive, leads to excessive removal of CO_2 from the body without proportionate increase in the intake of oxygen. The respiratory quotient is thereby raised to an abnormal height. On the cessation of the exercise the process of excessive CO_2 removal was still incomplete, and the respiratory quotient was at the stop and in the four minutes immediately after it still above unity. The excessive removal of CO_2

* We were compelled on Pike's Peak, owing to lack of space, to sit in a rather constrained position on the floor and this may very likely account for the fact that the oxygen consumption per minute is unduly high and variable.

† GEPPERT and ZUNTZ, 'PFLÜGER'S Arch.,' XLII., p. 189, 1888.

‡ LOEWY, 'PFLÜGER'S Arch.,' XLIX., p. 405, 1891.

§ DOUGLAS and HALDANE, 'Journ. of Physiol.,' XXXVIII., p. 420, 1909.

continued at a decreasing rate for the first quarter of an hour after the stop when the respiratory quotient gave a normal value. After this the effect of the gradual elimination of the lactic acid began to tell and CO_2 began to be retained in proportion, the respiratory quotient falling to a low figure and then returning once more to its normal value as the rate at which CO_2 was reaccumulating lessened to zero.

Judging from the respiratory quotient, therefore, the signs of lactic acid production in the muscles are an initial rise of the respiratory quotient during the exertion, a fall below the normal value after the stop, and a subsequent rise to the normal. Using this as an indication we investigated the effects of more moderate muscular work on the summit, choosing as our exercise walking at the rate of four miles an hour. The results of these experiments are given at the bottom of Table XXI. It will be seen that during the first twenty minutes after the stop the respiratory quotient shows hardly any variation from the value obtained just previously to the exercise. Referring to the results of the alveolar air analyses made under similar conditions and given in Table IX., it will be seen that though the alveolar CO_2 pressure did not rise during the exertion there was no appreciable alteration in the alveolar respiratory quotient, nor were the alveolar CO_2 pressure nor the respiratory quotient altered in any significant manner after the stop of the exercise. In two other instances we found this to hold good after the lapse of periods of twelve minutes and twenty minutes after the stop.

Our attempts therefore, so far as we went, to obtain indirect evidence of lactic acid production on Pike's Peak gave negative results up to the pace of four miles an hour. Coupled with the fact that the alteration of the respiratory quotient was quite evident when walking at two miles an hour and was not influenced by the duration of the exertion, this throws us back for an explanation on an alteration of the metabolism, which would mean that during the exercise a larger proportion of carbohydrate was utilised than in the resting period.

We make this suggestion with some diffidence as it is contrary to the accepted view, for the great majority at least of the previous observations have shown that the relative proportions of carbohydrate and fat consumed remain the same during work and rest.* Very likely a longer duration of the exercise than in our experiments would have given a lower value of the respiratory quotient, for if carbohydrate is being more readily used than fat, prolongation of the exercise must lead to a diminution of the amount of carbohydrate available. It is possible that our result is bound up with the fact that we were taking an ordinary diet with our meals at the usual times, and therefore had at all times no scarcity of carbohydrate in our tissues.

We admit, of course, that the nearer the respiratory quotient approaches to unity

* Since we wrote the above Dr. E. P. CATHCART has communicated to the Physiological Society the results of some experiments made with BENEDICT, which afford strong evidence of the greater utilisation of carbohydrate during muscular work. He has also drawn our attention to the work of AMAR ('Le Rendement de la machine humaine,' Paris, 1910), who has obtained results pointing in the same direction.

the more doubtful does this explanation become: for instance, in the second experiment on Pike's Peak, at a pace of about four and a quarter miles an hour, we obtained the respiratory quotient of 0·97, which is in itself strongly suggestive of the formation of lactic acid. Comparing it, however, with the preliminary standing rest experiment which gave a respiratory quotient of 0·869, it has only increased by 0·101, an increase which is exceeded in three of the experiments made at four miles an hour, where the oxygen consumption was from 100 to 260 c.c. per minute less, as well as in some of the experiments at Oxford at paces of four and four and a half miles an hour. Though we have obtained some evidence by following the alveolar air changes after the exercise that lactic acid is at least sometimes produced when walking at five miles an hour in the laboratory, we have not as yet been able to convince ourselves that that is the case when the pace is limited to four and a half miles an hour. The identification of lactic acid (or other substances which may exert the same effect) by studying the respiratory changes is a matter of considerable difficulty when the quantities to be dealt with are small and perhaps produced very gradually. We are not therefore prepared at present to express a positive opinion upon the cause of the respiratory quotients which are much above 0·90, especially if the resting respiratory quotient is below that obtained during the exercise by more than 0·10. Experiments are at present being undertaken in order to elucidate this question further.

Whatever the explanation of the variation of the respiratory quotients, we feel, however, that our results indicate that the metabolism on Pike's Peak was not sensibly different from that in Oxford so long as the oxygen consumption per minute did not exceed 1500 c.c. per minute and perhaps 1700 c.c.: that is, about six or seven times the oxygen consumption during complete rest. If the oxygen consumption rose higher than this value, there is evidence that shortage of oxygen in the muscles or respiratory centre made itself felt earlier on Pike's Peak than in Oxford: for an oxygen consumption per minute of about 2000 c.c. on Pike's Peak caused the respiratory quotient to rise above unity, a value which was not reached in Oxford even when the oxygen consumption rose to about 2500 c.c. per minute. The difference seems to us to be due probably to a difference in the method by which the shortage of oxygen arose in the two cases; on Pike's Peak the rate of introduction of oxygen into the body was not sufficient to keep the oxygen tension in the blood reaching the tissues sufficient during moderately severe work; in Oxford the limits of oxygen supply were determined by the capacity of the circulation to transport the oxygen to the tissues at a rapid enough pace.

VIII. *Observations on the Circulation.*

The principal question regarding the circulation upon which we have sought evidence was:—How and to what extent is the circulation rate—that is, the volume per minute of the aortic or pulmonary blood-stream—altered in persons acclimatised to low barometric pressure?

A considerable acceleration might perhaps be expected to occur. The quantitative adjustment of the blood-stream is quite as important in the gaseous exchanges of the body as is even the pulmonary ventilation itself. Increased respiration, augmented hæmoglobin, even a larger total volume of blood, would avail the body nothing if the volume of the stream of blood propelled by the heart through the lungs and out to the tissues were inadequate.

At the outset of any analysis of changes in the total circulation it is essential to keep in mind that the blood-stream per minute involves mathematically two factors: the pulse rate and the systolic discharge. The heart is both a meter and a pump. The blood current in any unit of time is the product of the number of heart-beats —that is, the pulse rate—multiplied by the volume discharged by a single stroke of the left ventricle. Unfortunately it is as difficult to measure the systolic discharge in a man as it is easy to count his pulse rate.

Consideration of such methods as had been proposed for estimating the circulation, *e.g.*, the method of PLESCH,* failed to convince us that they afford quantitatively reliable measurements. We therefore attempted to obtain merely estimates of the relative size, not absolute measurements in cubic centimetres, of the strokes of the heart at various times and under different barometric pressures. To accomplish even this little with a fair degree of certainty was, in the existing state of physiological knowledge, by no means an easy matter. Two distinct methods were employed: that of the pulse pressure and that of the recoil curve. They yielded concordant results.

Pulse Pressure Method.—The pulse pressure, or difference between systolic and diastolic arterial pressure, has been extensively used by clinicians as an index of the size of the heart strokes. The volume of the systolic discharge is undoubtedly the principal element in determining the amplitude of the pulse. Other factors, however, such as the form of the pulse-wave, the level of mean arterial pressure, variations in vaso-motor distribution, &c., also influence the pulse pressure.† Thus the pulse pressure is not an index of sufficiently precise quantitative character to justify the practice of those who multiply the pulse rate by the pulse pressure and take the product as a measure of the volume per minute of the blood-stream.

Nevertheless the pulse pressure has a considerable evidential value in regard to the systolic discharge. In normal persons under ordinary barometric pressures the pulse pressure usually amounts to between 25 and 40 per cent. of the systolic pressure. If in persons under low barometric pressure the volume of the heart strokes is considerably altered, some corresponding increase or diminution of the pulse pressure would almost certainly occur.

In Table XXII. are shown the pulse rates, systolic, diastolic and pulse pressures observed in ourselves at Colorado Springs, on the Peak, and again after our descent.

* PLESCH, J., 'Zeitsch. f. experim. Pathol. u. Ther.,' 1909, VI., p. 487; also 'Hæmodynamische Studien,' Berlin, 1909.

† *Cf.* YANDELL HENDERSON, 'American Journal of Physiology, 1909, vol. XXIII., p. 370.

TABLE XXII.—Arterial Pressures in mm. Hg and Pulse Rates.

Date.	DOUGLAS.				HALDANE.				HENDERSON.				SCHNEIDER.				Notes.
	Pulse rate.	Systolic pressure.	Diastolic pressure.	Pulse pressure.	Pulse rate.	Systolic pressure.	Diastolic pressure.	Pulse pressure.	Pulse rate.	Systolic pressure.	Diastolic pressure.	Pulse pressure.	Pulse rate.	Systolic pressure.	Diastolic pressure.	Pulse pressure.	
July 10	64	105	65	40	84	114	85	29	72	111	88	23	72	110	85	25	At Colorado Springs.
12	75	92	58	34	90	106	62	44	78	112	85	27	76	108	82	26	On Pike's Peak, 6 hours after ascent.
14	78	104	66	38	81	106	70	36	78	118	85	33	76	105	85	20	
21	84	108	84	24	78	106	85	21	90	106	85	21	98	108	86	22	
27	86	104	85	19	68	108	85	23	84	106	86	20	90	105	86	19	On Pike's Peak.
Aug. 1	90	102	82	20	63	110	82	28	72	110	85	25	87	110	85	25	
11	86	102	60	42	72	106	74	32	80	100	84	16	80	94	72	22	
16	72	—	—	—	69	—	—	—	66	—	—	—	84	—	—	—	Colorado Springs, 2 hours after descent.
17	68	102	58	44	84	108	84	24	65	108	84	24	74	112	—	—	At Colorado Springs.
20	80	116	64	52	85	108	68	40	70	114	84	20	72	110	82	28	
31	80	108	65	43	84	106	70	36	72	103	74	29	—	—	—	—	In New Haven.
Average Pulse Pressures.																	
				29				31				24				22	On Pike's Peak.
				45				32				24				26	At Colorado Springs, and in New Haven.

TABLE XXIII.—Pulse Rates and Arterial Pressures of J. E. FULLER and others.

Date.	Pulse rate.	Systolic pressure.	Diastolic pressure.	Pulse pressure.	Notes.
					J. E. FULLER.
July 25 . . .	115	126	115	11	On Pike's Peak. Mountain sick.
August 4 . . .	86	120	92	28	Soon after arrival on Peak. Feeling well.
5 . . .	96	106	88	18	At 7.30 a.m. Mountain sick.
5 . . .	110	—	—	—	At 9 a.m. Mountain sick.
6 . . .	102	115	98	17	Mountain sick.
17 . . .	69	112	86	26	Normal health in Colorado Springs.
					DAVID RUSSELL.
15 . . .	76	128	85	43	After three months on the Peak.
					H. H. ROBISON.
15 . . .	84	111	75	36	After three months on the Peak.
					P. J. DEVINEY.
15 . . .	102	106	—	—	After three months on the Peak.

In Table XXIII. are reproduced some observations on four other men. In all cases the subject had sat still for at least five minutes prior to the observation, and for an hour before had taken no strenuous exercise. The pressures were determined by means of a "Tycos" sphygmomanometer. This instrument was presented to the expedition by the Taylor Instrument Companies of Rochester, N.Y., and proved extremely satisfactory on account of its portability, ease of adjustment, and the sharpness of its diastolic readings. The gauge was repeatedly tested against a mercury manometer and found accurate to within 1 mm. of mercury. For the determination of systolic pressure the return of the radial pulse was taken as the criterion. The diastolic readings were made at the point at which, as the pressure in the armlet was gradually lowered, the vibrations of the needle of the gauge were maximal, and below which these movements suddenly decreased in amplitude.

It was found by SCHNEIDER and HEDBLOM* that moderate altitudes have no perceptible effect upon the pulse rate or arterial pressure of healthy persons. This conclusion is confirmed by our observations of July 10 at Colorado Springs, for the first row of figures on the table are for all of us practically the same as those which we have ordinarily observed in ourselves at sea-level.

On July 11, six hours after reaching the summit, the pulse rates of all of us were somewhat accelerated. The acceleration was, however, surprisingly slight—much less

* SCHNEIDER and HEDBLOM, 'American Journal of Physiology,' 1908, vol. XXIII., p. 90, also bibliography.

than that usually recorded by previous observers. It is to be remembered that we, unlike most investigators at great altitudes, had not been subjected to any physical exertion. The importance of this condition is shown by the fact that in all of us throughout our stay on the Peak any considerable physical exertion induced an acceleration of the pulse much greater than would have occurred at sea-level. Thus four days after arrival we found that two minutes' rapid walking up the railway (grade 1 in 4) brouhgt the pulse of HALDANE to 132 per minute, that of HENDERSON to 144, and that of SCHNEIDER to 156. This effect appeared most markedly in new-comers and especially in those inclined to be mountain-sick. After the first few days we were all able to walk about at ordinary gaits on such level space as the summit afforded with no more subjective indications of altered heart rate or force than at sea-level. On the other hand, in the case of FULLER, whose normal resting pulse rate in Colorado Springs is 69, two observations when he was feeling unwell on the Peak showed rates of 86 and 96, and merely strolling about on the level terrace in front of the Summit House raised the rate to 115 and 120.

In DOUGLAS, HENDERSON, and SCHNEIDER the resting pulse rates increased gradually to maxima 26, 18, and 26 beats per minute above normal at the end of 19, 9, and 9 days respectively. Thereafter in all three men the rates fell slowly. It appears improbable, however, that the rates would ever have quite returned to their sea-level values even if we had spent many months on the Peak. It is noteworthy that in RUSSELL, ROBISON, and DEVINEY (Table XXIII.), in whom this condition was fulfilled, the pulses were somewhat above ordinary rapidity.

In the case of HALDANE, whose pulse at sea-level is about 84, an entirely different reaction was observed. After the first few days the rate became gradually slower until his heart was beating some 15 or 20 times a minute *less* rapidly than ordinarily. At the same time he was in excellent health, and notably invigorated by the highland climate. After descending to Colorado Springs his pulse rate promptly rose again to 84. The rates for HENDERSON and SCHNEIDER correspondingly fell to their normal, while in DOUGLAS, after a temporary return to normal, the rate returned for a few days to the more rapid tempo of the Peak.

Turning now to the arterial pressure measurements in Table XXII., it will be noted that on the Peak the systolic pressures of all of us were somewhat less than under ordinary barometric pressure, but that the differences were inconstant and so slight as to fall for the most part within the error of observation. Equally little change occurred in the diastolic pressures, except in the case of DOUGLAS. The observations upon him show a distinct rise of the diastolic pressure, as noticed in some persons previously by SCHNEIDER and HEDBLOM.* Accordingly in DOUGLAS the pulse pressures were considerably less on the Peak than in Colorado Springs and New Haven. For SCHNEIDER the average on the Peak was 22 mm. (lowest 19 and highest 26), while his measurements in Colorado Springs were 25 and 28. In HALDANE and

* SCHNEIDER and HEDBLOM, *loc. cit.*

HENDERSON the average pulse pressures on the Peak were practically the same as in Colorado Springs and New Haven. It may be noted further (Table XXIII.) that in ROBISON and in RUSSELL (considering the high systolic pressure of the latter) in spite of their prolonged residence on the Peak, the pulse pressures were not unusually large. In the case of ROBISON this observation is especially significant in view of the fact that he has an unusually athletic physique, leads a very active life, and holds the record for the most rapid ascent of the Peak ever made, viz., 2 hours and 31 minutes for the 6000 and odd feet from Manitou.

Cheyne-Stokes breathing was of such common occurrence upon the Peak that frequent opportunities were afforded for noting the coincident variations in the circulation. These consisted in a slight quickening of the pulse and rise of arterial pressure just before and during the periods of breathing, and a corresponding slowing and fall of pressure as the respiratory pauses set in. Thus, for example, in HALDANE a few hours after arrival on the summit it was observed that during the apnœas the pulse rate was $6\frac{1}{2}$ in five seconds, systolic pressure 94, diastolic 56, and pulse pressure 38, while just before and during the return of respiration the pulse rose to 8 in five seconds, systolic pressure to 106, diastolic to 62, and the pulse pressure to 44.

Special interest attaches to the data obtained on FULLER in relation to the heart action during mountain-sickness. He is a man of strong physique and athletic habits, but quite susceptible to the ills of low barometric pressure. In Colorado Springs (his home town) his pulse pressure was 26 mm. On the Peak soon after arrival on August 4, and before he had begun to feel in any great degree the effects of the ascent, it was practically the same, viz., 28. On the other hand, on three days when he was more or less ill, his pulse pressure was only 11, 18, and 17 mm. respectively. The acceleration of his pulse rate at these times has already been mentioned. These observations suggest that in persons who are acutely mountain-sick the amplitude of the heart-beat may be so greatly reduced as to diminish the blood-stream much below normal in spite of the rapid pulse rate. This behaviour of the heart is similar to that observed by YANDELL HENDERSON* in the "cardiac tetanus" induced in dogs by excessive artificial respiration. It is probably the same sort of increased tonus which X-ray examination has shown in the hearts of athletes after prolonged and violent exertion.† Such excessive cardiac tonus and consequent great diminution in the systolic discharges of the heart may perhaps be an important factor in the syncope frequently observed by us on visitors to the Peak, and especially in those who made the ascent on foot.

A number of observations suggest that on the Peak, even in those well acclimated, some vaso-motor alterations occur of a character too subtle to be defined by the methods which we employed. Thus in HALDANE and HENDERSON the radial pulse was constantly much softer than usual, although, as already remarked, the arterial

* YANDELL HENDERSON, 'American Journal of Physiology,' 1908, XXI., p. 142.

† *Cf.* DIETLEN, 'Ergebnisse der Physiologie,' 1910, X., p. 598.

pressures were not considerably altered. In DOUGLAS and SCHNEIDER, on the contrary, the radial pulses felt perhaps even more than normally full and hard. In both the latter the dilatation and throbbing of the temporal arteries was a notable accompaniment of the headache of the first few days on the Peak. In SCHNEIDER the headache was to a great extent relieved during the day and while in erect positions, but for several successive nights returned and persisted when he was in bed. In FULLER the headache was at one time confined to one side of the head. Coincidently the ear on that side was noticeably congested as compared with the other. In HENDERSON throughout our stay on the Peak stooping over for even a few seconds induced a decided vertigo, a condition to which he is not at all prone at sea-level. On the other hand, emphasis should be laid upon the fact that neither in ourselves nor in others did we see any sign of such hæmorrhages as were described by the earlier observers, and are still popularly believed to occur. Among the thousands of people of all sorts and conditions who ascended the Peak during our stay nose-bleeds did not occur, so far as we could learn, in more than half a dozen cases.

A few weeks before starting on the expedition HENDERSON had, as a result of somewhat excessive smoking, developed a "tobacco heart." Although his pulse was always restored to regular rhythm by moderate exercise, he frequently lost one heart beat in eight or ten, and occasionally after sitting still for some time even one in three or four. This condition continued throughout the stay on the Peak and for some months thereafter. It was neither increased nor diminished on the Peak as compared with the condition before and afterward at sea-level, nor was the discomfort which it involved greater under one barometric pressure than the other.

Recoil Curve Method.—This method was described by YANDELL HENDERSON* some years ago. It is extremely simple and easy of application, and affords a graphic record of which the amplitude is an index of the volume of blood propelled by the heart in relation to the body weight. It depends upon the Newtonian principle that "every action has an equal and opposite reaction." In the original form of the method the man to be examined lay upon a plank suspended from a high ceiling by small ropes or wires. It was found that under these conditions the body, and with it the plank, was propelled at each heart beat alternately headward and feetward through a distance of about a tenth of a millimetre. These movements were found to be of quite definite and regular character in relation to the events of the cardiac cycle. They are the recoil of the body in one direction induced by the propulsion of blood in the opposite direction. By the mechanical principle above quoted the mass of the body multiplied by the distance through which it is moved must equal the algebraic sum of all the mass movements of blood occurring simultaneously within the body. Just as a gun "kicks" in proportion to the charge of powder or shot fired from it, so the recoil movements of the body will vary with the force and amplitude of the heart beat and the volume of blood propelled at each stroke.

* YANDELL HENDERSON, 'American Journal of Physiology,' 1905, XIV., p. 287.

In the original account of this method a modification was described in which the plank, or recoil board, instead of being hung from wires, was supported upon rubber

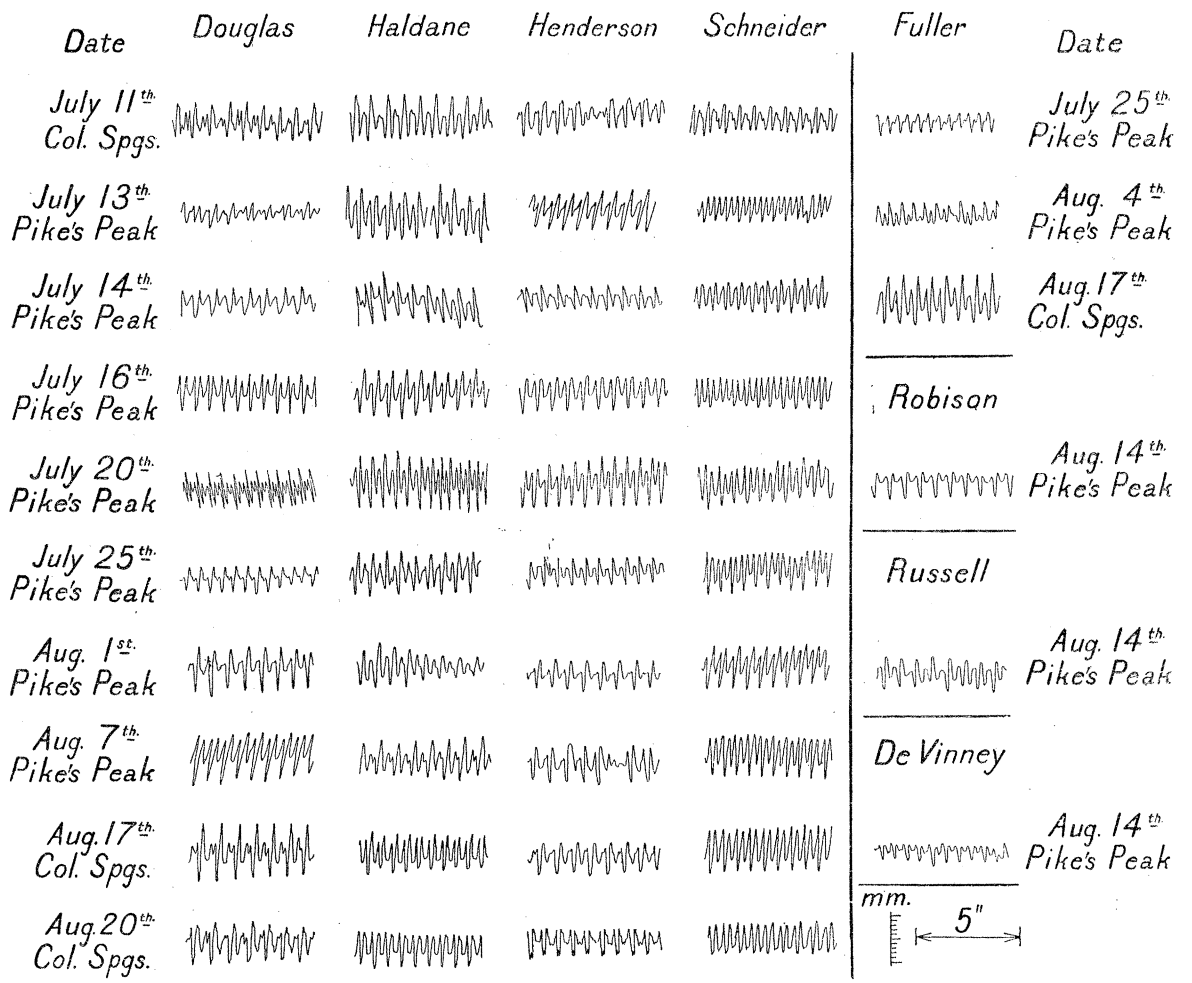

Fig. 16.

Recoil curves obtained with apparatus shown in fig. 17. The relative amplitude of the curve of any individual at any time is taken as an index of the systolic discharge of the heart. Note that the curves obtained in ourselves after acclimatisation to the altitude of the Peak were not sensibly different in size from the normals recorded in Colorado Springs. Nor are the curves of the regular summer inhabitants of the Peak, ROBISON, RUSSELL, and DEVINEY, notably different from those of men of corresponding physique at sea-level. Note also that in DOUGLAS on July 13, and in FULLER on July 25 and August 4, the condition of mountain sickness was accompanied by a marked diminution in the amplitude of the recoil curves. Somewhat the same phenomenon appears in the curve from HALDANE on August 1 after a carbonic oxide and low oxygen experiment. The occasional dropping of a heart beat in the records from HENDERSON was the result of tobacco, not altitude. In the right-hand lower corner are given the original scale of the height and duration of the curves.

stoppers, a large and a medium size stopper being placed one upon the other under each corner and under the middle of each side. Under such conditions the movements were found to be somewhat distorted from their true form. Their amplitude was not

altered, however, in any considerable degree, providing that the size and number of the stoppers supporting the plank were sufficient to support it without too great compression of the rubber. It was this form of the method which we employed in Colorado Springs and on the Peak.

The essential details of the recoil board are shown in the accompanying photograph, fig. 17. A small upright of wood was tacked to the board near its end and to this was attached a stiff wire hook. The hook connected with a lever in such manner that the movements of the board were magnified sixty times, and recorded upon a smoked drum. In the curves a downstroke shows a headward movement of the body and an upstroke a feetward movement. It was essential that during the few seconds required for an observation the subject should hold his breath, otherwise the recoil movements of the circulation were confused by those of respiration. It is unnecessary to consider here the form of the recoil curves obtained. It was particularly the amplitude of the curves to which our attention was directed, for the distance through which the body recoils affords, we believe, a fairly reliable index of the relative size of the heart beats in an individual at different times.

Fig. 17.

Photograph of recoil apparatus with which the curves of fig. 16 were obtained. It consists of a plank supported on rubber stoppers. The recording lever magnifies the recoil movements 60 times.

A glance at the graphic records reproduced in fig. 16 is sufficient to show that in HALDANE, HENDERSON, and SCHNEIDER the curves obtained on the Peak were practically the same size as the controls recorded in Colorado Springs before and after our stay at the summit. In the case of DOUGLAS the curves for July 13, 14, and 25 are noticeably smaller than his normals. The evidence obtained from the recoil curves is thus seen to be in general agreement with that afforded by the pulse pressure method. Both methods indicate a diminished systolic discharge in DOUGLAS, and no considerable alteration in any of the others.

Additional evidence that the systolic discharge is not considerably altered even by prolonged residence at a high altitude is afforded by the three curves here reproduced from ROBISON, RUSSELL, and DEVINEY, all three of whom live on the Peak for several months each year. The curve from DEVINEY is, in fact, of somewhat less than ordinary amplitude, which accords with the fact that the subject (a telegrapher) leads a sedentary life and is of rather frail physique. Similar small curves were found by YANDELL HENDERSON (*loc. cit.*) in persons of similar constitution and habits at sea-level.

Thus this case supports the view that acclimatisation to low barometric pressures (at least down to 450 mm.) does not *per se* alter the volume of the systolic discharge.

It was pointed out above that the pulse pressures obtained on FULLER while he was mountain-sick indicated a greatly diminished amplitude of heart beat in this condition. With this conclusion the evidence of the recoil curves is in striking accord. Thus it will be seen that the curve taken in Colorado Springs, when he was in normal condition, is of the size to be expected of an athletic young man. The three records above it, however, all of which were taken on the Peak when he was feeling more or less ill, are of decidedly subnormal amplitude. A similar diminution in the amplitude of the recoil curve is to be seen in the record from DOUGLAS while mountain-sick on July 13. The curve from HALDANE on August 1 starts at normal size and then dwindles strikingly while he held his breath to allow the recoil movements to be recorded. It was taken while he was still feeling decidedly out of sorts soon after a carbonic oxide and low oxygen breathing experiment.

Mention may be made here of a third method by which we tried to measure the circulation. It consisted of breathing from a bag or spirometer a mixture of oxygen with 30 or 40 per cent. of nitrous oxide. The latter gas is highly soluble and is generally supposed to be taken up by the blood by simple solution. It seemed possible that a determination of the amount absorbed in a certain time (*e.g.*, 30 seconds) would afford an index of the volume of blood flowing through the lungs. In preliminary tests of the method in New Haven rather promising results were obtained. Unfortunately on the Peak unforeseen difficulties were encountered—difficulties which make us unwilling to report the results until the method has been investigated further.

The principal conclusions to be drawn from our observations upon the circulation may be summarized as follows:—

(1) In HALDANE, HENDERSON, and SCHNEIDER the volume of the heart strokes continued practically the same on the Peak as under ordinary barometric pressure. In DOUGLAS the stroke volume was somewhat diminished during the greater part of the period on the Peak. In three men, who for some years past have annually spent several months at the summit, the amplitude of heart beat was essentially the same as in persons of similar physique at sea-level.

(2) In all of us a slight, but only a slight, acceleration of the resting pulse occurred in the first day or two on the Peak. In DOUGLAS, HENDERSON, and SCHNEIDER a progressive acceleration continued for about a fortnight, after which their pulse rates gradually became slower. Even after five weeks on the Peak they were, however, decidedly more rapid than their normal for sea-level. In HALDANE, on the contrary, the resting pulse rate became progressively slower until it was far below his ordinary rate. The pulse rates of other acclimated persons showed on the whole a slight acceleration.

(3) Taking the pulse rates and amplitudes of heart beat together, it appears that

the volume of the aortic blood-stream per minute, or circulation rate, was probably in the case of DOUGLAS neither considerably increased or decreased from its sea-level value. In HALDANE it was decidedly decreased. In HENDERSON and SCHNEIDER it was somewhat increased. On the whole, the slightness of the alteration in circulation rate observed by us in both its factors, *i.e.*, pulse rate and systolic discharge, is in striking contrast with the great increase in the rate of pulmonary ventilation, with the augmentation of hæmoglobin, and with the heightened activity of the lung epithelium.

(4) In persons who are mountain-sick the systolic discharge in some cases is greatly diminished: the resting pulse rate is accelerated; a great acceleration is induced by even a very moderate physical exertion. It is probable that a considerable element of vaso-motor derangement is involved in mountain-sickness, and that even in persons fairly well acclimated the vaso-motor equilibrium is less perfect than at sea-level. The alteration of arterial pressure is however very slight. The tendency to hæmorrhages upon which the early observers laid emphasis is a myth. All the disturbances of the circulation are secondary to oxygen want. Low air pressure *per se* has no direct influence whatever upon the circulation.

IX. *The Changes in the Blood.*

PAUL BERT was the first to surmise that the blood must adapt itself in some way to the diminished pressure of oxygen at high altitudes, and gives an account* of some experiments in which blood obtained from animals living at a high altitude in Bolivia was found to contain a larger percentage of oxygen than did blood taken from animals at sea-level when each of the samples was saturated with air. This increase in the capacity to take up oxygen he looked upon as a compensation for the decrease in the saturation of the hæmoglobin with oxygen due to the low oxygen pressure in the atmosphere at high altitudes. A little later VIAULT† observed the increase in the number of red corpuscles per cubic millimetre in himself and his companions as well as in men and animals resident in the place during a three weeks' visit to a height of 14,400 feet in Peru. MÜNTZ‡ found that the blood of animals living at a height of 9400 feet in the Pyrenees contained a larger percentage of iron than that of those living in the plains.

The subsequent observations which have been made on this question have been exceedingly numerous and have dealt with the phenomena both in men and animals, the earlier results having been confirmed beyond question.

The number of corpuscles per cubic millimetre and the percentage of hæmoglobin increase with the altitude, the increase following the change from a low to a high

* PAUL BERT, 'Comptes Rendus,' XCIV., p. 805, 1882.

† VIAULT, 'Comptes Rendus,' CXI., p. 917, 1890.

‡ MÜNTZ, 'Comptes Rendus,' CXII., p. 298, 1891.

altitude, rapidly according to some observations* or slowly according to others,† but in either case a constant level is reached for any given altitude. Very valuable evidence on the percentage of hæmoglobin which may be found in residents at different altitudes is contained in a succeeding paper by Miss FITZGERALD; her results are especially interesting in the present connection since her observations were made at places in the vicinity of Pike's Peak. On returning from a high altitude to a low one a reverse change in the blood is observed. The relation of the change to deficiency of oxygen was clearly established by JOLYET and SELLIER,‡ for they found that they could produce polycythæmia by keeping animals in air at normal barometric pressure but deficient in oxygen, while lowering of the barometric pressure proved ineffective so long as the oxygen percentage was kept high. A possible effect in this connection from the low temperature and low percentage of moisture in the atmosphere usually met with at high altitudes was negatived by the work of SCHAUMANN and ROSENQVIST§ and of JAQUET.‖ Thenceforward the bulk of the work has dealt with the facts underlying the increase in the percentage values of the red corpuscles and the hæmoglobin. The question at issue has been whether the alteration is brought about by the mere loss of fluid from the blood without any alteration in the total number of corpuscles or total amount of hæmoglobin in the body, or whether the essential thing is an actual overproduction of corpuscles and hæmoglobin. WEISS¶ was unable to detect any alteration in the amount of hæmoglobin per kilo body weight in animals kept at an altitude of 4000 feet, though he obtained the usual increase in the number of red corpuscles per cubic millimetre. JAQUET‖ however, found that animals kept in a chamber at sea-level under a barometric pressure of 640 mm. of mercury, equivalent to an altitude of about 5000 feet, experienced an alteration not only of the percentage values of the hæmoglobin in the blood but also of the total mass of hæmoglobin in the body, the volume of the blood remaining practically unaltered. ABDERHALDEN** a little later, in an extensive series of observations made on rabbits and rats in Basle and at St. Moritz (altitude 6100 feet) could not detect any alteration in the amount of hæmoglobin per animal, though the amount per kilo body weight as well as the percentage values of the hæmoglobin and red corpuscles rose, the weight of the St. Moritz animals being uniformly less than that of the Basle ones.

* ABDERHALDEN, 'Zschr. f. Biol.,' XLIII., p. 125, 1902; BUCKMASTER, 'The Morphology of Normal and Pathological Blood,' London, 1906.

† EGGAR, KARCHER, MIESCHER, SUTER, and VEILLON, 'Arch. f. exp. Path. u. Pharm.,' XXIX., p. 426, 1897.

‡ JOLYET and SELLIER, 'Compt. Rend. de la Soc. de Biol.,' p. 381, 1895.

§ SCHAUMANN and ROSENQVIST, 'Zschr. f. klin. Med.,' XXXV., p. 315, 1898; 'PFLÜGER'S Archiv,' LXVIII., p. 55, 1897.

‖ JAQUET, 'Arch. f. exp. Path. u. Pharm.,' XLV., p. 1, 1901.

¶ 'WEISS, 'Zschr. f. Physiol. Chem.,' XXII., p. 526, 1896–97.

** ABDERHALDEN, 'Zschr. f. Biol.,' XLIII., p. 125, 1902; *Ibid.*, p. 443; 'PFLÜGER'S Archiv,' XCII. p. 615 1902

ABDERHALDEN took this to indicate a concentration of the blood without over-production of hæmoglobin, arguing that it was fairer to consider the mass of hæmoglobin in relation to the animal rather than to unit of body weight, though ZUNTZ and his colleagues have taken the opposite view.*

This last series of experiments, like all the others preceding it, was made by a modification of WELCKER'S method for determining the blood volume. As the method entails the death of the animal, it is only possible to examine animals kept at the higher altitude and compare the results with those derived from another series of control animals of as nearly as possible the same size, age and breed, which have lived at the lower altitude. In order to avoid the errors which are inherent in such a method it is advisable to observe the blood volume, &c., in one and the same animal both at the low and at the high altitude by means of some procedure which can be employed *intra vitam* and does no harm to the animal. This we have endeavoured to do on the present expedition, employing the carbon monoxide method of HALDANE and LORRAIN SMITH † for the purpose on ourselves. The method consists in giving a known quantity of carbon monoxide to the subject, and determining colorimetrically ‡ the degree of saturation of the hæmoglobin in the blood with the gas. From this the total amount of carbon monoxide, or, what is the same thing, the total amount of oxygen which can be taken up by the hæmoglobin of the blood, can be calculated. Since the percentage oxygen capacity of the blood varies as its colouring power it can easily be estimated by the Haldane-Gowers hæmoglobinometer, whose standard is a 1 per cent. solution of blood having a percentage oxygen capacity of 18·5 c.c. From the values obtained for the total oxygen capacity and the percentage oxygen capacity the volume of blood can be readily calculated.

One of us§ had previously used this method in Teneriffe at an altitude of 7000 feet and had found it perfectly safe there, though on that occasion the stay at the high altitude was of insufficient length to produce any distinct change in either the hæmoglobin or the blood volume. One precaution must be observed in using this method and that is to allow sufficient time, after all the required volume of carbon monoxide has been administered to the subject, for the gas to distribute itself evenly throughout the body before taking the samples of blood for determining the saturation of the hæmoglobin with carbon monoxide. To insure this in the present series of experiments the carbon monoxide was given gradually in a small respiration apparatus as in HALDANE and LORRAIN SMITH'S original experiments during a period of 10 to 15 minutes. At the end of this time the subject left this apparatus and at once commenced to breathe into the larger respiration apparatus used in connection

* ZUNTZ, LOEWY, MÜLLER, and CASPARI, 'Höhenklima und Bergwanderungen,' Berlin, 1906.

† HALDANE and LORRAIN SMITH, 'Journ. of Physiol.,' XXV., p. 331, 1900.

‡ For the details of this titration see DOUGLAS and HALDANE, 'Journ. of Physiol.,' XLIV., p. 309, 1912.

§ DOUGLAS, 'Journ. of Physiol.,' XL., p. 471, 1910.

with the experiments on the oxygen tension in the arterial blood. The apparatus contained pure air and he continued to breathe into it for a further period of not less than 20 minutes before the blood samples were taken. The amount of carbon monoxide actually given out into this larger respiration apparatus was of course negligible. In some of the experiments the subject breathed throughout into the small apparatus, but for the same length of time as when the larger one was used in addition. A protocol of an experiment is given at the end of Section IV.

It has been possible in the case of two of us to make determinations by the carbon monoxide method over a prolonged period at Oxford (altitude 200 feet), and the figures obtained not only allowed us to establish a satisfactory average for this altitude but also serve to indicate the kind of variations from this average which are found. In the case of DOUGLAS twenty-nine determinations of the total oxygen capacity* were made between January 20, 1910, and May 29, 1911; in the case of HALDANE fourteen determinations were made between May 31, 1910, and May 26, 1911. In only one experiment in each of these two subjects during these periods did the observed variations lie outside a value 8 per cent. in excess or deficiency of the mean, and it is quite possible that such exceptional cases are due to purely chance errors and are not inherent in the method itself, as there is opportunity for them to occur since the experiments are somewhat prolonged and involve a considerable number of separate observations. The true experimental error of the method is bound in any case to be considerable, for the error of the carmine titration sums with those of the measurement and analysis of the carbon monoxide.† As was pointed out by HALDANE and LORRAIN SMITH, the carbon monoxide must certainly unite with any hæmoglobin in the muscles, &c., as well as with that in the blood, and though we give the value for the total oxygen capacity and calculate the blood volume from it as if all the hæmoglobin were in the blood, this fact should be remembered. All the figures for the blood volume are therefore too high by an unknown, though probably not very large, proportion, owing to the inability of the carbon monoxide method to discriminate between the hæmoglobin within and outside the circulation—in the case of normal rabbits BOYCOTT and DOUGLAS found that the hæmoglobin left in the muscles, bone marrow, &c., after washing out the blood-vessels as thoroughly as possible, was about 7 per cent. of the total amount of hæmoglobin in the body. Adding to this the fact that the blood volume is calculated in the HALDANE and LORRAIN SMITH method from the total and the percentage oxygen capacity, and that

* The value accepted by HÜFNER for the amount of oxygen which combines with one gramme of hæmoglobin is 1·34 c.c., but we prefer to give the equivalent of the hæmoglobin in terms of its oxygen capacity, as that is the value which was directly measured in our experiments.

† A comparison of the carbon-monoxide method with WELCKER'S method on rabbits, as well as the determination by the carbon-monoxide method of quantities of blood abstracted from, or transfused into, rabbits will be found in BOYCOTT and DOUGLAS, 'Journ. of Path. and Bact., XIII., p. 256, 1909, and in BOYCOTT, 'Journ. of Path. and Bact.,' XVI., p. 485, 1912.

the last has its own, though small, experimental error, it is clear that the values for the blood volume are the least reliable of the determinations.

In the previous series of experiments made by the carbon monoxide method at a high altitude it was noted that partial saturation of the blood with carbon monoxide seemed to interfere materially with the capacity for performing the necessary colorimetric titration accurately, if this was attempted immediately after absorbing the gas and whilst the hæmoglobin was still saturated up to 25 per cent. In our present series we have endeavoured to avoid this source of fallacy, and, so far as we can see, successfully. All the colorimetric titrations were done by HALDANE and were in duplicate and if necessary triplicate, so as to exclude accidental errors of reading, &c. When he was himself the subject of experiment a period of an hour or so was allowed to elapse after the close of the experiment before he did the titration. The saturation of the blood with carbon monoxide was purposely kept low in the experiments on the summit of Pike's Peak, the hæmoglobin being generally somewhat under 20 per cent. saturated as opposed to the 25 per cent. saturation which was reached in the Teneriffe series. At no time did we note any unpleasant symptoms due to this low saturation of the blood with carbon monoxide on the summit of the Peak.

The results of our experiments are given in Tables XXIV., XXV., XXVI., XXVII., and are shown graphically in fig. 23. For the purpose of rendering the results clear in the curves we have taken the mean normal values obtained before the ascent of the Peak (Oxford values for DOUGLAS and HALDANE, Colorado Springs values for HENDERSON and SCHNEIDER) as 100 and expressed the actual values obtained as percentages of these, and it should be noted that the 100 per cent. value in each of the curves refers only to the individual in question. The curves exhibit the variations undergone by the percentage of hæmoglobin as determined by the HALDANE-GOWERS hæmoglobinometer: the total oxygen capacity, *i.e.*, the total amount of hæmoglobin, and the volume of the blood. In the Tables are given in addition a number of counts of the red blood corpuscles and of hæmotocrit determinations of the relative volume of corpuscles to plasma in the blood. In the figure we have for convenience plotted the values obtained on DOUGLAS and HALDANE at Oxford before the start of the expedition without regard to time, as we wished to indicate the normal variations at sea-level without expanding the figures to an unnecessary length.

Unfortunately we were only able to make one determination of the total oxygen capacity and blood volume on HENDERSON and two on SCHNEIDER before ascending to the summit, and these were made at Colorado Springs. SCHNEIDER had already been at Colorado Springs for a week after spending five months at or near sea-level, while HENDERSON had been travelling for the fortnight previous at altitudes varying between sea-level and 7000 feet. This previous sojourn at a considerable altitude might have accounted for the high percentage of hæmoglobin and red corpuscles in HENDERSON'S case, but subsequent observations made by him two months after his

TABLE XXIV.

DOUGLAS.								Values expressed as percentage of mean normal for Oxford.			
Date.	Time of observation.	Percentage of hæmoglobin by Gowers-Haldane scale.	Total oxygen capacity in cubic centimetres.	Volume of blood in cubic centimetres.	Red corpuscles per cubic millimetre in millions.	Hæmatocrit reading.		Percentage of hæmoglobin.	Total oxygen capacity.	Volume of blood.	Red corpuscles per cubic millimetre.
1910.											
Jan. 20	—	96	783	4420	—	—	Oxford.	97	94	97	—
21	—	95	817	4640	—	—		96	99	102	—
Feb. 3	—	96	812	4600	—	—		97	98	101	—
9	—	100	808	4370	—	—		101	97	96	—
10	—	98	870	4810	—	—		99	105	105	—
14	—	94	849	4880	—	—		95	102	107	—
16	—	94	775	4460	—	—		95	93	98	—
18	—	94	894	5170	—	—		95	108	113	—
22	—	92	891	5240	—	—		93	107	115	—
26	—	100	806	4360	—	—		101	97	95	—
March 1	—	100	831	4500	—	—		101	100	99	—
5	—	100	880	4760	—	—		101	106	104	—
8	—	94	765	4400	—	—		95	92	96	—
11	—	96	816	4590	—	—		97	98	101	—
June 4	—	101	898	4800	—	—		102	108	105	—
?	—	—	852	—	—	—		—	103	—	—
27	—	—	817	—	—	—		—	98	—	—
July 1	—	—	923	—	—	—		—	111	—	—
Dec. 14	—	100	792	4300	—	—		101	95	94	—
16	—	102	795	4230	—	—		103	96	93	—
22	—	—	802	—	—	—		—	97	—	—
1911.											
Jan. 11	—	—	866	—	—	—		—	104	—	—
13	—	103	817	4280	—	—		104	98	94	—
16	—	—	804	—	—	—		—	97	—	—
Feb. 8	—	—	885	—	—	—		—	107	—	—
27	—	104	829	4320	—	—		105	100	95	—

April	5	—	106	—	—	5·06	—		107	—	—	104
	9	—	103	—	—	5·51	—		104	—	—	113
	14	—	101	—	—	5·24	—		102	—	—	107
May	2	—	101	—	—	4·70	—		102	—	—	96
	4	—	99	—	—	4·82	—		100	—	—	99
	10	—	99	—	—	4·57	—		100	—	—	93
	18	—	101	—	—	4·67	—		102	—	—	95
	23	—	100	822	4470	5·17	—		101	99	98	106
	27	—	96	792	4450	4·43	—		97	95	97	91
	29	—	97	791	4400	4·62	—		98	95	96	94
June	7	—	98	—	—	4·82	—		99	—	—	99
	17	—	104	—	—	4·80	—		105	—	—	98
	22	—	105	—	—	5·23	—		106	—	—	107
		—	**99**	**830**	**4566**	**4·89**	—	**Mean for Oxford.**	**100**	**100**	**100**	**100**
July	7	—	99	—	—	—	—	Colorado Springs before ascent of Pike's Peak.	100	—	—	—
	8	—	102	850	4500	—	—		103	102	99	—
	9	—	105	—	—	5·26	—		106	—	—	108
	10	—	100	—	—	—	—		101	—	—	—
	11	11 a.m.	103	—	—	—	—		104	—	—	—
	12	6 p.m.	105	—	—	—	—	Pike's Peak summit, 7 hours after arrival.	106	—	—	—
	13	11 a.m.	112	—	—	—	—		113	—	—	—
	14	9.30 ,,	111	—	—	5·60	—		112	—	—	115
	15	9.10 ,,	111	—	—	—	—		112	—	—	—
	16	8.25 ,,	113	—	—	—	—		114	—	—	—
	17	8 ,,	109	—	—	—	—		110	—	—	—
	18	10.30 ,,	113	—	—	5·35	—		114	—	—	109
	19	8.10 ,,	118	862	3960	—	—		119	104	87	—
	20	11.40 ,,	113	875	4190	5·44	—		114	105	92	111
	21	9.30 ,,	118	—	—	—	—		119	—	—	—
	22	9.30 ,,	113	—	—	—	—		114	—	—	—
	23	2 p.m.	116	—	—	—	—		117	—	—	—
	24	1 ,,	119	990	4520	—	—		120	119	99	—
	25	5 ,,	117	—	—	5·76	—		118	—	—	118
	26	9.30 a.m.	117	1041	4820	—	—		118	125	105	—
	28	4 p.m.	123	—	—	—	—		125	—	—	—
	29	4.30 ,,	117	—	—	—	—		118	—	—	—

TABLE XXIV. (continued).

DOUGLAS.									Values expressed as percentage of mean normal for Oxford.			
Date.		Time of observation.	Percentage of hæmoglobin by Gowers-Haldane scale.	Total oxygen capacity in cubic centimetres.	Volume of blood in cubic centimetres.	Red corpuscles per cubic millimetre in millions.	Hæmatocrit reading.		Percentage of hæmoglobin.	Total oxygen capacity.	Volume of blood.	Red corpuscles per cubic millimetre.
July	30	9 a.m.	124	—	—	—	—		126	—	—	—
	31	10.15 „	118	—	—	5·75	—		119	—	—	118
Aug.	1	2.15 p.m.	113	—	—	—	—		114	—	—	—
	2	11.40 a.m.	116	1063	4940	—	—		117	128	108	—
	3	2.10 p.m.	121	—	—	—	—		123	—	—	—
	4	10.40 a.m.	115	—	—	—	—		116	—	—	—
	5	9.15 „	124	—	—	—	—		126	—	—	—
	6	10.15 „	113	—	—	5·29	—		114	—	—	108
	7	8.45 „	120	—	—	—	—		122	—	—	—
	8	8.30 „	122	—	—	—	51		124	—	—	—
	9	8.45 „	124	—	—	—	—		126	—	—	—
	10	7.45 „	127	—	—	—	—		129	—	—	—
	11	10.30 „	117	—	—	—	—		118	—	—	—
	13	11.40 „	120	—	—	—	48·5		122	—	—	—
	15	8.45 „	121	1028	4590	—	—		123	124	101	—
	16	6 p.m.	110	—	—	—	—	Colorado Springs on return, 2½ hours after arrival.	111	—	—	—
	17	11.30 a.m.	110	—	—	—	44		111	—	—	—
	18	12.15 „	111	—	—	—	—		112	—	—	—
	19	1 p.m.	108	882	4520	—	—		109	106	99	—
	20	10.30 a.m.	110	—	—	5·23	45		111	—	—	107
	22	10.50 „	112	—	—	5·33	—		113	—	—	109
	28	11.15 a.m.	103	—	—	—	—	New Haven.	104	—	—	—
	29	10.50 „	105	975	5025	—	—		106	117	110	—
	31	11.30 „	105	—	—	5·08	48·5		106	—	—	104

Sept.	1	10.30 „	110	934	4380	—	—		111	113	96	—
	4	11.30 „	103	—	—	—	—		104	—	—	—
	5	11 „	105	880	4540	—	46		106	106	99	—
	6	—	103	—	—	—	44		104	—	—	—
	19	—	99	817	4460	—	—	Oxford.	100	98	98	—

TABLE XXV.

Date.	Time of observation.	HALDANE. Percentage of hæmoglobin by Gowers-Haldane scale.	Total oxygen capacity in cubic centimetres.	Volume of blood in cubic centimetres.	Red corpuscles per cubic millimetre in millions.	Hæmatocrit reading.		Values expressed as percentage of mean normal for Oxford. Percentage of hæmoglobin.	Total oxygen capacity.	Volume of blood.	Red corpuscles per cubic millimetre.
1910.											
May 31	—	—	876	—	—	—	Oxford.	—	97	—	—
June 1	—	99	—	—	—	—		98	—	—	—
3	—	—	880	—	—	—		—	98	—	—
8	—	—	1025	—	—	—		—	114	—	—
15	—	—	902	—	—	—		—	100	—	—
28	—	—	932	—	—	—		—	103	—	—
Dec. 17	—	105	840	4330	—	—		104	93	90	—
19	—	—	843	—	—	—		—	94	—	—
20	—	103	888	4650	—	—		102	99	97	—
21	—	103	919	4810	—	—		102	102	100	—
1911.											
Jan. 23	—	—	879	—	—	—		—	98	—	—
Feb. 10	—	103	923	4870	—	—		102	102	101	—
11	—	97	951	5310	—	—		96	106	110	—
May 24	—	96	911	5140	4·53	—		95	101	107	97
26	—	101	867	4640	4·96	—		100	96	96	106

TABLE XXV. (continued).

Date.	Time of observation.	HALDANE. Percentage of hæmoglobin by Gowers-Haldane scale.	Total oxygen capacity in cubic centimetres.	Volume of blood in cubic centimetres.	Red corpuscles per cubic millimetre in millions.	Hæmatocrit reading.		Values expressed as percentage of mean normal for Oxford. Percentage of hæmoglobin.	Total oxygen capacity.	Volume of blood.	Red corpuscles per cubic millimetre.
June 19	—	99	—	—	4·67	—		98	—	—	100
22	—	101	—	—	4·50	—		100	—	—	96
	—	**101**	**902**	**4821**	**4·67**	—	**Mean for Oxford.**	**100**	**100**	**100**	**100**
July 7	—	87	—	—	—	—	Colorado Springs.	86	—	—	—
8	—	96	927	5225	—	—		95	103	108	—
9	—	88	—	—	—	—		87	—	—	—
10	—	94	—	—	4·56	—		93	—	—	98
11	10 a.m.	101	—	—	—	—		100	—	—	—
12	6 p.m.	104	—	—	—	—	Pike's Peak summit, 7 hours after arrival.	103	—	—	—
13	9.15 a.m.	102	—	—	—	—		101	—	—	—
14	8.30 ,,	104	—	—	—	—		103	—	—	—
15	8.45 ,,	100	—	—	—	—		99	—	—	—
16	7.10 ,,	104	—	—	—	—		103	—	—	—
17	7.55 ,,	108	—	—	—	—		107	—	—	—
18	8.10 ,,	105	—	—	—	—		104	—	—	—
19	5.30 p.m.	108	—	—	—	—		107	—	—	—
20	1.10 ,,	107	—	—	—	—		106	—	—	—
21	8.20 a.m.	107	1060	5360	—	—		106	118	111	—
23	2.10 p.m.	112	—	—	—	—		111	—	—	—
24	9.45 a.m.	112	—	—	—	—		111	—	—	—
25	7 ,,	110	—	—	5·18	—		109	—	—	111
26	1.30 p.m.	112	—	—	—	—		111	—	—	—

Aug. 27	10.25 a.m.	114	—	—	—		113	—	—	—	—	—
28	12.40 p.m.	112	1137	5510	—		111	126	114	—	—	—
29	8.40 a.m.	117	—	—	—		116	—	—	—	—	—
30	8.50 ,,	117	—	—	—		116	—	—	—	—	—
31	8.55 ,,	115	—	—	5·43		114	—	—	—	—	116
1	10 ,,	115	1141	5360	—		114	127	111	—	—	—
3	9.15 ,,	118	—	—	—		117	—	—	—	—	—
5	9 ,,	116	—	—	—		115	—	—	—	—	—
6	10.50 ,,	107	—	—	5·11	47	106	—	—	—	—	109
7	8.30 ,,	116	—	—	—	—	115	—	—	—	—	—
8	9 ,,	113	—	—	—	—	112	—	—	—	—	—
9	8.30 ,,	120	—	—	—	50	119	—	—	—	—	—
11	10 ,,	114	—	—	—	—	113	—	—	—	—	—
13	8.40 ,,	116	1100	5120	—	—	115	122	106	—	—	—
15	8.55 ,,	118	—	—	—	48	117	—	—	—	—	—
							Colorado Springs on return, 2 hours after arrival.					
16	6 p.m.	113	—	—	—	—	112	—	—	—	—	—
17	11 a.m.	112	—	—	—	—	111	—	—	—	—	—
18	10.30 ,,	106	1050	5360	—	47	105	116	111	—	—	—
19	11.30 ,,	106	—	—	—	—	105	—	—	—	—	—
20	10.20 ,,	107	—	—	4·65	46	106	—	—	—	—	100
22	12.30 p.m.	107	—	—	—	—	106	—	—	—	—	—
							New Haven.					
28	10.45 a.m.	101	—	—	—	—	100	—	—	—	—	—
29	2.40 p.m.	98	1043	5760	—	—	97	116	120	—	—	—
30	10.10 a.m.	100	—	—	—	—	99	—	—	—	—	—
31	Noon.	103	—	—	4·54	—	102	—	—	—	—	97
Sept. 1	12.15 p.m.	101	1058	5650	—	—	100	118	117	—	—	—
4	11.30 a.m.	100	—	—	—	—	99	—	—	—	—	—
5	11.45 ,,	101	1045	5590	—	45	100	116	116	—	—	—
6	—	101	—	—	—	43	100	—	—	—	—	—
							Oxford.					
19	—	100	926	5000	—	—	99	103	104	—	—	—

TABLE XXVI.

HENDERSON.								Values expressed as percentage of mean normal for Colorado Springs.			
Date.	Time of observation.	Percentage of hæmoglobin by Gowers-Haldane scale.	Total oxygen capacity in cubic centimetres.	Volume of blood in cubic centimetres.	Red corpuscles per cubic millimetre in millions.	Hæmatocrit reading.		Percentage of hæmoglobin.	Total oxygen capacity.	Volume of blood.	Red corpuscles per cubic millimetre.
1911.											
July 10	—	111	871	4250	—	—	Colorado Springs.	100	100	100	—
11	11.30 a.m.	111	—	—	6·3	—		100	—	—	100
		111	**871**	**4250**	**6·3**	—	**Mean for Colorado Springs.**	**100**	**100**	**100**	**100**
13	9.30 a.m.	112	—	—	6·4	—	Pike's Peak summit, day after arrival.	101	—	—	102
14	9.15 ,,	114	—	—	7·0	—		103	—	—	111
15	10 ,,	120	—	—	7·0	—		108	—	—	111
16	8.35 ,,	122	—	—	6·4	—		110	—	—	102
17	8.5 ,,	121	—	—	6·8	—		109	—	—	108
18	8.20 ,,	122	—	—	6·6	—		110	—	—	105
19	4.50 p.m.	121	—	—	6·6	—		109	—	—	105
20	9.30 a.m.	125	—	—	6·6	—		113	—	—	105
21	11.15 ,,	129	—	—	—	—		116	—	—	—
22	9.30 ,,	128	1071	4520	7·1	—		115	123	106	113
23	2.20 p.m.	120	—	—	—	—		108	—	—	—
24	9.15 a.m.	121	—	—	7·2	—		109	—	—	114
25	7.10 ,,	128	—	—	—	—		115	—	—	—
26	9.30 ,,	129	—	—	7·0	—		116	—	—	111
28	9.30 ,,	129	—	—	7·1	—		116	—	—	113
29	8.30 ,,	133	1167	4740	—	—		120	134	112	—
30	10 ,,	133	—	—	7·8	—		120	—	—	124
31	11.30 ,,	131	—	—	—	—		118	—	—	—
Aug. 1	11.15 ,,	129	—	—	—	—		116	—	—	—
3	9.20 ,,	130	—	—	—	—		117	—	—	—

4	4.45 p.m.	124	—	7·3	—		112	—	—	116
5	9.10 a.m.	133	—	—	—		120	—	—	—
6	11.15 ,,	124	—	—	—		112	—	—	—
7	8.55 ,,	134	—	—	—		121	—	—	—
8	8.45 ,,	132	—	—	54		119	—	—	—
9	7 ,,	128	1221	—	—		115	140	121	—
	9.40 ,,	130	5150	6·7	53		117	—	—	106
11	11.15 ,,	132	—	—	—		119	135	114	—
12	12.30 p.m.	127	4820	—	—		114	—	—	—
13	12.30 ,,	134	1176	7·2	—		121	—	—	114
14	8.30 a.m.	134	—	—	—		121	—	—	—
15			—	—	—			—	—	—
						Colorado Springs on return, 2 hours after arrival.				
16	6 p.m.	125	—	—	—		113	—	—	—
17	11.45 a.m.	122	—	—	48		110	—	—	—
18	10.35 ,,	126	—	—	—		114	—	—	—
19	11 ,,	124	—	—	—		112	—	—	—
20	10 ,,	129	1070	6·5	49		116	123	105	103
						New Haven.				
28	3.15 p.m.	122	1021	—	—		110	117	106	—
29	12.45 ,,	121	—	—	—		109	—	—	—
30	5 ,,	120	—	—	—		108	—	—	—
31	Noon.	115	1089	—	—		104	125	120	—
Sept. 4	12.20 p.m.	113	1063	—	—		102	122	120	—
5	—	114	—	—	52		103	—	—	—
6	—	113	—	—	49		102	—	—	—
Oct. 2	11 a.m.	108	—	—	—		97	—	—	—
3	11 ,,	112	—	—	—		101	—	—	—
4	11 ,,	110	—	—	—		99	—	—	—
5	11 ,,	107	—	—	—		96	—	—	—
6	11 ,,	110	—	—	—		99	—	—	—
7	11 ,,	108	—	—	—		97	—	—	—
1912.										
Jan. 6	11 ,,	110	—	—	—		99	—	—	—
8	11 ,,	109	—	—	—		98	—	—	—
10	11.30 ,,	111	—	—	—		100	—	—	—
13	11 ,,	109	—	—	—		98	—	—	—
26	11 ,,	110	—	—	—		99	—	—	—

TABLE XXVII.

SCHNEIDER.								Values expressed as percentage of mean normal for Colorado Springs.			
Date.	Time of observation.	Percentage of hæmoglobin by Gowers-Haldane scale.	Total oxygen capacity in cubic centimetres.	Volume of blood in cubic centimetres.	Red corpuscles per cubic millimetre in millions.	Hæmatocrit reading.		Percentage of hæmoglobin.	Total oxygen capacity.	Volume of blood.	Red corpuscles per cubic millimetre.
1911.											
July 8	—	97	—	—	—	—	Colorado Springs.	99	—	—	—
9	—	98	721	3990	—	—		100	99	98	—
10	—	96	739	4160	5·6	—		98	101	102	99
11	11.45 a.m.	101	—	—	5·7	—		103	—	—	101
		98	**730**	**4075**	**5·65**	—	**Mean for Colorado Springs.**	**100**	**100**	**100**	**100**
13	9.50 a.m.	103	—	—	6·0	—	Pike's Peak summit, day after arrival.	105	—	—	106
14	8.40 „	111	—	—	7·0	—		113	—	—	124
15	9.20 „	113	—	—	6·6	—		115	—	—	117
16	Noon.	107	—	—	6·0	—		109	—	—	106
17	8.40 a.m.	108	—	—	6·4	—		110	—	—	113
18	8.35 „	115	—	—	6·1	—		117	—	—	108
19	5 p.m.	109	—	—	6·3	—		111	—	—	111
20	9.45 a.m.	113	—	—	6·2	—		115	—	—	110
21	9.50 „	113	—	—	—	—		115	—	—	—
22	10.45 „	111	—	—	6·3	—		113	—	—	111
23	8.45 „	116	918	4270	6·6	—		118	126	105	117
24	10.30 „	116	—	—	6·2	—		118	—	—	110
25	7 „	117	—	—	—	—		119	—	—	—
26	8.10 „	122	—	—	6·4	—		124	—	—	113
27	8.30 „	115	—	—	—	—		117	—	—	—
28	8.30 „	120	—	—	6·8	—	In Colorado Springs, night of 28th.	122	—	—	120
29	4.25 p.m.	116	—	—	—	—		118	—	—	—

											124
											—
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											124
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											113
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											—
											—
											—
											103
											—
											99
											—
30	10.10	a.m.	118	—	7·0	—	In Colorado Springs, night of 9th.	120	—	—	124
31	9.20	,,	119	4360	—	—		121	131	107	—
Aug. 1	10.45	,,	114	—	—	—		116	—	—	—
2	8.15	,,	123	—	—	—		125	—	—	—
3	8.30	,,	120	—	—	—		122	—	—	—
4	4.30	p.m.	120	—	7·0	—		122	—	—	124
5	9.25	a.m.	119	—	—	—		121	—	—	—
6	11.30	,,	116	—	—	46·5		118	—	—	—
7	8.40	,,	121	—	—	—		123	—	—	—
8	9.30	,,	116	4550	—	—		118	134	112	—
9	9	,,	115	—	—	49		117	—	—	—
11	9.20	,,	119	—	6·4	48		121	—	—	113
12	11.45	,,	119	4210	—	—		121	127	103	—
13	11.50	,,	120	—	—	—		122	—	—	—
14	11.30	,,	123	—	—	—		125	—	—	—
15	8.40	,,	121	—	—	—		123	—	—	—
16	6	p.m.	114	—	—	—	Colorado Springs on return, 2 hours after arrival.	116	—	—	—
17	9.45	a.m.	114	—	—	47		116	—	—	—
18	11.30	,,	106	4700	5·8	—		108	126	115	103
19	10.15	,,	105	—	—	—		107	—	—	—
20	11.20	,,	101	—	5·6	43		103	—	—	99
22	11.30	,,	106	4570	—	—		108	123	112	—

return to New Haven gave equally high hæmoglobin percentages (a mean of 109 as compared with 111 at Colorado Springs).

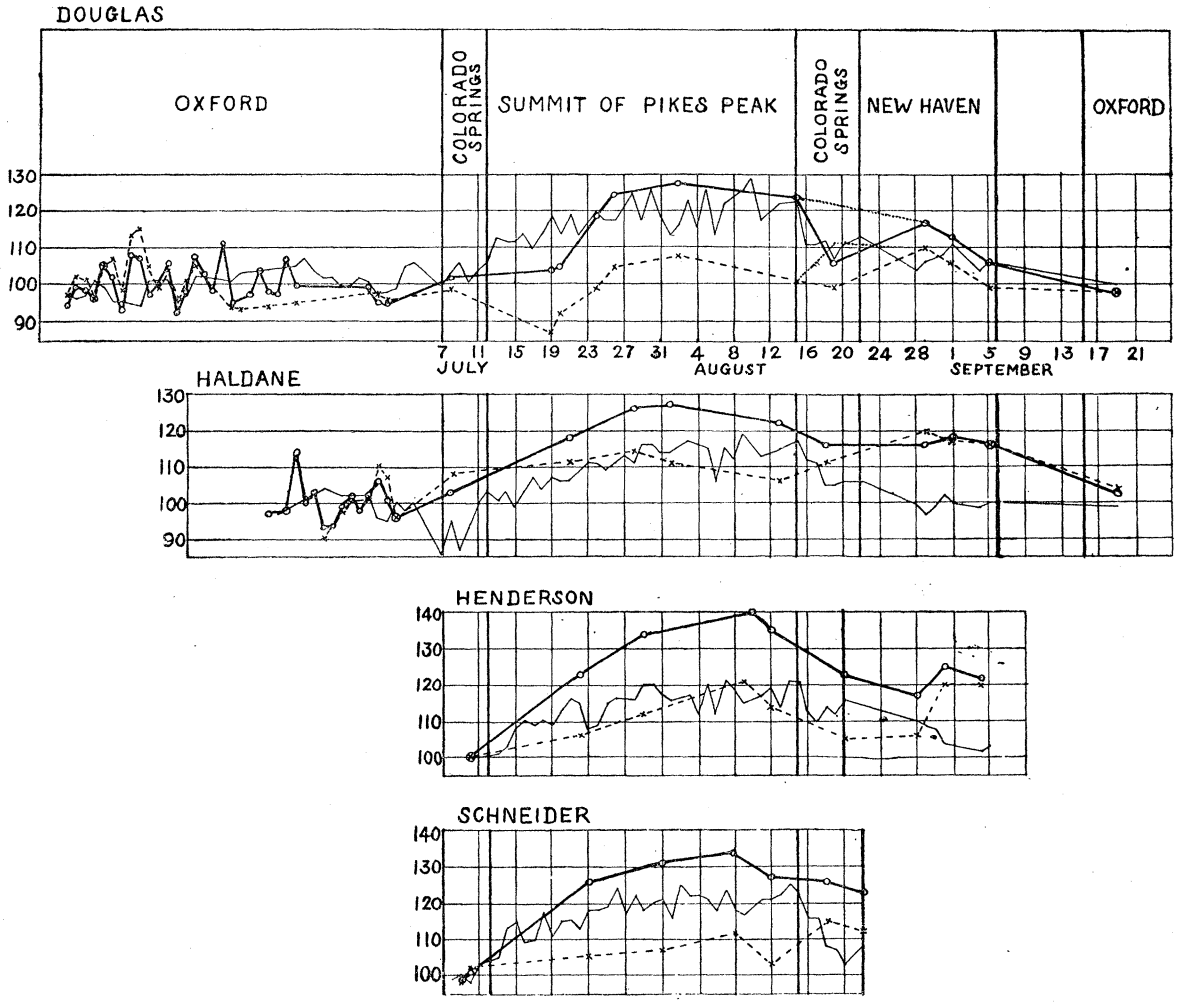

Fig. 18.

Abscissæ and ordinates on the same scale in each case.

Ordinates represent percentages of the average values obtained before ascending the Peak (Oxford and Colorado Springs) on the particular subject.

Continuous thick line = total oxygen capacity or total amount of hæmoglobin.

Continuous thin line = percentage of hæmoglobin.

Interrupted line = blood volume.

The values for DOUGLAS and HALDANE in Oxford before the start of the expedition are plotted without relation to time.

The changes which occurred on the summit were similar in character in each of us. The percentage of hæmoglobin and the number of red corpuscles commenced to rise at

once, this rise being especially rapid in the first two or three days in all of us except HALDANE, in whose case it was very gradual. The increase continued for about the first three weeks and then the hæmoglobin percentage remained steady for the last fortnight of our stay. We were obliged to postpone our determination of the total oxygen capacity for several days owing to the onset of mountain-sickness and the subsequent pressure of other work. The first determinations by the carbon monoxide method were made on DOUGLAS on the seventh and eighth days after the ascent and gave concordant values for the total oxygen capacity only 5 per cent. greater than the normal for sea-level. The percentage of hæmoglobin at this time was about 15 per cent. above the sea-level normal, so that the volume of the blood was considerably reduced. These two observations are the only ones we have which indicate directly that an actual concentration of the blood by loss of fluid from the vessels may occur on ascending to a high altitude. Such was very likely the case in both HENDERSON and SCHNEIDER: for they, like DOUGLAS, showed a very rapid increase in the hæmoglobin percentage during the first day or two after reaching the summit, a rapidity which renders it extremely doubtful whether the increase could have been entirely produced by a new formation of hæmoglobin. The first determinations of the total oxygen capacity on HALDANE, HENDERSON, and SCHNEIDER, made on the ninth to the twelfth days after arrival, gave values respectively of 18, 23, and 26 per cent. above the normal, with a slight increase in the volume of the blood. On the twelfth day after arrival DOUGLAS had a total oxygen capacity 19 per cent. in excess of his normal, and his blood volume had returned to its normal value. Subsequent observations showed that the increase of total oxygen capacity in each of us continued for a considerable time. The maxima reached were for DOUGLAS 28 per cent. above normal on the 21st day after the arrival on the summit, for HALDANE 27 per cent. above normal on the 20th day, for HENDERSON 40 per cent. above normal on the 28th day, and for SCHNEIDER 34 per cent. above normal on the 27th day. The last determinations made on the summit just before we left gave values for the total oxygen capacity in each case slightly below the maximum; but the difference is perhaps hardly sufficient to justify us in believing that it is a real one.

The rise in the total oxygen capacity after it was definitely established exceeded that of the percentage of hæmoglobin, and the blood volume was therefore distinctly increased during this period. It is true that this deduction would have been falsified if there had been simultaneously any increase in the capacity of the hæmoglobin to take up oxygen; but we made definite experiments to test this on August 10 by comparing the percentage oxygen capacity as deduced from the hæmoglobinometer with direct observations by means of the Barcroft-Haldane ferricyanide blood-gas apparatus. We used two hæmoglobinometers which had been carefully standardised with the blood-gas apparatus against DOUGLAS' blood and against ox blood in Oxford before leaving. The results were as follows:—

TABLE XXVIII.

	By hæmoglobinometers.		By ferricyanide apparatus.
	Hæmoglobin percentage.	Percentage oxygen capacity.	Percentage oxygen capacity.
Blood of DOUGLAS (1)	128	23·7	24·0
Blood of DOUGLAS (2)	129	23·9	
Blood of HALDANE (1)	125	23·1	22·8
Blood of HALDANE (2)	126	23·3	
Mean	127	23·5	23·4

Clearly the hæmoglobin had not altered at all in its capacity for taking up oxygen.

On our return to Colorado Springs the most noticeable change was a practically immediate reduction in the percentage of hæmoglobin, which fell in a day or two to a level corresponding to that which appears to be about the normal for the altitude of Colorado Springs, namely, 110 per cent. Simultaneously there was a distinct decrease in the total oxygen capacity, but this decrease was not nearly so marked nor did it develop so rapidly as the decrease in the hæmoglobin percentage in the case of HALDANE and SCHNEIDER. The blood volume in these two cases was therefore as high as, if not higher than, the maximum value obtained on the summit. A determination made on HENDERSON on the fourth day after the descent showed that the fall in the total oxygen capacity was about proportional to the fall in the percentage of hæmoglobin, and that his blood volume was but little above his normal. We are inclined to discard the values obtained for the total oxygen capacity and for the blood volume at Colorado Springs on the return in the case of DOUGLAS, as in comparison with the subsequent observations they appear to be abnormally low and do not agree at all with the observations made on the other members of the expedition: the values found are, in fact, compatible with the assumption that there was a gross error of 25 c.c. in the initial reading of the measuring cylinder containing the carbon monoxide.* Perhaps the real state of affairs would be indicated by the dotted lines, and if this were so the blood volume would have been markedly increased. Unfortunately we did not have the opportunity of making another observation on DOUGLAS at Colorado Springs. The remaining observations on DOUGLAS, HALDANE, and HENDERSON were made at New Haven, at sea-level, the last determinations there

* The old cylinder had been broken on the journey down, and the graduation of the new one was somewhat confusing.

being made three weeks after leaving the summit of the Peak. The percentage of hæmoglobin showed a further decrease during this period, in fact in the case of HALDANE the first determinations made at New Haven on August 28 showed that he had attained his normal sea-level value, and this was maintained during the whole of the time we were at New Haven. In HENDERSON'S case the hæmoglobin percentage fell gradually so that it almost reached the value shown at the start of the expedition on September 4. DOUGLAS showed a distinct decrease of the hæmoglobin percentage as compared with the value at Colorado Springs after returning from the Peak, but never quite regained his normal sea-level value whilst in America. DOUGLAS was the only one of the three to show a gradual return of the total oxygen capacity towards his normal value during the same period. In the case of both HALDANE and HENDERSON the total oxygen capacity remained at about the same level as it had been just previously in Colorado Springs, and the blood volume of these two was therefore considerably above normal. Determinations made on HALDANE and DOUGLAS in Oxford on September 19, a fortnight after the last observations in New Haven and five weeks after leaving the summit of the Peak, gave perfectly normal values for the total oxygen capacity and percentage of hæmoglobin and for the blood volume.

On the whole, making allowance for the large experimental error of hæmocytometer observations, the number of red corpuscles per cubic millimetre ran parallel throughout with the percentage of hæmoglobin, and there was no real indication in our experiments of any alteration of colour index such as has in some instances been found by previous observers. We employed two hæmocytometers, one a Bürker's instrument which was used for the determinations on HALDANE and DOUGLAS, and the other a Thoma-Zeiss instrument which was used in the case of HENDERSON and SCHNEIDER: DOUGLAS made the determinations with the former instrument and SCHNEIDER with the latter. It should be noted that the values obtained on the same sample of blood were different with the two instruments: the Thoma-Zeiss gave readings 11 per cent. higher than the Bürker, this discrepancy accounting for the obvious difference in the blood counts of the different individuals shown in the tables. We do not know which of the two instruments was most nearly correct.

Our hæmatocrit determinations were not very satisfactory, as unfortunately we did not obtain an instrument until the beginning of our last week on the summit, and we have therefore no observations made prior to our ascent of the Peak. On the whole the values obtained on the summit and at Colorado Springs agree with the percentage of hæmoglobin, but the tendency seemed to be to get values disproportionally large when we reached sea-level. As we were able to make but few determinations we are, however, not prepared to lay any great stress on our results.

We may therefore sum up the results of our experiments as follows. The effect of living at the high altitude was to induce an increase in the percentage of hæmoglobin and of red corpuscles in the blood. In the main this increase was due to an actual

overproduction of new red corpuscles of, so far as can be judged, normal character.* We obtained, however, definite evidence in one case that the change in the percentage values was initiated by a concentration of the blood owing to a loss of plasma, and it is probable that the same held good in two other cases. So soon as the new formation of red cells was well under way, the volume of the blood apparently commenced to increase. We say "apparently" because we have not taken into account in this connection a possible increase in the amount of hæmoglobin in the muscles; if there had been such an increase the real volume of the blood would have been less than the apparent, and might, in fact, had the increase of muscle hæmoglobin been very great, have been the same as under normal circumstances at sea-level. We have, however, no direct information bearing on this question, and in the light of our observations at the beginning and just after the end of our stay on the Peak, a change of blood volume is rendered more probable. Such an increase of blood volume might have two explanations. It might be merely a reaction to the increased viscosity of the blood as the concentration of red corpuscles rises,† for one method of compensation for increased viscosity would be to increase generally the calibre of the blood-vessels. Such a vaso-dilatation would necessitate an increase in the volume of blood occupying those vessels. The increase of blood volume might on the other hand be due merely to the operation of a function normally in existence, which is directed to maintaining the volume of the plasma constant—a function which perhaps does not owe its existence only to changes in a physical factor such as viscosity. That is to say, in either case, that two opposing factors came into play during our residence at the high altitude; the one tended to effect an increase in the concentration of hæmoglobin and red corpuscles, the other to reduce the concentration of the blood, the former of these two factors overpowering the latter. There seems to be little doubt that alteration of the partial pressure of the oxygen in the atmosphere, and through that alteration in the oxygen tension of the arterial blood reaching the tissues, is mainly at least responsible for the alteration in concentration of the hæmoglobin; practically all the results obtained at high altitudes are alike in showing an increase in the percentage of hæmoglobin, while an increase in the

* An examination of stained-blood films did not disclose any distinct abnormality in the character of the red corpuscles.

† For the influence of concentration of the red cells on the viscosity of the blood see DU PRÉ, DENNING, and WATSON, 'Roy. Soc. Proc.,' LXXVIII., p. 328, 1900.

Alteration in the viscosity of the blood as a possible factor in stimulating red-cell destruction after intravenous transfusion of homologous blood into rabbits has been discussed by BOYCOTT and DOUGLAS ('Journ. of Path. and Bact.,' XIV., p. 294, 1910), but in such cases of transfusion the question is complicated by the exaltation of the capacity of dealing with the injected red cells owing to the "foreign" nature of the blood used for transfusion, even though that blood has been derived from another individual of the same species. In our present experiments, however, this last factor does not appear, since the polycythæmia was due to the production of excess of red cells by the animal himself as a response to a natural stimulus.

partial pressure of the oxygen in the atmosphere, such as may be obtained in compressed air, seems to tend to produce anæmia.* Consequently in our experiments the most rapid effect produced by returning to a lower altitude was shown on the percentage of hæmoglobin, for the stimulus necessary for keeping up the concentration of hæmoglobin being removed, the factor responsible for decreasing the concentration of the blood was unrestrained, and the blood volume showed a tendency to a further increase. The volume of the blood was gradually restored to normal as the total amount of hæmoglobin and red cells was diminished. Our bodies, therefore, seemed to prefer to work with a volume of blood in excess of our normal rather than with blood of unnecessarily great concentration.

An analysis of the rate at which the total oxygen capacity increased in each of us during the first part of our stay on the summit is rather interesting, but as our observations are few in number in any one case such an analysis can be but rough. In Table XXIX. we have collected some data on this point, expressing the average excess oxygen capacity developed per day as a percentage of the total oxygen capacity in Colorado Springs, in the first instance over a limited period at the commencement of our stay on the summit and in the second over the period which elapsed until the total oxygen capacity reached its maximum value. We have presumed for this purpose that the values obtained at Colorado Springs remained unaltered until we actually ascended to the higher altitude.

The figures show, as do the curves given previously, that the rate of generation of excess hæmoglobin is most rapid during the earlier days at the high altitude, and gradually diminishes as the hæmoglobin nears its maximum amount. A maximum rate of the growth of hæmoglobin is given by the experiments on DOUGLAS on July 20 and 26, for on the former date his total oxygen capacity was hardly above his sea-level normal, whilst on the latter it had nearly reached its greatest value. Over this period an average of 27·6 c.c. of oxygen capacity, say 20·6 gr. of hæmoglobin, was generated daily without taking into consideration the amount of hæmoglobin necessary to replace the ordinary daily loss. Very likely a similar rate held good over a limited period in the case of the other members of the expedition who showed the same type of alteration as DOUGLAS in their percentage of hæmoglobin, but, owing to insufficiency of data, we have been compelled to calculate the rates from the moment of reaching the summit, and we have therefore dealt with the results on DOUGLAS in the same way for comparison. Calculated in this way, the average daily amounts of excess total oxygen capacity generated show individual variations if absolute figures are regarded,

* ADELE BORNSTEIN, 'PFLÜGER'S Archiv,' CXXXVIII., p. 609, 1911. As pointing in the same direction, we may mention the result of an examination by one of us in 1912 of the blood of fifteen men who had worked daily (except Sundays) $1\frac{3}{4}$ hours for 12 weeks, breathing nearly pure oxygen while using mine-rescue apparatus in the work of recovering Norton Colliery, near Stoke-on-Trent, after an explosion. The average percentage of hæmoglobin found with a standardised instrument was 94·9, as compared with the normal of 100.

especially during the earlier period, but if the values are expressed—as indeed appears more reasonable for comparative purposes—as percentages of the total oxygen capacity of the particular individual immediately before he was subjected to the influence of the high altitude, they are remarkably constant. The average daily rate at which we generated the excess oxygen capacity was about 2 per cent. of the total oxygen capacity in Colorado Springs during the first eleven days or so of our stay on the summit, and about 1·3 per cent. for the whole period which elapsed before the total oxygen capacity reached its maximum value.

TABLE XXIX.

Subject.	Total oxygen capacity in Colorado Springs in cubic centimetres.	Length of stay on Peak.	Total oxygen capacity in cubic centimetres at end of foregoing period.	Excess oxygen capacity generated in cubic centimetres.	Excess oxygen capacity generated per day as percentage of total oxygen capacity in Colorado Springs.	Average excess oxygen capacity in cubic centimetres generated per day.
DOUGLAS	850	July 12 to 26	1041	191	1·60	13·6
		„ 20 „ 26	1041	166	3·25	27·6*
HALDANE	927	„ 12 „ 21	1060	133	1·60	14·8
HENDERSON . . .	871	„ 12 „ 22	1071	200	2·30	20·0
SCHNEIDER . . .	730	„ 12 „ 23	918	188	2·34	17·1
DOUGLAS	850	July 12 to Aug. 2	1063	213	1·19	10·1
HALDANE	927	„ 12 „ „ 1	1141	214	1·15	10·7
HENDERSON . . .	871	„ 12 „ „ 9	1221	350	1·44	12·5
SCHNEIDER . . .	730	„ 12 „ „ 8	978	248	1·26	9·2

* This value has been inserted as we had definite data in this case on which to base the calculation, but we have given as well the value of the oxygen capacity as generated between July 12 and July 26 for comparison with the other data.

In connection with these conclusions it is interesting to consider the observations on his own blood of Mr. RICHARDS in connection with a journey to a mine in the Andes. These observations are recorded in Appendix II. In the four days during and just after an ascent from sea-level to 12,500 feet, his hæmoglobin percentage rose from 94 to 126—an average of 8 per cent. per day. That such a rapid rise could have been brought about in any other way than mainly by concentration of the blood is, to say the least, extremely improbable; for if new formation of hæmoglobin were responsible for the rise, the rate of new formation would be far in excess of what might be

expected from the results of experiments on animals and observations on men as to regeneration of the blood after hæmorrhages. It seems much more probable that concentration of the blood occurs at first, though to varying extents in different individuals and different species, while new formation of blood occurs more gradually, and by degrees overtakes the original concentration.

In a recent paper,* BOYCOTT has discussed the rate of regeneration of hæmoglobin in rabbits and rats after they have been subjected to a hæmorrhage equivalent to about 40 per cent. of their hæmoglobin, and has shown that the smaller animals regenerate blood at a faster rate than the larger, and the younger individuals of the species at a faster rate than the older individuals. His average figures for the oxygen capacity regenerated per day expressed as a percentage of the normal total oxygen capacity before the hæmorrhage are 1·6 for large rabbits, 2·3 for small rabbits, 4·6 for large rats, and 6·1 for small rats. Our results on Pike's Peak on man seem at first sight to be at variance with these, for we generated hæmoglobin at a rate of the same order of magnitude as the rabbits. Further consideration of the facts in the two cases convinces us, however, that it would be unfair with the knowledge at our disposal at present to draw such a conclusion from a comparison of the two series of experiments. The conditions in the two series were entirely different, for in BOYCOTT'S experiments the animals were making good a loss, in our experiments the subjects were making excess, and we are not sure that we are justified in referring BOYCOTT'S values to the total oxygen capacity immediately after the hæmorrhage instead of to the normal before the hæmorrhage, in order to better the comparison. The stimuli provoking the regeneration were, moreover, different in the two cases, though BOYCOTT notes that he has found that the rate of formation of red cells in rats may be as quick under the stimulus of reduced atmospheric pressure as after hæmorrhage.

The blood-forming apparatus is normally only adapted for producing a sufficient number of red corpuscles to compensate for the small daily destruction of effete corpuscles; a rapid rate of regeneration can only be brought about by an increased activity and probably hypertrophy of this apparatus, a matter which requires time. So far as we can judge from our present experiments, it is this delay which may lead to a rapid compensation by mere concentration of the blood during the first few days; there may, therefore, at the start be more in the compensation than hyperactivity of the bone marrow. The rate of diminution of the total oxygen capacity on our return to the lower altitudes was also a slow one, perhaps because the extra red cells which we had produced were in no sense foreign, and therefore did not cause the stimulus to active destruction which is given by increasing the number of red blood corpuscles in an animal by injecting blood of another species, or even of different individuals of the same species, if its power of dealing with these is exalted by repeated injection.

It may be that the simultaneous action of the two factors which we have suggested

* BOYCOTT, 'Journ. of Path. and Bact.,' XVI., p. 269, 1911.

TABLE XXX.—Hæmoglobin Percentage in the Blood at Different Times of the Day at Pike's Peak and Colorado Springs.

	DOUGLAS.
	Pike's Peak.
July 18	116 (8 a.m.); 113 (10.30 a.m.).
20	121 (8.40 a.m.); 113 (11.40 a.m.); 116 (2.15 p.m.).
21	121 (6.30 a.m.); 118 (9.30 a.m.); 112 (1.45 p.m.); 113 (5.30 p.m.).
24	121 (8.50 a.m.); 119 (1 p.m.).
25	123 (7 a.m.); 125 (8.45 a.m.); 117 (5 p.m.).
26	121 (7.15 a.m.); 117 (9.30 a.m.).
Aug. 8	122 (8.30 a.m.); 115 (5 p.m.).
	Colorado Springs.
Aug. 17	110 (11.30 a.m.); 113 (5.50 p.m.).
19	103 (10 a.m.); 108 (1 p.m.).
	New Haven.
Aug. 31	105 (11.30 a.m.); 110 (3.30 p.m.); 106 (4.10 p.m.).
	HALDANE.
	Pike's Peak.
July 13	102 (9.15 a.m.); 103 (7 p.m.).
14	104 (8.30 a.m.); 104 (3.30 p.m.).
15	100 (8.45 a.m.); 105 (10.30 a.m.).
25	110 (7 a.m.); 110 (4.50 p.m.).
28	110 (8.20 a.m.); 113 (12.40 p.m.).
Aug. 1	115 (10 a.m.); 114 (2.20 p.m.).
	Colorado Springs.
Aug. 20	107 (10.20 a.m.); 103 (4 p.m.).
	HENDERSON.
	Pike's Peak.
July 25	128 (7.10 a.m.); 124 (5 p.m.).
26	129 (9.30 a.m.); 128 (12.30 p.m.).
31	131 (11.30 a.m.); 123 (5 p.m.)*; 123 (5.30 p.m.); 127 (6 p.m.).
Aug. 9	128 (7 a.m.); 129 (9.40 a.m.); 130 (2 p.m.); 128 (5.15 p.m.).
	SCHNEIDER.
	Pike's Peak.
July 16	110 (8.15 a.m.); 107 (mid-day).
21	114 (6.45 a.m.); 113 (9.50 a.m.); 112 (1.15 p.m.).
25	117 (7 a.m.); 117 (8.30 a.m.).
26	122 (8.10 a.m.); 117 (10.20 a.m.); 115 (12.15 p.m.); 117 (2.10 p.m.).
27	122 (7 a.m.); 115 (8.30 a.m.); 114 (12.10 p.m.); 114 (2.10 p.m.); 115 (5 p.m.); 116 (7 p.m.).
Aug. 3	117 (7 a.m.); 120 (8.30 a.m.).
	Colorado Springs.
Aug. 18	106 (11.30 a.m.); 105 (4.40 p.m.).

* After 55 minutes' walk up cog-wheel track.

above as operating when the excess production of red corpuscles was well established accounts for the rather great oscillations which we found in the percentage of hæmoglobin from day to day which are noticeable in the tables, as well as for the very distinct tendency in two of us to an alteration of this percentage within the course of a single day. Table XXX. contains a number of observations made on each of us at different times of the day.

It will be seen that in the case of DOUGLAS and SCHNEIDER the percentage of hæmoglobin was highest on rising in the morning whilst on the summit, and that it fell rather rapidly after breakfast, to remain roughly constant from the middle of the morning onwards. Neither HALDANE nor HENDERSON showed this tendency on the summit, nor did any of the party, with the possible exception of HALDANE, after the return to Colorado Springs. HALDANE, however, had shown the same phenomenon in a rather marked manner at Colorado Springs previous to the ascent of the Peak, which accounts for the low values recorded in the table for this time, the observations being made well on in the day in this instance.

While we were at Colorado Springs we were inclined to attribute the unusual variability of HALDANE'S hæmoglobin percentage to the heat, and the significance of the variation did not strike us until we reached the summit, when we had occasion to do hæmoglobinometer determinations frequently, and it became all the more imperative to compare the blood count with the hæmoglobinometer reading made at the same time; fortunately we had always done this as a matter of routine. In the tables the figures for the percentage of hæmoglobin whilst on the summit were in the majority of instances obtained between 8 and 11 o'clock in the morning; in a few instances it has, however, been necessary to use a figure obtained later in the day either for the sake of comparison with the blood count (this can be ascertained by comparing Table XXX. with the preceding general tables), or because it happened to be the only observation made on that day. An examination of the figures and the times of day at which they were obtained shows us that the daily variation is hardly sufficient to account altogether for the oscillations shown from day to day. We may note, too, that on August 6 three of the party had distinctly low percentages of hæmoglobin, the observations being made between 10.15 and 11.15 a.m.; the only thing which might account for this was a fairly long and fatiguing walk involving the descent and ascent of 2,800 feet taken on the afternoon of the 5th.*

We have collected in Table XXXI. a number of observations upon the percentage of hæmoglobin and number of red corpuscles per cubic millimetre which were made upon various men in residence at the Summit House. The blood counts were made with the Thoma-Zeiss hæmocytometer mentioned above, and are about 11 per cent. higher than they would have been had the Bürker instrument been used.

* Subsequent observations in Oxford on DOUGLAS showed that there was a similar diurnal variation in the hæmoglobin percentage at the low altitude, though it was a good deal less extensive than on Pike's Peak. The variation of the hæmoglobin from day to day was also much less in Oxford than on Pike's Peak.

It will be seen that those who had come into residence most recently showed the same long lasting and slow increase in the percentage values that we found in ourselves, and doubtless their method of accommodation was the same as ours. On the other hand ROBISON and RUSSEL, who had been in residence for nearly three months, had apparently reached a steady level.

TABLE XXXI.

Subject and occupation.	Date of arrival on summit.	Date of observation.	Percentage of hæmoglobin.	Red corpuscles per cubic millimetre in millions.
H. H. Robison (manager)	Apr. 29	July 13	144	7·7
		Aug. 13	146	7·5
D. Russel (coloured cook)	Apr. 29	July 20	138	7·4
		Aug. 13	135	7·5
M. H. Brockman* (caretaker of rooms)	May 25	Aug. 1	118	7·2
E. A. Gaston (attendant at lunch counter) . . .	July 3	July 21	125	7·5
P. S. Deviney (telegraph operator)	July 3	Aug. 1	142	7·8
		Aug. 13	153	8·2
S. C. Fulkerson (attendant at lunch counter) . .	July 9	July 24	113	5·6
V. C. Harmony (engineer)	July 14	Aug. 1	122	7·2
		Aug. 14	136	7·4
— Kennedy† (deputy sheriff)	July 27	July 27	114	5·7
		Aug. 13	126	7·0

* Vegetarian. † Has lived for 21 years in Colorado, altitude 6400 feet.

It will be noted that our results are different from those which ABDERHALDEN obtained on rabbits, and yet we are not prepared to accept absolutely the criticism of ZUNTZ and his colleagues, though they support it by experiments on dogs. In the case of ABDERHALDEN'S experiments the real difficulty lies in choosing the unit to which the volume of the blood is to be referred; the choice rests between the individual animal and its weight, and it certainly is not obvious which of the two is the right one. It is very likely that different species of animals and perhaps different individuals of the same species react in different ways or to different degrees to a change of altitude, and it would be rash to attempt to explain the results obtained on rabbits by our own observations on a limited number of men. The striking point in ABDERHALDEN'S series of experiments is the rapidity with which the very marked changes in the concentration of the blood were produced—a rapidity which we should agree could most easily be explained by a passage of fluid out of or into the blood,

though at the same time we confess that we view with scepticism the prospect of an animal continuing its existence for long periods with a volume of blood diminished below its normal, for the normal animal seems to be very conservative in respect to its blood volume. This tendency, in fact, for the hæmoglobin to become concentrated above its normal value, whether that concentration be due merely to a diminution in the amount of plasma in the blood or to an actual overproduction of red cells, is rather remarkable. Apparently we do not get it in those cases where the effective tension of oxygen in the blood reaching the tissues is not interfered with. Thus after hæmorrhage the blood volume is usually restored quickly, and there is no tendency in this case to keep the concentration of hæmoglobin at even the normal level. Very likely the organism makes up for the diminution in the quantity of oxygen per unit of blood in this case to some extent at least by increasing the general rate of the circulation. The quantity of oxygen reaching the tissues is here at fault, but not necessarily its tension.

Besides the effect of low atmospheric oxygen pressures we have other evidence that deficiency of oxygen tension in the blood reaching the tissues, produced by other means, is equally potent in causing an increase of the hæmoglobin percentage and number of red corpuscles above the normal values. Thus congenital heart disease and most cases of chronic cyanosis are accompanied by polycythæmia, and in some of these cases which have been investigated directly* a real excess production of red cells and an increase in the volume of the blood comparable with, though much greater than, the observations on ourselves on the Peak, have been found. In such pathological cases there is every reason to believe that the oxygen tension of the arterial blood reaching the tissues is lowered owing to a disappearance of oxygen in the blood on its way to the tissues consequent on a slowing of the general rate of the circulation, or on the passage past the lungs into the arterial blood of abnormal amounts of easily oxidisable substances given off by the tissues when their oxygen supply is rendered deficient. An apparent anomaly in this rule will be found in the experiments of NASMITH and GRAHAM,† where prolonged interference with the oxygen-carrying power of the blood of guinea-pigs by partial saturation of the blood with carbon monoxide led to the

* LORRAIN SMITH and M'KISACK, 'Trans. Path. Soc.,' London, LIII., p. 136, 1902; PARKES WEBER and DORNER, 'Lancet,' January 21, p. 150, 1911. This case was investigated carefully by means of the carbon-monoxide method by two of us, with attention to those precautions which have been indicated earlier in this paper. The subject was a man, aged 22 years, weight, without clothes, 46 kilos., with congenital heart disease, great cyanosis and extreme polycythæmia (10 million red corpuscles per cubic millimetre). At the time of the investigation the percentage of hæmoglobin in his blood was 180, his total oxygen capacity was found to be 2010 c.c., and his blood volume 6040 c.c., *i.e.*, 4·37 c.c. of oxygen capacity and 13·13 c.c. of blood per 100 gr. body weight. How much these figures are above the normal is seen by a comparison with those obtained on DOUGLAS and HALDANE (Tables XXIV. and XXV. above), who, with a percentage of hæmoglobin of about 100, have respectively per 100 gr. body weight about 1·305 and 1·135 c.c. of oxygen capacity, and 7·19 and 6·06 c.c. of blood.

† NASMITH and GRAHAM, 'Journ. of Physiol.,' XXXV., p. 32, 1906.

onset of polycythæmia, whose development and subsequent disappearance after eliminating the gas from the atmosphere breathed by the animals resembled closely the development and disappearance of a high-altitude polycythæmia. At first sight it looks as though such partial saturation of the hæmoglobin with carbon monoxide ought to have much the same effect as reduction of the oxygen-carrying power of the blood to a similar extent by hæmorrhage, and that the behaviour of the blood ought to be the same in the two cases. There is, however, another factor to be taken into account here. It has been shown* that partial saturation of the hæmoglobin with carbon monoxide causes the dissociation of the oxyhæmoglobin to take place at much lower partial pressures of oxygen than under ordinary circumstances, which means to say that in order to abstract a given quantity of oxygen from the blood in the tissues its partial pressure must be lowered to an abnormal extent, and the *effective* tension of the oxygen in the tissues is therefore lowered.

X. *The Process of Adaptation to High Altitudes.*

The observations detailed above leave no shadow of doubt that a very marked process of adaptation to high altitudes occurs. The blueness of the face and general symptoms of mountain sickness disappeared within two to seven days on Pike's Peak, while the tendency to periodic breathing, and the hyperpnœa on exertion, also diminished. Our experiments disclosed three definite adaptive changes. These were (1) a rise in the arterial oxygen pressure; (2) a fall in alveolar CO_2 pressure and corresponding rise in alveolar oxygen pressure; (3) an increase in the percentage and total amount of the hæmoglobin in the blood. In the present section we propose to discuss the process of adaptation in the light of the new data obtained.

We may first remark that all three changes were of a permanent character, and showed no sign of diminishing in amount with further stay on Pike's Peak. The stimulus producing them must therefore be equally permanent in its action, and must still have been in operation to some extent after adaptation, although it was doubtless acting most intensely at first. There can be no doubt, as already shown in the third section, that this stimulus was the diminished oxygen pressure in the air, and in particular the reduced oxygen pressure in the lung alveoli.

How does this stimulus act? The first and most natural answer to this question would be that the saturation of the arterial blood in the lungs is diminished, and that consequently a smaller quantity of oxygen is carried at each round of the circulation to the tissues, and a shortage of oxygen thus arises, to which the body responds with adaptive changes. A slight shortage in the amount of oxygen carried by the blood was doubtless present at the beginning of our stay, for the arterial oxygen pressure in Mr. FULLER'S blood when he first came up was only 52·7 mm., at which pressure the blood would only be about 83 per cent. saturated with oxygen, instead of

* DOUGLAS and HALDANE, 'Journ. of Physiol.,' XLIV., p. 293, 1912; also J. B. S. HALDANE, 'Journ. of Physiol.,' XLV., p. 22, 1912.

96 per cent. saturated, as at normal atmospheric pressure. But after a short time the arterial oxygen pressure rose to 88 mm., with the blood 95 per cent. saturated. The hæmoglobin percentage was also increased by an average of 19 per cent., so that the arterial blood actually carried 18 per cent. more oxygen than at sea-level. Deficiency in the quantity of oxygen carried by the blood was thus certainly not the stimulus. We know also from previous work of Miss FITZGERALD* that the percentage of hæmoglobin may be enormously diminished in the blood without there being any sign in the alveolar CO_2 pressure of oxygen want affecting the body during rest.

The next supposition that naturally occurs is that, though the quantity of oxygen carried by the blood is not deficient, the partial pressure of this oxygen is abnormally low. The rate at which oxygen is given off by the red corpuscles passing through the capillaries of the body depends, not on the quantity but on the partial pressure of the oxygen in each corpuscle; and if this pressure is diminished shortage in the oxygen supply must occur. Let us see how far this consideration will help to explain the facts. We may assume, as was done above, that the hæmoglobin of average venous blood during rest is 64 per cent. saturated with oxygen; also that, as indicated by the experiments described in Section VIII., the circulation rate was unaltered on Pike's Peak, so that the quantity of oxygen extracted from the blood in each round of the circulation was the same. The difference between the percentage saturations of arterial and venous blood would thus also remain the same if the percentage of hæmoglobin were the same. But the hæmoglobin percentage was increased by about 19 per cent. in our cases on Pike's Peak; hence the difference in percentage saturation between arterial and venous blood would only be $32 \times \frac{100}{119} = 27$ per cent., instead of 32 per cent. as at sea-level. The arterial blood after acclimatisation was 95 per cent. saturated, as against 96 per cent. at sea-level. Hence the venous blood would be $95-27 = 68$ per cent. saturated on Pike's Peak, as compared with 62 per cent. at sea-level. The oxygen pressure corresponding to 62 per cent. saturation on the dissociation curve (fig. 10) is 36·1 mm., as against 39·5 mm. at 68 per cent. In the case of persons with a greater increase in the hæmoglobin percentage (for instance, ROBISON or DEVINEY, who were living on Pike's Peak) the excess of venous oxygen pressure would be still greater. If we calculate the mean oxygen pressure in the blood of the capillaries the result is still in favour of the blood on Pike's Peak, in spite of the fact that the initial oxygen pressure at sea-level would be greater for a moment. Even if we take into account the fact that the blood loses a good deal less oxygen in the central nervous system than in the muscles, the calculation shows no diminution in the capillary oxygen pressure on Pike's Peak as compared with that at sea-level.

We thus seem forced to the conclusion that the continued stimulus of oxygen want cannot be explained by mere reference to diminished saturation of the hæmoglobin, or correspondingly diminished arterial oxygen pressure. At lower altitudes the same

* 'Journal of Pathology and Bacteriology,' XIV., p. 329, 1910.

argument would hold good, and would, moreover, do so for the general circulation, even if we assumed that there is no active secretion inwards of oxygen by the lungs. The lower alveolar oxygen pressure at high altitudes must thus act in some other way than by merely failing to saturate the hæmoglobin of the blood leaving the lungs, and the theory at once suggests itself that there is a failure in the oxidation of some substance other than hæmoglobin.

It is well known that PFLÜGER* brought forward evidence of the presence in blood, when first shed, of very rapidly oxidisable substances in small amounts. He found that not only does arterial blood become a little darker during the first minute or two after it is shed, but that some of the oxygen disappears. The low values obtained by the ærotonometer method for the arterial oxygen pressure indicate the same thing, as pointed out by DOUGLAS and HALDANE;† and there is further evidence of a similar process in venous blood.‡ Finally, BOHR and HENRIQUES§ found that there is a considerable disappearance of oxygen and formation of CO_2 in the blood passing through the lungs, and particularly under conditions where there was oxygen-want in the tissues on account of a restricted circulation. It seems probable that at high altitudes the mean oxygen pressure in the blood passing through the lung capillaries is insufficient to effect the normal amount of oxidation of these easily oxidisable substances. The result of this will be that they are present in abnormal amounts in the blood, and may either act directly as a stimulus to the blood-forming and other organs, and to the lung epithelium, or else act indirectly by continuing to consume oxygen after the arterial blood has left the lungs, and thus lowering seriously the oxygen tension before this blood reaches the tissues. Against this indirect action is the fact that the lips and faces of acclimatised persons on Pike's Peak seemed to be of a particularly bright healthy colour. In favour of it, on the other hand, was the particularly cyanosed appearance of some of the newcomers. It was difficult to imagine that the blood as it left their lungs could be so blue as to account for the colour of their lips. There is the same difficulty in connection with the cyanosis often observed in heart-disease, &c. The extraordinary effects of oxygen in clearing up this cyanosis certainly seem to suggest that the oxygen acts by destroying easily oxidisable substances in the lungs; for the oxygen cannot well increase to an appreciable extent the saturation of the hæmoglobin in the lungs, or give to the blood more than a very limited amount of oxygen in simple solution.

The theory that the stimulus to the lung epithelium at high altitudes arises from unoxidised metabolic products present in abnormal amounts in the blood agrees well with what is already known. DOUGLAS and HALDANE concluded that the active secretion inwards of oxygen by the lungs during muscular work and CO poisoning

* 'Centralbl. für die Med. Wissenschaften,' 1867, pp. 321, 722.

† 'Journ. of Physiol.,' XLIV., p. 305, 1912.

‡ See HALDANE and LORRAIN SMITH, 'Journ. of Physiol.,' XXII., p. 247, 1897.

§ 'Archives de Physiologie,' 1897, pp. 459, 590.

must be excited in this way, whether the excitation is direct or produced through the nervous system. T. G. LONGSTAFF,* who has had much personal experience of climbing at high altitudes, lays great stress on the influence in preventing mountain sickness of previous training in muscular work; and the effect of such training would presumably be to strengthen the power of the lung epithelium to react promptly and powerfully to the stimulus of which we are presuming the existence, as well as to increase the muscular efficiency.

The fall in alveolar CO_2 pressure, and consequent rise in alveolar oxygen pressure, seems undoubtedly to be due to diminished alkalinity of the blood. The fact that the alkalinity of the blood is diminished at high altitudes was first demonstrated by GALEOTTI,† though it was already known that lactic acid is produced in large amounts in animals exposed to great want of oxygen. BOYCOTT and HALDANE‡ furnished indirect evidence that the fall in alveolar CO_2 pressures at low atmospheric pressure is due to the presence in the blood of lactic acid or other acid substances which have the same influence as CO_2 on the respiratory centre, so that less CO_2 is required to excite it. Lactic acid is also known to be produced by excessive muscular exertion, as a consequence, doubtless, of lack of oxygen in the active muscles. The fall in alveolar CO_2 pressure, produced by the lactic acid, was demonstrated by DOUGLAS and HALDANE,§ and the actual presence of excess of lactic acid in the blood by RYFFEL,‖ while GEPPERT and ZUNTZ,¶ and BOYCOTT and CHISOLM** (in man) also demonstrated the reduction in alkalinity of the blood. But this excess of lactic acid disappears again within an hour, together with its effects on the alveolar CO_2 pressure. If the diminished alkalinity of the blood at high altitudes were simply due to lactic acid formed in excess we should similarly expect this diminished alkalinity to disappear and appear rapidly, and similarly with the changes in the alveolar CO_2 pressure. We have seen, however, that though some lowering of the alveolar CO_2 pressure may develop quickly, it takes many days for the full lowering to develop. Moreover, the lowering progressively increases while the more acute symptoms of oxygen-want are passing off. It also takes many days for this lowering to pass off on a return to higher atmospheric pressure, whereas a rapidly produced lowering, as by going for two or three hours to greatly diminished atmospheric pressure, passes off within an hour or two.

In view of these facts it does not seem probable that the diminished alkalinity of the blood at high altitudes is due merely to an excessive production of lactic acid.

* LONGSTAFF, 'Mountain Sickness,' London, 1906.

† 'Travaux du laboratoire scientifique internationale du Monte Rosa,' 1903, p. 1.

‡ 'Journ. of Physiol.,' XXXVII., p. 355, 1908.

§ 'Journ. of Physiol.,' XXXVIII., p. 432, 1909.

‖ 'Journ. of Physiol.,' XXXIX., p. XXIX., 1910.

¶ 'PFLÜGER'S Archiv,' XLII., p. 189, 1888.

** 'Biochemical Journal,' V., p. 23, 1910.

It looks more as if the change were due to some adaptive alteration in the regulation of blood alkalinity. The "fixed" alkalinity of the body as a whole, including the blood, is evidently regulated normally by the action of the kidneys, although the liver, by varying the amount of ammonia in the blood, may also contribute to the regulation. A slight and gradual adaptive alteration in what one may call the exciting threshold of alkalinity for the kidneys would explain the reduced fixed alkalinity of the blood in acclimatised persons. Without some such assumption we are placed in the difficulty of having to assume that more lactic acid or other abnormal metabolites due to oxygen want are formed in the body after acclimatisation has occurred than before the acclimatisation, at a time when the body is evidently suffering from want of oxygen.

A lowering of the exciting threshold for CO_2 in the respiratory centre might seem, at first, to be a simpler and more direct method of raising the alveolar oxygen pressure, and so increasing the oxygen supply to the alveolar blood. A little consideration will show, however, that such a change would diminish, and not increase, the oxygen supply to the tissues. For the dissociation curve of the oxyhæmoglobin in the blood would be shifted to the left in consequence of the absence of CO_2, and the oxygen pressure in the blood passing through the capillaries would have to fall lower than usual in order that the oxygen should be given off. Any slight advantage in the lungs would thus be far more than lost in the tissues. Moreover, there would be a complete upset of what one may call the total reaction of the blood (the hydrogen ion concentration). What actually occurs is that diminished "fixed" alkalinity is compensated for by diminished concentration of CO_2, with the result, as BARCROFT first showed, that the dissociation curve of oxyhæmoglobin is sensibly unaltered; and presumably also the total reaction or hydrogen ion concentration is also almost unaltered, while the advantage of a raised alveolar oxygen pressure is secured. The same advantage is doubtless also secured by a mere accumulation of lactic acid or other abnormal acid metabolites in consequence of acute want of oxygen in the tissues; but if, as we think probable, the advantage is secured after acclimatisation, without the presence of more than very slight want of oxygen, there is a great gain. The permanent changes in the regulation of breathing at high altitudes can thus be placed in the same category with numerous other true physiological adaptations, including those connected with the lung epithelium and the increase of hæmoglobin at high altitudes.

The stimulus to the slight permanent alteration in the exciting threshold of blood reaction for the kidneys is probably the presence in the blood of abnormal quantities of the metabolites which have escaped oxidation in the lungs. Whether they act directly, or by producing through their continued oxidation a lowering of the oxygen pressure of the blood, we cannot say.

We come, lastly, to the changes in blood concentration at high altitudes. Of the stimulus to these changes no more can be said than of the stimulus to the change

in alkalinity. As affording some support, however, to the idea that abnormal oxidation of metabolites in the blood causes an actual fall in the percentage saturation of the blood within the average capillaries, we may mention the fact that it seemed to us that the samples of blood drawn from the fingers on Pike's Peak were on the whole darker in colour than similar samples taken at sea-level. We were at any rate somewhat struck by the contrast between the dark colour of these samples and the particularly bright colour of the lips, face, &c.

As shown in Section IX., there are two distinct reactions in connection with the increase in the hæmoglobin percentage at high altitudes. These are (1) a rapid diminution in the blood volume, occurring at first on exposure to low atmospheric pressure, with a corresponding rapid increase in blood volume on return to normal pressure; (2) a slow increase in the total number of red corpuscles and mass of hæmoglobin, with a corresponding slow diminution on returning to normal pressure. Associated with (2) is a slight increase in blood volume at the high altitude; and this increase is probably simply due to the necessity of diminishing the viscosity of the blood, or making room for the new corpuscles without unduly diminishing the volume of plasma. The reason why the second reaction occurs so much more slowly than the first would seem to be that it is much more easy to alter the amount of plasma in the blood than to form or get rid of red corpuscles.

It remains to discuss the physiological importance of the three kinds of adaptive change disclosed by our investigations. Beginning with the secretory activity of the long epithelium, the influence of this is to raise the arterial oxygen pressure by 35 mm. during rest. During moderate work, such as walking at an ordinary pace on the level, there is probably a similar effect; but in hard continuous work, such as ascending a steep incline, the absorption of oxygen was in our cases too rapid to allow of a sufficient increase in arterial oxygen pressure; and blueness of the face, with excessive hyperpnœa, indicating deficient saturation of the arterial blood, resulted. In persons better acclimatised, or in better training, the alveolar epithelium could probably do much more, as indicated, for instance, by the extraordinary feat, referred to above, of the ascent by ROBISON from Manitou to the summit of Pike's Peak in 151 minutes. Probably, also, the alveolar epithelium is much less easily fatigued in persons who are well acclimatised and trained.

The lowering of the threshold exciting level of alveolar CO_2 pressure brought about, as shown in Section III., a rise in the alveolar oxygen from 38 mm. to 53 mm. That is to say that if the breathing had been regulated so as to give the same alveolar CO_2 pressure on Pike's Peak as at sea-level the alveolar oxygen pressure would have been 38 mm.; whereas it was 53 mm. on Pike's Peak, in consequence of the diminished level of alveolar CO_2 pressure. During severe work, however, the level of alveolar CO_2 went still lower, and the respiratory quotient was increased; the result being that the alveolar oxygen pressure sometimes went as high as 70 mm. during short bursts of hard work, or 60 mm. during longer efforts after the respiratory quotient had

fallen to about normal. In spite of this raising of alveolar oxygen pressure, and of all that the alveolar epithelium could do, we still got blue during long exertions. Without a great lowering of the threshold alveolar CO_2 pressure life would be quite impossible at very great altitudes. At a barometric pressure of 280 mm., for instance, the oxygen pressure of the alveolar air would (if the rate of oxygen absorption remained normal) be nil but for the lowered CO_2 threshold; and at such a pressure, in an acclimatised person, the lowered alveolar threshold for CO_2 would be necessary in order to give the lung epithelium the opportunity of raising the arterial oxygen pressure sufficiently to support life.

It is more difficult to estimate the physiological value of the increased hæmoglobin percentage at high altitudes. We have seen above that the hæmoglobin of arterial blood as it leaves the lungs is 95 per cent. saturated as compared with 96 per cent. saturated at sea-level. The difference is quite inappreciable; and if we were only to take this difference into account we should be compelled to conclude that the increased hæmoglobin percentage at high altitudes is of no use whatsoever and only a blind response to a want which it does not meet under the particular circumstances of a low barometric pressure. We were, in fact, inclined at first to take this view. An increased hæmoglobin percentage would clearly tend to compensate for a diminished circulation rate, as in heart disease, or for a diminished oxygen-carrying power of the blood, as in anæmia or chronic carbon monoxide poisoning; but it is not at all so clear that it would help in a case where the defect lies, not in the oxygen-carrying power or rate of circulation of the blood, but in the aeration of the blood in the lungs. The more hæmoglobin there was in the blood the lower would its percentage saturation tend to become, and the lower, also, would the arterial oxygen pressure tend to become.

On further consideration, however, we believe that this reasoning is incorrect. Reasons have already been given for concluding that at low barometric pressures easily oxidisable metabolites pass through the lungs into the arterial blood in abnormally high proportions. It is only reasonable to believe that the oxidation of these substances is continued in the blood on its way through the body, and that oxygen which would otherwise have been available for the needs of the tissues is thus consumed. Against this process an increased percentage of hæmoglobin will be of great service, since the oxygen pressure in the tissues will not fall so low as would otherwise be the case, the diminished fall being in proportion to the percentage increase in the hæmoglobin. The increased percentage of hæmoglobin thus plays, in all probability, a very important part in adaptation to high altitudes.

On Pike's Peak, as we have seen, there was no clear indication of an increased circulation rate after adaptation had occurred; but an increased circulation rate, such as perhaps does occur before acclimatisation is established, might be of the same service as increased hæmoglobin in maintaining a higher average oxygen pressure in the blood passing through the tissues. The net effect would, however, be very

difficult to predict, and we had no opportunity of studying this question experimentally.

In concluding this section it is of interest to consider the effects of acclimatisation from a more practical standpoint. We may first endeavour to compare the effects of a given reduction of oxygen pressure in the inspired air before and after acclimatisation. This difference was, of course, very evident on Pike's Peak, both in ourselves and others; but the full extent of the difference has not hitherto been realised. Men have reached lower pressures in balloons and steel chambers without losing consciousness than they have hitherto reached by climbing; and in the absence of proper consideration of the difference in circumstances and in the symptoms observed, this has led to wrong conclusions. In very high mountain ascents the mere physical difficulties have been very great and have nevertheless been overcome up to an altitude of 24,580 feet, or a barometric pressure of 312 mm. The physiological difficulties have only rendered progress slow, and liable to be cut short occasionally by an attack of mountain sickness. Those who have reached the highest points seem to have felt quite well on the whole, and could certainly have gone higher. In balloons and steel chambers a pressure of 310 mm. seems to be on the limit of what unacclimatised persons can bear without loss of consciousness after a time; and for many persons it is far beyond the limit. People who had come up by train sometimes fainted after twenty minutes or half-an-hour on Pike's Peak at 457 mm.; and in a steel chamber BOYCOTT fainted at 356 mm. after an exposure of about half-an-hour, and HALDANE was markedly affected. To judge from the symptoms of unacclimatised persons in steel chambers and balloons it would be utterly impossible for anyone unacclimatised to encounter the physical difficulties of a mountain ascent at a pressure of less than 350 mm., or to escape from severe mountain sickness.

PAUL BERT* quotes a graphic account of his symptoms by Tissandier, the sole survivor of a fatal balloon ascent in 1875; and we may reproduce part of this account to illustrate what happens:—

> "I now come to the fateful moments when we were overcome by the terrible action of reduced pressure. At 7000 metres [320 mm.] we wère all below in the car. . . . Torpor had seized me. My hands were cold and I wished to put on my fur gloves; but without my being aware of it, the action of taking them from my pocket required an effort which I was unable to make. At this height, I wrote, nevertheless, in my notebook almost mechanically, and reproduce literally the following words, though I have no very clear recollection of writing them. They are written very illegibly by a hand rendered very shaky by the cold. 'My hands are frozen. I am well. We are well. Haze on the horizon, with small rounded cirrus. We are rising. Crocé is panting. We breathe oxygen. Sivel shuts his eyes. Crocé also shuts his eyes. I empty aspirator. 1.20 p.m., −11°,

* 'La Pression Barométrique,' p. 1063.

B. 320. Sivel is dozing. 1.25, −11°, B = 300. Sivel throws ballast. Sivel throws ballast.' (The last words are scarcely legible.) . . . I had taken care to keep absolutely still, without suspecting that I had already perhaps lost the use of my limbs. At about 7500 metres [300 mm.] the condition of torpor which comes over one is extraordinary. Body and mind become feebler little by little, gradually and insensibly. There is no suffering. On the contrary one feels an inward joy. There is no thought of the dangerous position; one rises and is glad to be rising. The vertigo of high altitudes is not an empty word; but so far as I can judge from my own impressions this vertigo appears at the last moment, and immediately precedes extinction, sudden, unexpected, and irresistible. . . . I soon felt myself so weak that I could not even turn my head to look at my companions. I wished to take hold of the oxygen tube, but found that I could not move my arms. My mind was still clear, however, and I watched the aneroid with my eyes fixed on the needle, which soon pointed to 290 mm. and then to 280. I wished to call out that we were now at 8000 metres; but my tongue was paralysed. All at once I shut my eyes and fell down powerless and lost all further memory. It was about 1.30."

In this ascent the balloon continued to rise till a minimum pressure, registered automatically, of 263 mm. was reached. When Tissandier recovered consciousness Sivel and Crocé-Spinelli were dead. They were all provided with oxygen, ready to breathe; but all were paralysed before they could raise the tubes to their lips. Tissandier's notes are characteristic of the mental condition when oxygen-want is becoming dangerous. These notes, and the behaviour of all three men in the balloon, are exactly similar to notes made by Sir Clement le Neve Foster and his behaviour and that of his companions when they were nearly overcome by carbon monoxide in Snaefell Mine in 1897.*

It should be remembered that in persons exposed to an atmosphere dangerously low in oxygen pressure the dangerous cerebral symptoms do not, as a rule, appear at first. The respiratory centre usually, but not in all persons, has time to respond with some lowering of the exciting threshold for CO_2 and often a very marked lowering. The consequence is that great hyperpnœa may be produced temporarily. This raises the alveolar oxygen pressure, thus averting the cerebral symptoms, and must have done so partially in the balloon ascent just referred to. But the body is rapidly losing CO_2 in consequence of the hyperpnœa. HALDANE and POULTON, for instance, observed respiratory quotients as high as 3·0 in this stage. When the excess of preformed CO_2 is exhausted, the hyperpnœa passes off, and the alveolar oxygen pressure consequently falls. Consciousness then fails, painlessly and without a struggle. In unacclimatised persons the lowering of the alveolar CO_2 threshold is much less than in the acclimatised; and in addition to this the alveolar epithelium fails to respond

* FOSTER and HALDANE, 'The Investigation of Mine Air,' 1907, p. 157.

with the same amount of secretory activity. Moreover, the hæmoglobin percentage is lower. Complete helplessness thus results in unacclimatised persons in an atmosphere which can be borne with ease by the acclimatised. The disappearance of hyperpnœa has been ascribed to gradual failure in the excitability of the respiratory centre; but there is no such failure. The centre does its duty up till the last gasp. It still responds, as it has done all along, to the existing threshold of CO_2 pressure, and it is the supply of CO_2 that has failed. When this has been sufficiently exhausted by artificial respiration no amount of oxygen-want will excite the centre to a single respiratory gasp, as HENDERSON's experiments have clearly proved.*

It would be absolutely hopeless for an unacclimatised person to climb to the height of Mount Everest, or to reach it by aeroplane or dirigible balloon, without the use of oxygen; but there seems to be no physiological reason why an acclimatised person should not succeed in climbing it, dangerous as the attempt might be.

There are other points in connection with life at high altitudes to which our attention has been given. From the results on Pike's Peak it seems probable that even at moderate altitudes the oxygen supply to the body during rest is dependent to an appreciable extent on the activity of the lung epithelium. If this is so any cause tending to paralyse this activity may have serious effects. Now it seems to be a common experience all over the world that pneumonia is very dangerous at high altitudes. We were informed that this is so well known in the Cripple Creek mining district, near Pike's Peak, that it is customary to put pneumonia patients in the train and send them down to Colorado Springs. In a private letter to one of us Dr. RAVENHILL mentions that in towns at high altitudes in Chile and Bolivia pneumonia is also very fatal. The very serious mortality from pneumonia at Johannesburg is also well known. It seems probable that the common cause of the extra fatality of the cases is deficient aeration of the blood in consequence of injury to the alveolar epithelium and consequent interference with secretion or diffusion of oxygen. This danger might be averted by the use of chambers containing air with an increased oxygen percentage, or at increased pressure. In air with increased oxygen percentage the danger from fire would, of course, need to be carefully guarded against; and perhaps the object might sometimes be sufficiently attained by simply adding CO_2 to the air, without lowering the oxygen percentage. This would, of course, raise the alveolar oxygen percentage. Chambers of this kind might, indeed, be of use in treatment, even at sea-level, provided they were used with an intelligent knowledge of the physiological conditions.

It is possible, also, that at quite moderate altitudes the slight stimulus to the alveolar epithelium may have a considerable effect in promoting the nutrition of the lungs and assisting in the prevention or cure of pulmonary tuberculosis. The favourable influence on phthisis of the climate about Colorado Springs and Denver and at highly situated Swiss health resorts is well known; and it is possible that the

* 'American Journ. of Physiol.,' XXV., pp. 310, 385 (1910).

effect may be partly due to the reduced oxygen pressure, which gives the lung epithelium something to do during rest. The blood changes at high altitudes, and particularly the leucocytosis of which Dr. WEBB gives some account in Appendix I., must also be taken account of, however.

XI. *Summary.*

1. The symptoms observed on Pike's Peak before acclimatisation occurred were constant blueness of the lips and face, loss of appetite, nausea and vomiting, intestinal disturbances, headache, fainting in some persons, periodic breathing, and great hyperpnœa on exertion. All these symptoms are referable, directly or indirectly, to want of oxygen, produced by the diminished partial pressure of oxygen in the air.

2. After two or three days on the Summit very distinct signs of acclimatisation began to show themselves, and the above-mentioned symptoms disappeared, except that hyperpnœa on exertion or on holding the breath was still much greater than usual; that periodic breathing was still observed occasionally; and that blueness of the lips could still be produced by powerful and continuous exertion, such as walking uphill.

3. After acclimatisation the resting arterial oxygen pressure had risen to about 35 mm. of mercury above the alveolar oxygen pressure, whereas at or near sea-level the resting arterial oxygen pressure is no higher than the alveolar oxygen pressure. The raising of arterial oxygen pressure is attributable to secretory activity of the cells lining the lung alveoli, and is a most important factor in the acclimatisation. On breathing air rich in oxygen the secretory activity was rapidly diminished.

4. The alveolar carbon dioxide pressure required to excite the respiratory centre gradually fell within about a fortnight to about two-thirds of the normal value at sea-level, with a corresponding increase in the volume of air breathed, and rise in the alveolar oxygen pressure which would otherwise have existed on Pike's Peak; this being a second important factor in the acclimatisation. With very hard work, however, the aeration of the arterial blood became defective, and there was in consequence a still further lowering of alveolar carbon dioxide pressure for the time, and corresponding increase of hyperpnœa; the net result being that for short and considerable exertions the volume of air breathed was about three times as great as for equal exertions near sea-level. On returning to sea-level it took about a fortnight for the alveolar carbon dioxide pressure to return to normal.

5. The periodic breathing was dependent on the influence of want of oxygen being superadded to that of carbon dioxide in exciting the respiratory centre, and was promptly abolished by the respiration of pure oxygen.

6. The respiratory exchange on Pike's Peak was unaltered or only slightly increased, whether during rest or during work.

7. So far as we could ascertain there was very little change in the circulation rate on

Pike's Peak after acclimatisation. Pulse and blood-pressure were but little affected. In most cases, however, there was a slight increase in pulse-rate.

8. The percentage of hæmoglobin in the blood increased for several weeks on the summit of Pike's Peak, and varied in various acclimatised persons from 115 to 154 per cent. on the scale of the Gowers-Haldane hæmoglobinometer, corresponding to a percentage oxygen capacity of from 21 to 28·5 c.c. of oxygen per 100 c.c. of blood. The number of red corpuscles increased parallel with the hæmoglobin and there was no change in the relation between colouring power and oxygen capacity of the hæmoglobin, or in the dissociation curve of the oxyhæmoglobin in the arterial blood. On coming down from Pike's Peak the hæmoglobin percentage rapidly fell to normal.

9. The increased percentage of hæmoglobin on Pike's Peak was apparently due in part, during the first few days, to concentration of the blood; but afterwards entirely to a large increase in the total amount of hæmoglobin (determined by the carbon monoxide method). Along with this increase there was (except in the first few days) a slight increase in the blood volume. The diminished percentage of hæmoglobin on coming down was due at first mainly to dilution of the blood, with corresponding increase of blood-volume. The total hæmoglobin in the blood, and the increased blood-volume, took several weeks to fall again to normal.

10. In the process of acclimatisation three factors are concerned: (1) Increased secretory activity of the lining cells of the lung alveoli; (2) Lowering (in consequence of diminished alkalinity of the blood) of the exciting threshold of alveolar carbon dioxide pressure; (3) Increased percentage of hæmoglobin in the blood. The stimulus to these compensatory changes is deficient aeration of the blood passing through the lungs; and the compensation attained is, though very considerable, not complete. The process of acclimatisation is rapid during the first two or three days, but takes several weeks to become complete. In unacclimatised persons, as in balloon ascents, &c., the symptoms produced by a given diminution of atmospheric pressure are far more serious than in acclimatised persons, and life is threatened at a correspondingly smaller diminution of pressure.

ADDENDUM (December, 1912).

The Duke of the Abruzzi's *Expedition in the Himalayas.*

While this paper was passing through the press, there appeared the full and very interesting account,* by Dr. Filippo di Filippi, of the recent explorations in the Himalayas by the Duke of the Abruzzi and his party. The physiological conclusions from the expedition are summed up as follows (p. 363):—

"The Duke's expedition offers the clearest proof that men can live for extended periods of time, in possession of healthy functional activity of all their organs, at an atmospheric pressure little more than half of normal. Twelve Europeans and fifteen coolies lived for about two months at above 17,000 feet of altitude, working regularly, and not showing a single case of illness, even of the most fleeting character, attributable to mountain sickness. At the end of our campaign seven Europeans spent nine days at a height of more than 20,700 feet, during which time four of them camped for the night at 21,673 and 22,843 feet, and this without even the inconvenience of sleeplessness. They likewise made two steep ascents, through deep soft snow, to 23,458 and 24,600 feet, without exhaustion, without lowering of *morale*, without exaggerated difficulty of breathing, palpitation, or irregularity of the pulse, and with no symptom of headache, nausea, or the like. The fact of the immunity admits of but one interpretation—*rarefaction of the air, under ordinary conditions of the high mountains, to the limits reached by man at the present day* ($12\frac{9}{32}$ *inches*) *does not produce mountain sickness.* Moreover, rarefaction of the air is not incompatible with mountaineering work, if this is done very slowly and methodically. From this it follows that the phenomena which have to this day been considered to be the result of rarefaction are, in reality, phenomena of fatigue, or merely incapacity (temporary or permanent) of the system to sustain the exertion of climbing, manifesting itself with special symptoms under the presence of the particular external conditions which prevail in the mountains.

"None the less, the experience of the expedition was not one of absolute immunity. The atmosphere of these heights did work some evil effect, revealing itself only gradually, after several weeks of life above 17,000 feet, in a slow decrease of appetite and consequent lack of nourishment, without, however, any disturbance of the digestive faculties. . . . . Of course, in the long run, this insufficient nourishment would cause a lowering of vitality, loss of flesh, and a certain amount of anæmia. However, the process is so slow that we were still at the end of two months in condition to make long marches without experiencing excessive fatigue."

* 'Karakoram and Western Himalaya, 1909,' Constable and Company, London, 1912.

We have already (p. 204) referred, in the light of a short account published by the DUKE OF THE ABRUZZI in the 'Journal of the Italian Alpine Club,' to the physiological significance of the achievements of his Expedition. It appears from the detailed account that no serious physiological difficulties were encountered during the highest climb to 24,600 feet (barometer 312 mm.). The physical conditions were extremely trying. The party were in thick mist, in a very dangerous position, the snow being deep, soft, and very treacherous. It was only, however, when they had to use their hands as well as their feet in climbing walls of rock that they suffered seriously from breathlessness. But for the physical difficulties they could apparently have gone much higher.

It is unfortunate that no more definite physiological observations were made in the course of the Expedition. In common with many other mountaineers, Dr. FILIPPI was mistaken as to the results of physiological experiments at low pressures in steel chambers and the experience of balloonists at high altitudes. In the Introduction (p. 185) he remarks that "the results of these experiments appear to show that life is possible under atmospheric pressure reduced far below the limit marked by the barometer on the highest summits of the earth," and from this he argues that the severe physical exertion, &c., on high mountains is responsible for mountain sickness. As shown in detail above, exposure of unacclimatised persons breathing ordinary air to low pressures, such as were withstood with impunity by the Expedition, produces rapid incapacitation, and although muscular exertion may be a contributory cause, mountain sickness is due simply to want of oxygen in consequence of the diminished pressure. The conclusion which Dr. FILIPPI prints in italics in the summary quoted above is mistaken.

The absence of mountain sickness in the DUKE OF THE ABRUZZI'S Expedition was undoubtedly due to the acclimatisation insured by the conditions under which the Expedition was carried out, and no better example can be found of the enormous influence exercised by acclimatisation. In the Himalayas, where the ascent to high altitudes is necessarily gradual, there is nearly always time for acclimatisation to occur; whereas in the Alps, Andes, or Rocky Mountains the ascent may be so rapid as to outstrip the physiological process of acclimatisation, with the result that mountain sickness is easily produced at comparatively moderate altitudes.

The gradual loss of appetite and falling off in general condition among the members of the DUKE OF THE ABRUZZI'S Expedition indicates, not that acclimatisation was absent, but that, as might be expected, there is a limit to the completeness of the process. The point at which this limit begins to make itself distinctly felt would seem to vary considerably in different individuals and under different physiological conditions. Had the physiological conditions in the Expedition to the Himalayas been as favourable as during our stay on Pike's Peak it is possible that the limit would not have been reached, even at 17,000 feet.

APPENDIX I.

The Effect of Altitude on the White Blood Cells.

By GERALD B. WEBB, Colorado Springs.

It is notorious that observations on white blood cells in regard to both number and character are open to wide variations.

It is recognised that many factors, such as sleep, digestion, exercise or time of day, render exact comparisons between white cell counts very treacherous, and in addition the technique for both total white cell count and differential percentage estimation is also open to not inconsiderable error.

The explanation of the different normals given by various authorities probably lies in these difficulties for exact determinations and comparisons.

LEVADITI* gives the normal white blood cells per cubic millimetre in healthy adults as 7000–8000, whereas KJER-PETERSEN† claims 4000–5000 as correct.

The differential white cell picture is according to :—

	Polymorpho-nuclears.	Lymphocytes and large mononuclears.	Transitionals.	Eosinophiles.	Mast.
JOLLY*	61·7	35·2	2·2	0·9	—
EHRLICH*	71	23·5	2	3	0·5

It has long been recognised that although the red blood corpuscles per cubic millimetre were supposedly increased by the effect of altitude, the total number of white blood cells per cubic millimetre remained the same as at sea-level. In 1908 we called attention‡ to some observations which seemed to indicate that although the total number of white blood cells remained the same in Colorado Springs (altitude 6100 feet) as at sea-level, in human beings and some laboratory animals, yet there appeared to have taken place a rearrangement in the percentage of the different types of leucocytes, the lymphocytes increasing whilst the polymorphonuclear cells decreased; this change, together with the known increase in erythrocytes, causing the blood picture at an altitude to simulate that of childhood.

* LEVADITI, 'Handbuch der Technik und Methodik der Immunitätsforschung,' 1909.

† KJER-PETERSEN, 'Uber die numerische Verhältnisse der Leukocyten bei der Lungentuberculose,' Würzburg, 1906.

‡ WEBB and WILLIAMS, "Some Hæmatological Studies in Tuberculosis," 'Transactions V., Annual Meeting National Association for the Study and Prevention of Tuberculosis.'

The following table represents such change :—

	Polymorpho-nuclear.	Mononuclear.	Eosinophiles.	Mast cells.
Children.				
Colorado Springs	37·3	60·3	2·0	0·4
Sea-level	53	46	1·0	0·0
Adults.				
Colorado Springs	54	43·6	2·0	0·4
Sea-level	61·7	37·4	0·9	0
Rabbits.				
Colorado Springs	31	65	0	4
Sea-level	43	52	0	5
Guinea Pigs.				
Colorado Springs	19	81	0	0
Sea-level	60	40	0	0
Monkeys (*Macacus Rhesus*).				
Colorado Springs	31	65·9	1	0
Sea-level	40	55	4	1

These figures are prepared from a large number of counts in each class.

BUNTING* (working at an elevation of nearly 1000 feet) has recently called attention to the lymphocyte percentage of healthy young adults (college students) as being 43, and thinks the figures quoted in text-books are too low. He is under the impression that the modified Romanowsky stains now in general use show up more lymphocytes than the original Ehrlich stains. However, when we at this altitude collect figures from a similar type of adult, we find the percentage of lymphocytes is 49.

It has not been possible to obtain blood specimens from many healthy adults before

* BUNTING, "The Normal Differential Leucocyte," 'American Journal of the Medical Sciences,' November, 1911.

coming to Colorado and after residence here, but the following is an example of some twenty cases we have so observed :—

Dr. B.	Polymorpho-nuclears.	Small lympho-cytes.	Large lympho-cytes.	Large mono-nuclears.	Transi-tionals.	Total lympho-cyte element.	Eosino-philes.	Mast.
8.12.09 on arrival	70·5	21·5	2	4	1	(28·5)	1	0
	Leucocytes per cubic millimetre 8592. Lymphocytes 2448.							
8.17.09	59	17·5	16	0	0	(33·5)	6·5	1
8.19.09	63·5	12	20·5	0	1·5	(34)	2·5	0
	Leucocytes per cubic millimetre 10,260. Lymphocytes 3488.							
8.26.09	53	27	18	1	0	(46)	1	0
	Leucocytes per cubic millimetre 9024. Lymphocytes 4149.							
9.6.09	62	20	14·5	1	·5	(36)	2	0
	Leucocytes per cubic millimetre 8972. Lymphocytes 3229.							
9.16.09	55	20	21	0	1	(42)	2	1
	Leucocytes per cubic millimetre 8556. Lymphocytes 3591.							
10.14.09	55	18	23	0	1	(42)	2	1

It has been shown in the subjects of chronic carbon monoxide poisoning that not only the erythrocytes but also the large lymphocyte cells are numerically increased by the response of the marrow cells to maintain normal oxidation. The increase of red blood corpuscles and hæmoglobin in the blood of dogs in high altitudes was shown by ZÜNTZ* to be due to marrow hyperplasia. The thought, therefore, occurred that the same explanation might be sought for the lymphocyte increase reported and if marrow hyperplasia was responsible then marrow hyperæmia might bring about similar results.

It was found in rabbits and man† that gentle continued hyperæmia of the extremities caused a large increase, in the peripheral blood, of both erythrocytes and lymphocytes.

The blood pictures resulting, therefore, from chronic CO poisoning and artificial

* ZÜNTZ 'Höhenklima und Bergwanderungen,' 1906.

† WEBB, WILLIAMS, and BASINGER, "Artificial Lymphocytosis in Tuberculosis," 'Transactions VI., Annual Meeting National Association for the Study and Prevention of Tuberculosis.'

bone marrow hyperæmia seemed to coincide with those we have observed at this altitude in respect to both erythrocyte and lymphocyte increase.

During the recent expedition to Pike's Peak we obtained blood films from the investigators before and after their ascent and during their several weeks' stay on the summit. The blood was obtained in every instance before breakfast. We were unable to make complete leucocyte estimations, but all our work has indicated the sufficient accuracy for drawing deductions for total lymphocytes from the differential blood pictures. The results are given in the accompanying charts, and indicate on an average a very marked increase in the percentage of lymphocytes.

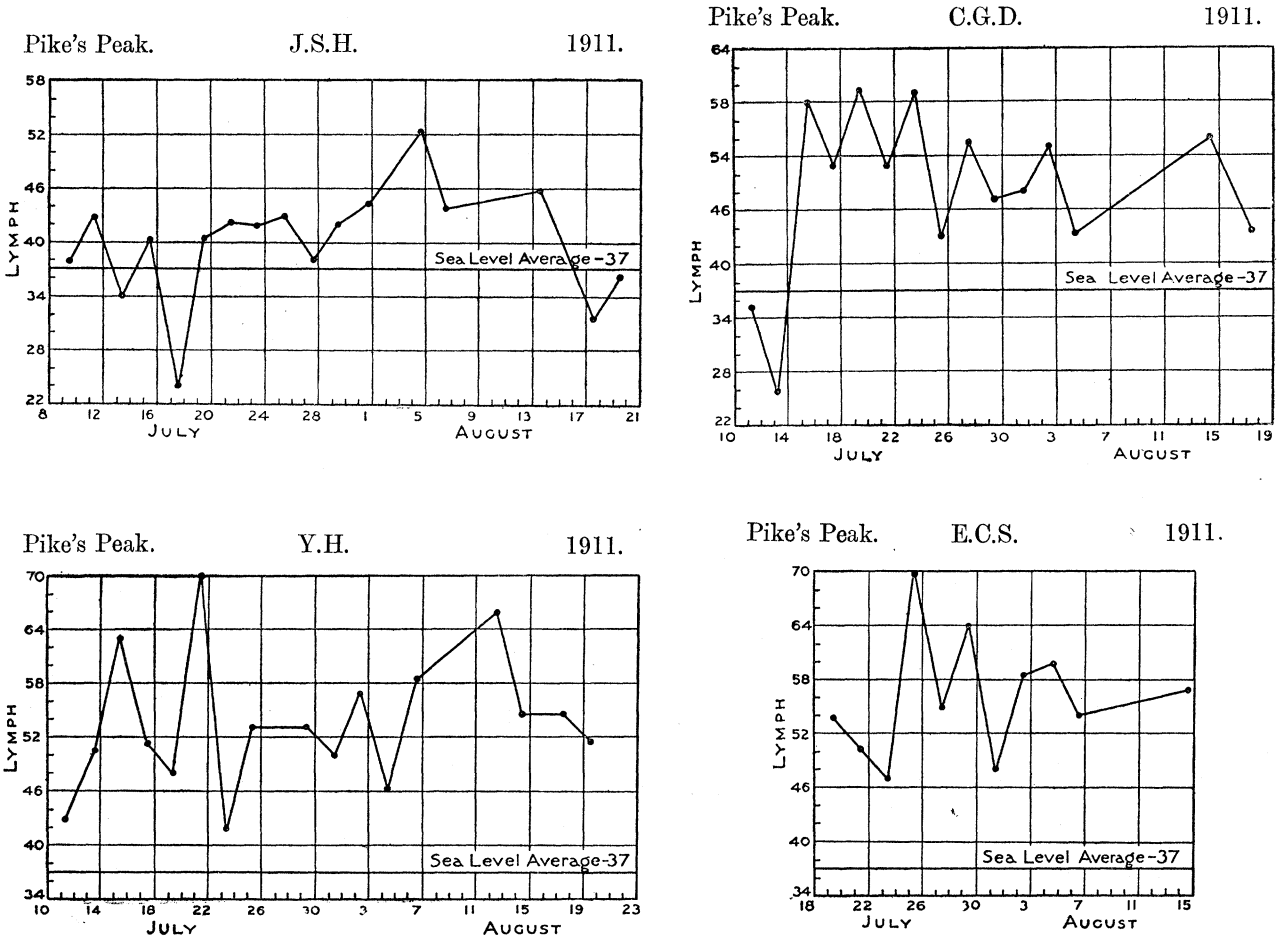

Fig. 19.

J.S.H. could hardly be considered as normal, he having persistently 15,000 leucocytes per cubic millimetre.

The only observations before the ascent were those on July 10 and 12. The drop in C.G.D., July 14, was during a somewhat severe attack of mountain sickness. The only observations made immediately after the descent were those of August 18 and 20.

APPENDIX II.

Observations by J. RICHARDS, *Mining Engineer, on the Increase of Hæmoglobin Percentage at a High Altitude in Bolivia.*

The following observations were kindly carried out for one of us by Mr. J. RICHARDS in connection with a journey to Bolivia when Mr. RICHARDS assumed the management of a tin mine at Pazña, at an altitude of 15,000 feet above sea-level. Mr. RICHARDS left Liverpool on November 10, reaching Buenos Aires on December 5, and Valparaiso on the 8th, after a two days' journey overland. He then sailed up the west coast to Antofagasta and started thence on the 15th up-country, reaching a height of 12,500 feet on the 17th, and staying at this height till the 24th, when he moved to a height of 15,000 feet, at the mine.

The hæmoglobin determinations were made with a specially constructed Gowers hæmoglobinometer, the standard tube being filled with picro-carmine jelly, as coal-gas or carbon monoxide was not readily available. The instrument was carefully standardised by Dr. HALDANE and was kept in the dark when not in use. It was

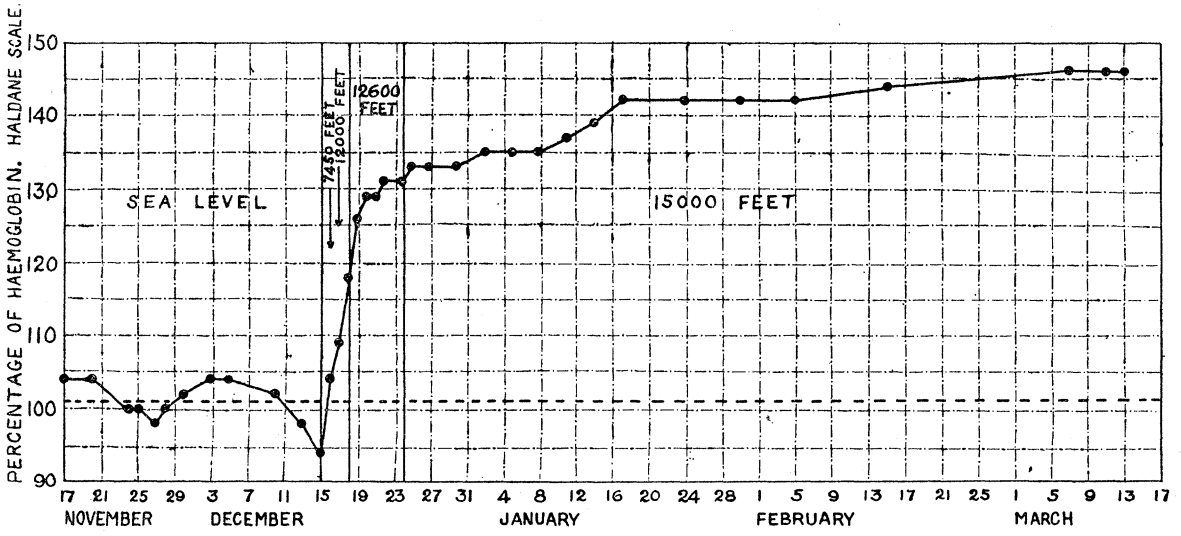

Fig. 20.

The interrupted line represents the mean percentage of hæmoglobin at sea-level.

found to give readings 8 per cent. too low as compared with a standard Gowers-Haldane hæmoglobinometer. It was returned to England at the close of the observations, and re-standardised, when it gave the same result within 1 per cent. as compared with the standard, so that the picro-carmine had not sensibly altered. All the readings are corrected so as to correspond with the Gowers-Haldane standard.

The results were as follows:—

		Hæmoglobin percentage (Gowers-Haldane scale).
November 17	Off Lisbon	104
,, 20	—	104
,, 24	Lat. N. 1° 40′	100
,, 25	Lat. S. 3° 38′	100
,, 27	Lat. S. 12° 35′	98
,, 28	—	100
,, 30	At Rio Janeiro	102
December 3	Lat. S. 34° 22′	104
,, 5	At Buenos Aires	104
,, 10	At Valparaiso	102
,, 13	Sailing up West Coast	98
,, 15	At Antofagasta	94
,, 16	At Calama, 7,420 feet above sea	104
,, 17	,, Uyuni, 12,000 ,, ,,	109
,, 18	,, Tatoral, 12,600 ,, ,,	118
,, 19	,, ,, ,, ,, ,,	126
,, 20	,, ,, ,, ,, ,,	129
,, 21	,, ,, ,, ,, ,,	129
,, 22	,, ,, ,, ,, ,,	131
,, 24	At the Mine, 15,000 feet above sea	131
,, 25	,, ,, ,, ,, ,,	133
,, 27	,, ,, ,, ,, ,,	133
,, 30	,, ,, ,, ,, ,,	133
January 2	,, ,, ,, ,, ,,	135
,, 5	,, ,, ,, ,, ,,	135
,, 8	,, ,, ,, ,, ,,	135
,, 11	,, ,, ,, ,, ,,	137
,, 14	,, ,, ,, ,, ,,	139
,, 17	,, ,, ,, ,, ,,	142
,, 24	,, ,, ,, ,, ,,	142
,, 30	,, ,, ,, ,, ,,	142
February 5	,, ,, ,, ,, ,,	142
,, 15	,, ,, ,, ,, ,,	144
March 7	,, ,, ,, ,, ,,	146
,, 11	,, ,, ,, ,, ,,	146
,, 13	,, ,, ,, ,, ,,	146

Fig. 20 shows graphically the rise which occurred in the hæmoglobin percentage. This rise was much sharper and greater than occurred in any of the members of our expedition on Pike's Peak. It will be seen that the rise averaged 8 per cent. daily for the first three days. It is very improbable that such a rapid rise could have been due to anything but a concentration of the blood, similar to what ABDERHALDEN found in rabbits.

After being for some weeks at the mine Mr. RICHARDS made five determinations of the red corpuscles with a hæmocytometer. The average result was 7,200,000 per cubic millimetre, or 144 per cent. of the normal. This agrees exactly with the rise in hæmoglobin percentage.

A number of miners were also tested with the hæmoglobinometer, and gave results varying from 124 to 156 per cent.

Mr. RICHARDS had an attack of mountain-sickness on the day of his first visit to the mine, and suffered somewhat from headaches for some days, but afterwards felt very well. He could walk on the level at $3\frac{1}{2}$ miles an hour at 15,000 feet without the least inconvenience.

We regard the slow rise of the hæmoglobin percentage in the weeks following the initial rapid rise as indicative of a gradual real overproduction of hæmoglobin and red corpuscles.

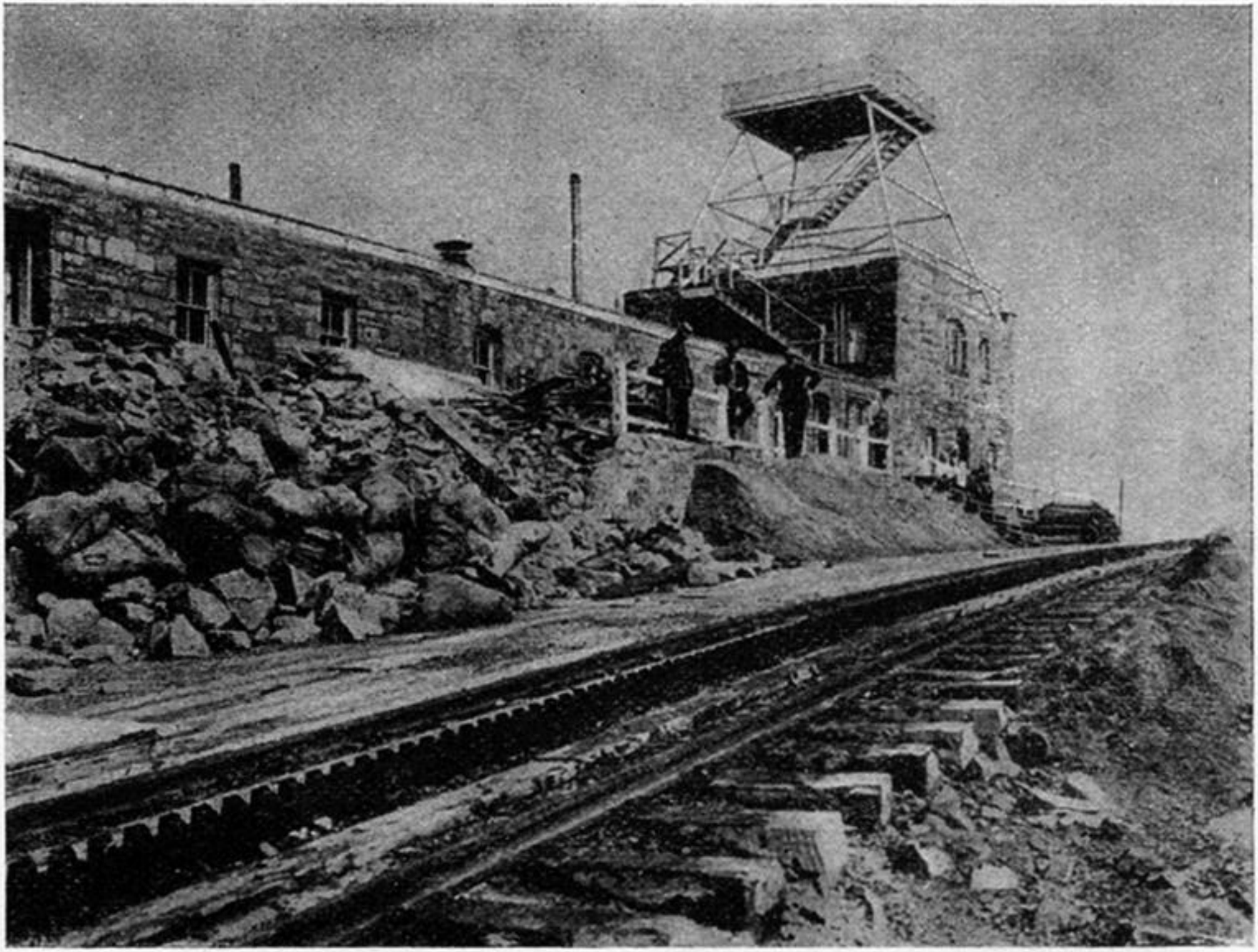

Fig. 1.

The Summit House and terminus of the cog railway.

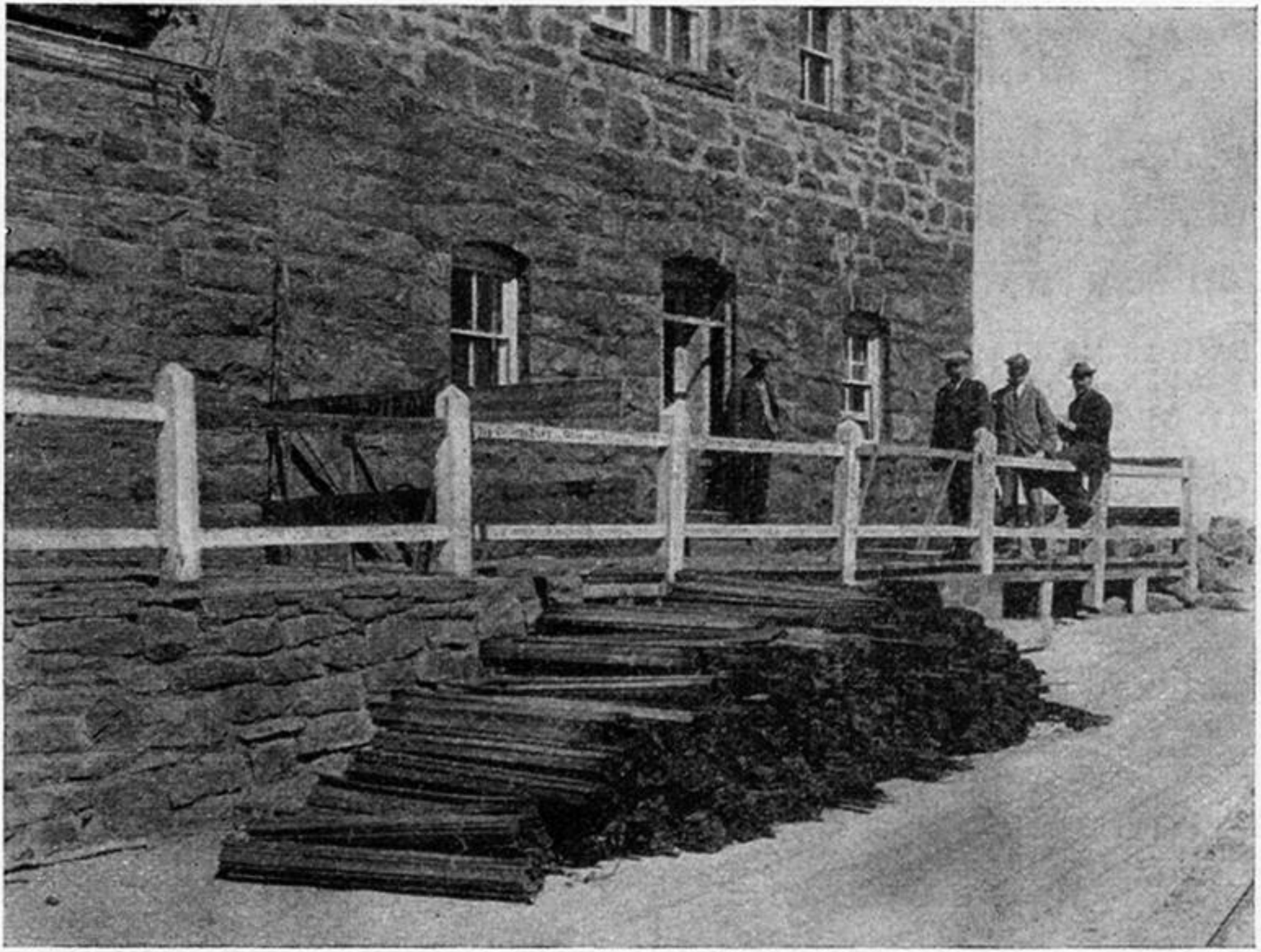

Fig. 2.

Exterior of our laboratory.

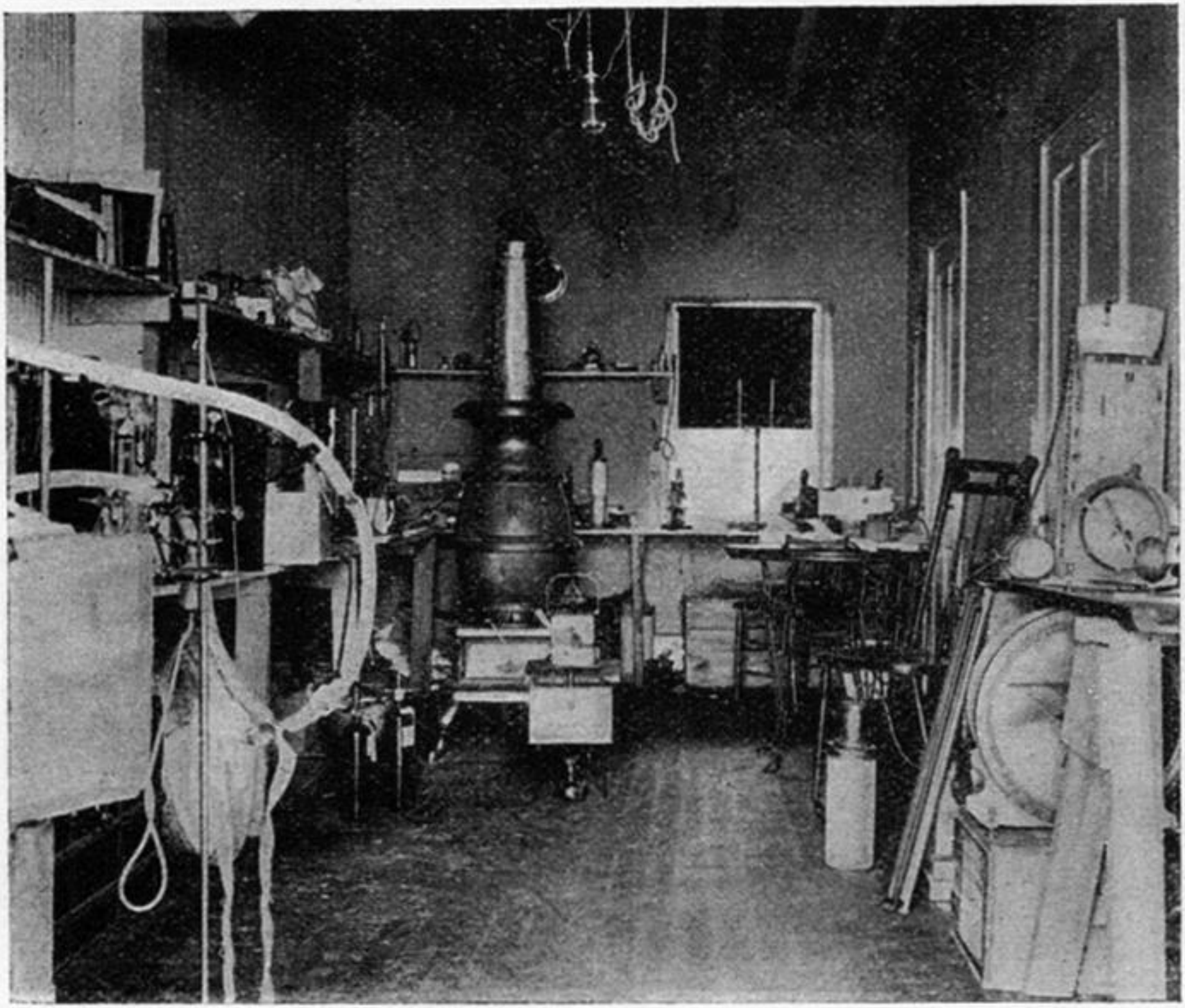

Fig. 3.

Interior of our laboratory.

Fig. 4.

The terrace outside the Summit House at sunrise. The remnant who were able to watch the sunrise out of about two hundred tourists who had come up for that purpose.

Fig. 7.

Determination of the total respiratory exchange whilst walking on the flat.

Fig. 8.

The highest portion of the 1 in 4 grade on the cog railway: an experiment on the total respiratory exchange in progress.

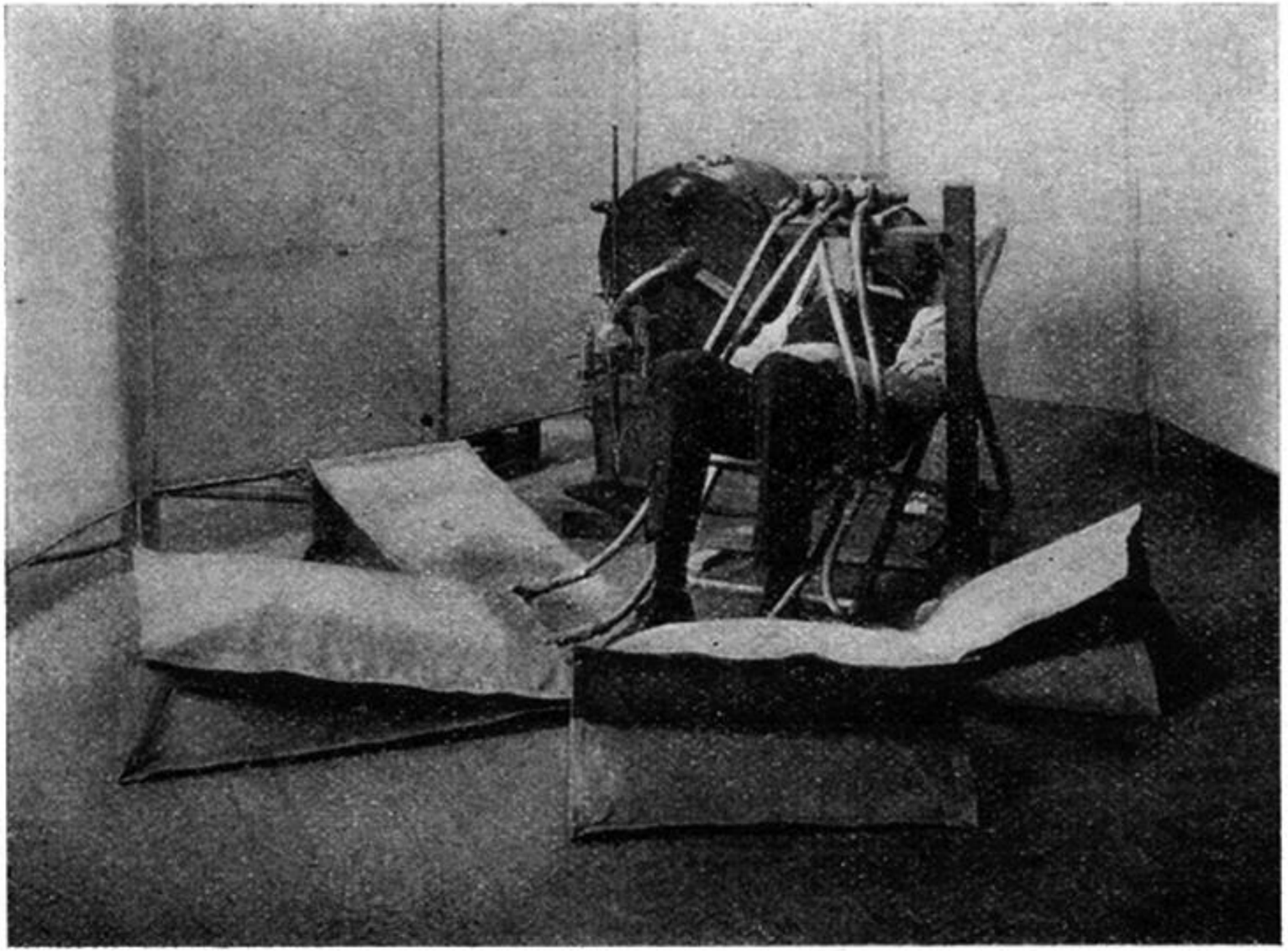

Fig. 15.

Arrangement of apparatus for determining the total respiratory exchange at different intervals after the cessation of muscular work.

Fig. 17.

Photograph of recoil apparatus with which the curves of fig. 16 were obtained. It consists of a plank supported on rubber stoppers. The recording lever magnifies the recoil movements 60 times.