EXPERIMENTS ON ACCLIMATISATION TO REDUCED ATMOSPHERIC PRESSURE.

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The experiments of Paul Bert proved that the characteristic physiological effects of lowered atmospheric pressure, as met with at high altitudes, are due, not to lowering of the mechanical pressure of the air, but solely to lowering of its oxygen pressure and consequent insufficient oxygenation of the blood. There is now, however, abundant evidence that, within limits, acclimatisation to high altitudes takes place. The present experiments were undertaken, in connection with a projected expedition by one of us (A. M. K.) to the Himalayas, in order to throw further light on acclimatisation and discover to what extent it can be obtained by discontinuous and comparatively short exposures to progressively lower atmospheric pressures. We wished also to gain further knowledge as to the possibility of reaching on foot the higher peaks of the Himalayas, and using a small supply of oxygen to facilitate the climbing work.

The physiological factors concerned in acclimatisation up to moderate altitudes were investigated by the Anglo-American Pike's Peak Expedition (1), and further experiments under similar conditions in a steel chamber have been made at Copenhagen by Hasselbalch and Lindhard (2). The factors hitherto discovered may be enumerated as follows: (*a*) Increased active secretion of oxygen inwards, by the epithelium of the lung alveoli. (*b*) A modification in the composition of the blood, with the result that its hydrogen ion concentration remains normal with a diminished concentration of the free carbonic acid present in it. An increase in the volume of air breathed is thus necessitated, and in this way the partial pressure of oxygen in the air of the lung alveoli is raised beyond what it would otherwise be, and the want of oxygen correspondingly diminished. (*c*) Increase in the percentage of hæmoglobin in the blood, in consequence of which the partial pressure of oxygen in the blood of the systemic capillaries is prevented from falling as low as it

otherwise would. In our experiments we have paid attention to all of these factors, and at the same time endeavoured to obtain some further information as to the effects on unacclimatised persons of exposure for varying periods to definite reductions of atmospheric pressure.

We are indebted for financial and other help to the Oxygen Uses Committee of the Department for Scientific and Industrial Research. Through the courtesy of Messrs Siebe Gorman and Co. the preliminary experiments were made in the small steel chamber erected by the firm several years ago for the purpose of testing oxygen appliances for airmen. The acclimatisation experiments were carried out in the large steel chamber (3) presented to the Lister Institute by the late Dr Mond, in which there is ample room for apparatus, including a Martin bicycle ergometer. The ventilation of this chamber is provided for by a powerful pump capable of extracting about 100 cubic feet of air per minute. In connection with all the arrangements for the use of this chamber and apparatus attached to it we are very specially indebted to Professor C. J. Martin, Director of the Lister Institute. But for his constant and active cooperation the work would have been impossible. The analyses of urine were carried out by Dr Kennaway at the Bland-Sutton Institute of Pathology, Middlesex Hospital. In the preliminary experiments we did not trouble about analyses of the alveolar air, as this subject had already been pretty fully investigated on unacclimatised persons by Boycott and Haldane (4) in the Lister Institute Chamber. Our aim in this series was to observe in several persons the symptoms and after-effects of rather low pressures, with exposures of an hour or more.

Preliminary experiments.

The first experiments were made in order to observe more definitely the effects of exposure for some time to a pressure of half an atmosphere. It is well known that unacclimatised persons in ordinary health can expose themselves to a pressure of half an atmosphere for a short time without marked symptoms during rest, and without unpleasant after-symptoms; but we wished to observe the effects of at least an hour's exposure. Four persons made observations in pairs, as the chamber would only hold two comfortably. J. S. H. and A. M. K. were the first two observers, the second two being Captains H. W. Davis, R.A.M.C. and J. B. S. Haldane. A pressure of 380 mm. (corresponding to about 19,000 feet above sea level) was reached in about 5 minutes, and the pressure then kept steady by means of a tap. The effects observed varied somewhat in the different persons, and may be summarised as follows:

Respiration. In J. S. H. and J. B. S. H. there was at first a very noticeable increase in the depth and frequency of the respiration. After a few minutes, however, this became much less, and there was no subjectively appreciable increase of breathing in J. S. H. or variation from the normal rate. In J. B. S. H., however, the rate remained abnormally high—about 26. In A. M. K. and H. W. D. hardly any abnormality of respiration was observed. In J. S. H. the breathing became periodic readily for a time after it had been held or forced, but not in A. M. K.

Pulse. In all the observers the pulse-rate was markedly increased at first (in J. S. H. to 120 and H. W. D. to 118), but diminished later, though not quite to normal.

Cyanosis. In every case there was noticeable blueness of the lips, etc.; but the degree of blueness varied considerably. It was most marked in A. M. K. and H. W. D., and only very slight in J. S. H. and J. B. S. H. The cyanosis did not diminish as time passed. On taking two or three breaths from a bag of oxygen the lips, etc., became at once bright red in all of us.

Mental and sensory symptoms. No impairment of mental functions was noticed, but on taking two or three breaths of oxygen the light suddenly became brighter to all of us, and sounds louder. On raising the pressure rapidly the same brightening of light was observed.

Capacity for muscular work. Moderate work with a hand ergometer was quite easy, but produced more hyperpnœa than usual. On pressing the work to about 3500 foot-pounds per minute there was great hyperpnœa, increased blueness of the face, very rapid pulse, and feeling of confusion and inability to continue.

On the whole, the subjective symptoms diminished with stay in the chamber, and after an hour there was practically no discomfort.

After coming out none of us had any unpleasant symptoms or loss of appetite. There was no trace of mountain sickness, though a much longer stay would certainly have produced this.

In the second series of preliminary experiments, about ten days later, it was our intention to remain for an hour at about the lowest pressure possible without very serious impairment of our faculties for observation. This limit was, however, involuntarily overstepped, in the case, at least, of three of us, and the notes were consequently imperfect. The observers were the same as in the previous experiments, except that Mr C. D. Maitland, of St Thomas' Hospital, took the place of Captain Davis.

A. M. K. and J. S. H. went first into the chamber, and the pressure was rapidly reduced to 445 mm. (about 15,000 feet) and kept there for a

short time for observation. It was noticed that in J. S. H. there was at first distinct hyperpnœa with increase in frequency of breathing from about 16 to 24, and in pulse from 85 to 112. In A. M. K. the increases were much less. In a few minutes these increases had practically disappeared. In J. S. H. the lips were very slightly bluish; but the blueness was more evident in A. M. K. The pressure was then reduced rapidly to 360 mm. (about 21,000 feet). This brought back the hyperpnœa in J. S. H., with respirations at 28 and a distinct feeling of "abnormality," but only slight blueness. A. M. K. was much bluer, but felt quite well. Shortly afterwards the pulse was 102 in both J. S. H. and A. M. K. The pressure was then gradually reduced to 340 mm. J. S. H. felt "rather wobbly," but was still only slightly blue, and felt better after a few minutes, the hyperpnœa diminishing. Handwriting rather shaky. A. M. K. very blue, but felt quite fit. The pressure was then reduced to 320 mm. (24,500 feet). This increased temporarily the hyperpnœa in J. S. H., whose lips were now of a rather dull colour, with pulse 112 and respirations 27. He also had great difficulty in making observations or even counting his pulse, and especially in calculating the pulse from a 20 seconds observation, or remembering at what point on the seconds hand the observation had begun. Writing was also very shaky. In a few minutes he thought he felt better, but a further note 10 minutes later was "very wobbly" in scarcely legible writing. He then handed the note-book to A. M. K., who was extremely blue, but felt all right and could still write quite normally, with a pulse at 102. J. S. H. remained sitting in one position, with his head rather low, but continued to answer all questions, so that A. M. K. considered him quite sensible, and mentally alert. Ten minutes later the pressure fell to 300 mm., and for a minute or two to 295 mm. (26,500 feet), but J. S. H. asked A. M. K. to keep the pressure steady at 320 mm. Meanwhile A. M. K. continued to feel fit, and at various times he noted his pulse as 90 to 93. He could quite easily stand up to regulate the inlet tap or read the barometer. To all his questions about changing the pressure J. S. H. replied with apparent deliberation "keep it at 320." Persons outside were somewhat impatient and anxious, and put up messages on the window, but A. M. K. only smiled, and referred to J. S. H., who invariably gave the old answer. After $1\frac{1}{4}$ hours at or below 320 mm. A. M. K. noted that J. S. H. was "still determined." Shortly afterwards, however, J. S. H. consented to an increase of pressure to 350 mm. He then began to regain his faculties, and took up a mirror to look at his lips, though some little time elapsed before he realised that he was looking at the back, and not the front, of

the mirror. He became, also, partly aware of the lapse of time, and consented to coming down. At about 450 mm. he woke up more completely and noticed a returning sensation of the existence of his legs. He had no recollection of the long stay at 320 mm., or of anything else after he handed the note-book to A. M. K., but seems to have been conscious and under the influence of a fixed idea that it was necessary to stay at a pressure of 320 mm. On coming out of the chamber he was somewhat unsteady in gait for a short time and inclined to be unreasonable. A. M. K. was much less affected. He could remember everything, and his handwriting remained quite steady, although his face was extremely blue and presented an alarming appearance to persons who saw him through the window.

The experiment was then repeated with the two other subjects, but with instructions not to go beyond 330 mm. This pressure was reached in about 10 minutes, but the subsequent notes are rather confused and the handwriting of both observers very bad and hardly legible. There was great difficulty in counting the pulse or respirations, and figures given are queried, though both pulse and respiration rates were apparently much increased. At first the respirations noted were 88 (?) for J. B. S. H. and 28 for C. D. M., with pulse 136 for J. B. S. H., while that of C. D. M. could not be counted. J. B. S. H. seems to have been bluer than C. D. M. After about half-an-hour one note is "like last stages of drunk. J. B. S. H. respirations 45. Pulse can't take." On observation from without it appeared that neither observer could stand properly, and both looked very blue and shaky. The emergency tap was therefore opened so as to raise the pressure. There is a corresponding indignant and just legible note "some bastard has turned tap," after which the notes become quite legible again as the pressure rose.

All four observers suffered somewhat from headache for several hours after these experiments, but there was no nausea or loss of appetite. The analyses of urine will be referred to later.

Acclimatisation experiments.

About a fortnight later the acclimatisation experiments were begun at the Lister Institute. Each morning the alveolar CO_2-pressure was determined in the two subjects (J. S. H. and A. M. K.) before they entered the chamber. The figures given, whether for observations inside or outside the chamber, are always the average of two samples—one taken at the end of inspiration, and the other at the end of expiration.

The hæmoglobin percentages by the ordinary Haldane scale were also taken each morning.

First day. Alveolar CO_2-pressure before entering, J. S. H. 40·7 mm., A. M. K. 34·6. Hæmoglobin, J. S. H. 93 p.c., A. M. K. 101 p.c. Decompression started at 11.40. Pressure at once lowered to 525 mm. (10,200 feet), and gradually lowered further during the next 8 hours to 500 mm. (11,600 feet). At several times the air in the chamber was analysed, and found to contain only about ·04 p.c. of CO_2. The ventilation was thus more than ample. The alveolar CO_2-pressures of J. S. H. in millimetres were 36·0 at 12.5, 36·8 at 1.10, 35·7 at 2.35, 35·3 at 4.5, 35·7 at 6.10, 34·0 at 6.50, and 34·9 at 7.25. His pulse, which averages 85 at normal pressure, was 72 at 12.40 and 74 at 1.0, but afterwards about 84. Respirations 13 to 15, the latter being about the ordinary frequency in the sitting position. Moderate work on the ergometer (about 3300 foot-pounds) could be kept up continuously quite easily, but seemed to cause a little more panting than usual. He felt quite normal throughout, and had no headache or nausea afterwards.

Alveolar CO_2-pressures of A. M. K. were 31·0 at 3.5, 29·9 at 4.5, and 32·2 at 7.30. Pulse and respiration were normal, and moderate work on the ergometer seemed about as easy as usual. No after-effects of any sort.

Second day. Alveolar CO_2 before entering, 39·5 in J. S. H., and 33·4 in A. M. K. Hb. = 107 p.c. in A. M. K. and 100 p.c. in J. S. H. Decompression at 11.30. Pressure lowered at once to 450 mm. (14,600 feet), and gradually reduced during next 8 hours to 430 mm. (16,000 feet). Alveolar CO_2-pressure in J. S. H. 32·9 at 12.10, 30·5 at 1.0, 31·2 at 3.0, 31·3 at 3.40, 30·4 at 5.45, 30·9 at 7. Alveolar oxygen pressure 41·9 mm. at 5.45. At 11.50 lips seemed slightly bluish, but on repeated subsequent examinations up till decompression no blueness was visible. The respiration frequency was normal throughout, at any rate after the first few minutes. Pulse averaged about 94, but rapidly came back to the normal of 84 when the pressure was raised. Could only hold a deep breath for about 30 seconds. Could keep up work of 3300 foot-pounds on ergometer, but with so much panting that harder work would have been difficult. Felt quite well throughout, and no nausea, depression, or loss of appetite afterwards, but a very slight tendency to headache for an hour or two.

Alveolar CO_2-pressure in A. M. K., 30·0 at 12.20, 28·2 at 6.5, 25·9 at 7.10. Slight blueness of lips throughout. Pulse about 80 to 90 throughout, but only 68 ten minutes after pressure restored to normal. Respirations about 19 or 20. Could keep up 3300 foot-pounds on ergometer quite easily, and 6000 foot-pounds without much difficulty. No tendency

to periodic breathing after forced respirations, though in J. S. H. this tendency was marked. Felt normal throughout, and no after-effects.

Third day. Alveolar CO_2-pressure before entering, 37·9 in J. S. H., and 31·8 in A. M. K. Hb. = 109·5 in A. M. K. and 101 in J. S. H. As an unacclimatised control subject, J. B. S. H. also entered the chamber. The pressure was lowered to 380 mm. at 11.50, and about half-an-hour later to 360 mm. (21,000 feet), and kept at this. Alveolar CO_2-pressure in J. S. H. 26·3 at 12.0, 23·9 at 1.30. Alveolar oxygen-pressure 33·4 mm. at 1.30. Pulse remained about 100 and respirations 15. Very slightly blue and not quite so quick as usual in doing gas analyses. J. B. S. H. was slightly blue and felt a little abnormal at 12.5. Respirations 51 and pulse 91. At 12.20 face bluer, hands tingling and light seemed less bright. Very sleepy, and fullness in head. 12.55, looks blue and seems stupid. Respirations 38. 2.5 looks more blue and shaky. Sitting with head down and very quiet. 2.20 looks very blue and seems stupid. In A. M. K. alveolar CO_2-pressure 25·7 at 12.40, 23·8 at 1.35. Pulse 84 at 12.15, and afterwards remained at 88. Respirations 23 at 12.15, and afterwards 24 to 25. Lips distinctly blue throughout. About 1.0 a little drowsy, and light-intensity seemed diminished.

At 2.35 the pressure was raised to normal to let J. B. S. H. out. On raising the pressure he felt tingling all over and rather acute aching of the head and eyes. Some unsteadiness and difficulty of speech on coming out. Could remember hardly anything of the last hour in the chamber. Before that he remembered having a strong inclination to sing. The headache lasted for some time, but there was no nausea. A. M. K. and J. S. H. noticed hardly any symptoms when the pressure was raised; but unfortunately both gas analysis apparatus were disabled owing to potash or pyrogallic acid being driven over, and this caused considerable delay. About 4.30 p.m. the alveolar CO_2-pressure was taken before lowering the pressure again, and was found to have risen to 30·4 in A. M. K. and 37·6 in J. S. H.

At 5 the pressure was lowered straight to 360 mm. and then kept at this. Alveolar CO_2-pressure of J. S. H. 26·7 at 5.15, and 23·3 at 6.45; alveolar oxygen pressure 31·6 at 5.15 and 34·1 at 6.45. Pulse remained at 96 to 100 and respiration rate about normal. Till about 6 felt a little abnormal, and lips a little dull in colour. After tea about 6, lips of normal colour, and feeling better. Out at 7.35. Felt distinctly shaky on coming out. Also got some headache, which lasted more or less till after dinner. No loss of appetite. In A. M. K. alveolar CO_2-pressure 27·1 at 5.40 and 23·8 at 6.45. Pulse 82 to 89 and respiration about 22. Light seems only

slightly less bright than usual. Work of 3300 foot-pounds a minute on ergometer could easily be maintained. No abnormal symptoms noticed after coming out.

Fourth day. Alveolar CO_2-pressure before entering, 39·2 in J. S. H., and 34·0 in A. M. K. Hæmoglobin 97·5 in A. M. K. and 87 in J. S. H. Decompression at 1.10 to 360 mm. J. S. H. felt the effects distinctly at first. Lips slightly bluish, and got distinctly redder with oxygen. Felt better after a few minutes. Pulse 84 (normal) and respirations 15. At 2.0 pressure reduced to 312 mm. (25,000 feet), and kept at about this. J. S. H. again affected, but felt better later. Pulse 96, respirations 20. Lips only slightly blue. At 2.50 alveolar CO_2 19·8 and alveolar oxygen 30·1 mm. At 3.30 he got on ergometer and did 3300 foot-pounds a minute for 4 minutes, but could not continue, as he was exhausted and vision was becoming blurred. He also became quite blue. Oxygen was then added to his inspired air through the latest form of Haldane mask as supplied to the Army for oxygen administration. One litre a minute (measured at normal pressure) was turned on shortly after the work was stopped. The effect was very striking. The light seemed to increase and there was a short apnœa. At the same time the lips and face became bright red. It now became quite easy to do the work, which was accordingly increased to 5000 foot-pounds. After 1½ minutes of this, however, the panting was so great as to be exhausting, though vision remained clear and there seemed to be no evident lack of oxygen. Calculating from the oxygen delivery and the probable volume of air breathed, the alveolar oxygen pressure would be raised to about 45 mm., and this appeared to be sufficient to make pretty hard work possible. Came out about 4 p.m., as it was necessary to catch a train. Only trifling after-symptoms. In A. M. K. the subjective symptoms of oxygen want were very definitely less than in J. S. H., but blueness of the lips and face were much more evident. Even at 360 mm. the lips were distinctly blue, and changed to red on breathing oxygen. The pulse was then 76 and respirations 24. At 312 mm. the cyanosis was marked, and the pulse had risen to 95 and respirations to 27, but there was no shakiness or apparent loss of coordination or mental power, though the light seemed less bright. The alveolar CO_2-pressure was 20·5 mm. There were no after-symptoms.

Observations on the urine.

As an important factor in acclimatisation is a diminution in the alkaline salts ("alkaline reserve") of the blood, the urine, except in the first of the preliminary experiments, was analysed with the view of

seeing whether retention of acid and inhibition of ammonia-formation occurred during the stays in the chamber.

The connection between acclimatisation to high altitudes and the regulatory functions of the kidneys and liver in maintaining the exact degree of slight alkalinity which prevails within the body was pointed out in the report of the Pike's Peak Expedition (p. 302), but no analyses of the urine were carried out. Hasselbalch and Lindhard have, however, in the papers already referred to, shown that at reduced atmospheric pressures there is a very distinct diminution in the excretion of ammonia and the ratio of ammonia nitrogen to total nitrogen in the urine. They also made a number of determinations of the hydrogen ion concentration of the urine. We have not repeated the latter, as we wished to have a more definite measure of the excretion of acid and, as L. J. Henderson (14) has pointed out, titration of the urine is necessary for this purpose, since the urine, like the blood, contains "buffer substances," and these prevent the hydrogen ion concentration from affording a definite measure of the acid excreted.

Our first observations were made on samples collected during and before the second pair of preliminary experiments. Owing to the short periods of exposure and rather unsatisfactory control samples, these observations need not be quoted in detail; but they pointed clearly to the conclusion that both the excretion of acid and the ammonia-nitrogen ratios were much diminished during the short exposure to reduced pressure.

The urine was collected in sterilised bottles containing chloroform, and the titrations were carried out as soon as possible. Duplicate estimations were made (1) of titratable acidity and ammonia by the method of Folin (titration to phenolphthalein before and after addition of formalin), (2) of total nitrogen (Kjeldahl). Table I shows the results obtained during the period covered by the acclimatisation experiments. Each day's urine was collected in two portions, (1) during the period, usually 8 hours, spent in the air-chamber, and (2) during the remainder of the 24 hours. For the sake of brevity this latter time will be spoken of as a "night period," although it includes a part of the day.

It is at once evident from Table I that the titratable acid of the urine at reduced pressure was from one-half to one-third of what it was during the rest of the day; but since the comparison of night urines with day urines is of course unsatisfactory for the present purpose, a further series of controls was made after the conclusion of the experiments when the subjects were carrying on their usual occupations (Table II). The urines

TABLE I. Comparison of urine secreted during four reduced pressure experiments with that secreted during intervening periods at atmospheric pressure. Results obtained at reduced pressures are indicated by italics.

		Duration of exp. in hours	Volume of urine c.c. per hour	c.c. 0·1 N. per cent. acid	c.c. 0·1 N. per cent. NH_3	c.c. 0·1 N. per hour acid	c.c. 0·1 N. per hour NH_3	NH_3 per cent. of acid + NH_3	Total nitrogen mg. per cent.	Total nitrogen mg. per hour	NH_3 nitrogen per cent. of total nitrogen
J. S. H.	I. 8.30 p.m. 22nd to 11.30 a.m. 23rd	15	34·7	64·4	50·0	22·3	17·3	43·7	1751	607	4·0
	II. 11.30 a.m. to 7.45 p.m. 23rd	$8\frac{1}{4}$	*36·4*	*52·3*	*35·7*	*19·0*	*13·0*	*40·6*	*1744*	*634*	*2·86*
	III. 7.45 p.m. 23rd to 11.30 a.m. 24th	$15\frac{3}{4}$	35·2	57·4	41·0	20·2	14·4	41·7	1731	609	3·32
	IV. 11.30 a.m. to 7.30 p.m. 24th	8	*38·8*	*19·4*	*29·4*	*7·5*	*11·4*	*60·2*	*1664*	*645*	*2·42*
	V. 7.30 p.m. 24th to 11.30 a.m. 25th	16	49·4	40·7	31·7	20·1	15·6	43·8	1301	642	3·41
	VI. 11.30 a.m. to 7.30 p.m. 25th	8	*26·2*	*21·5*	*24·6*	*5·6*	*6·5*	*53·3*	*1176*	*309*	*2·93*
	VII. 7.30 p.m. 25th to 12.40 p.m. 26th	$17\frac{1}{6}$	45·4	31·8	30·9	14·4	14·0	49·3	1100	833	3·93
	VIII. 12.40 p.m to 4.0 p.m. 26th	$3\frac{1}{3}$	*49·5*	*9·0*	*17·4*	*4·4*	*8·6*	*66·0*	*776*	*384*	*3·14*
I, III, V, VII, at atmospheric pressure. II, IV, VI, VIII, at reduced pressure. Means see Table III.											
A. M. K.	I. 8.30 a.m. to 8.0 p.m. 22nd	$11\frac{1}{2}$	80·0	11·4	22·0	9·1	17·6	65·9	543	434	5·67
	II. 11.40 a.m. to 7.45 p.m. 23rd	$8\frac{1}{12}$	*48·2*	*8·0*	*22·4*	*3·8*	*10·8*	*73·7*	*1211*	*584*	*2·59*
	III. 11 p.m. 23rd to 11 p.m. 24th minus IV	16	34·4	36·5	50·8	12·5	17·4	58·2	1199	412	5·93
	IV. 11.30 a.m. to 7.30 p.m. 24th	8	*81·0*	*5·4*	*16·0*	*4·4*	*13·0*	*74·8*	*658*	*535*	*3·40*
	V. 11 p.m. 24th to 11 p.m. 25th minus VI	16	45·6	28·7	41·8	13·1	19·0	59·3	907	414	6·45
	VI. 11.40 a.m. to 7.40 p.m. 25th	8	*53·0*	*9·8*	*25·1*	*5·2*	*13·3*	*71·9*	*887*	*470*	*3·96*
	VII. 11 p.m. 25th to 11 p.m. 26th	$20\frac{2}{3}$	53·1	24·3	31·7	12·9	16·9	56·6	725	386	6·12
	VIII. 12.40 p.m. to 4.0 p.m. 26th	$3\frac{1}{3}$	*60·0*	*5·3*	*12·8*	*3·2*	*7·7*	*70·7*	*547*	*328*	*3·27*
I, III, V, VII, at atmospheric pressure. II, IV, VI, VIII, at reduced pressure. Means see Table III.											

TABLE II. Further Control Observations at atmospheric pressure.

J. S. H.	I	8 p.m. 7th to 1 p.m. 8th	17	36·5	51·1	48·0	18·6	17·5	48·4	1613	588	4·17
	II.	1 p.m. to 6.30 p.m. 8th	5½	56·4	28·8	31·1	16·2	17·5	51·9	1188	670	3·67
	III.	1.30 a.m. 11th to 1.30 a.m. 12th minus IV	16¾	37·0	43·7	40·4	16·2	14·9	48·0	1336	494	4·23
	IV.	12.30 p.m. to 7.45 p.m. 11th	7¼	45·5	43·8	36·8	19·9	16·7	45·6	1230	560	4·18
	V.	2 a.m. 20th to 2 a.m. 21st minus VI	16¼	45·1	42·2	34·4	19·0	15·5	44·9	1235	557	3·89
	VI.	12 noon to 7.45 p.m. 20th	7¾	56·8	37·8	32·3	21·4	18·4	46·1	1075	610	4·20
	VII.	11.55 p.m. 24th to 11.55 p.m. 25th minus VIII	18⅓	46·7	40·6	36·1	18·9	16·8	47·0	1307	610	3·86
	VIII.	1.20 p.m. to 7 p.m. 25th	5⅔	62·6	25·9	28·0	16·2	17·5	51·8	1232	772	3·18

I, III, V, VII, Night periods. II, IV, VI, VIII, Day periods. Means see Table III.

A. M. K.	I.	1.15 p.m to 6.15 p.m. 10th	5	76·6	16·6	28·3	12·7	21·7	63·0	674	517	5·87
	II.	8.30 a.m. to 8 p.m. 22nd	11½	80·0	11·4	22·0	9·1	17·6	65·9	543	434	5·67
	III.	11 p.m. 20th to 11 p.m. 21st minus IV	16	51·9	29·3	38·6	15·2	20·0	56·8	825	428	6·54
	IV.	11.30 a.m. to 7.30 p.m. 21st	8	41·2	38·6	44·8	15·9	18·5	53·8	1002	413	6·27
	V.	12.30 a.m. to 12 midnight 25th minus VI	15½	34·0	42·1	60·2	14·1	20·2	58·8	1554	521	5·42
	VI.	12 noon to 8 p.m. 25th	8	58·8	15·9	33·7	9·3	19·7	67·8	1260	740	3·75
	VII.	12.30 a.m. to 12 midnight 26th minus VIII	16½	38·0	43·8	58·8	16·7	22·4	57·3	1469	561	5·60
	VIII.	1 p.m. to 8 p.m. 26th	7	24·3	74·1	90·5	18·0	22·0	55·0	1902	462	6·66
	IX.	12.30 a.m. 27th to 12.30 a.m. 28th minus X	15	64·7	14·8	27·2	9·6	17·6	64·9	823	532	4·63
	X.	11.30 a.m. to 8.30 p.m. 27th	9	63·3	26·0	39·2	16·4	24·8	60·1	930	589	5·90

III, V, VII, IX, Night periods. I, II, IV, VI, VIII, X, Day periods. Means see Table III.

TABLE III. Means of all observations at atmospheric and at reduced pressure.

J. S. H.		Volume of urine c.c. per hour	c.c. 0·1 N. per cent. acid	c.c. 0·1 N. per cent. NH_3	c.c. 0·1 N. per hour acid	c.c. 0·1 N. per hour NH_3	NH_3 per cent. of acid + NH_3	Total nitrogen mg. per cent.	Total nitrogen mg. per hour	NH_3 nitrogen per cent. of total nitrogen
Controls at atmospheric pressure	Table I 4 night periods	41·2	48·6	38·4	19·2	15·3	44·3	1471	673	3·66
	,, II 4 ,, ,,	41·3	44·4	39·7	18·2	16·2	47·1	1373	562	4·04
	,, II 4 day periods	55·3	34·1	32·0	18·4	17·5	48·8	1181	653	3·81
At reduced pressure	*Table I 4 day periods*	*37·7*	*25·5*	*26·8*	*9·1*	*9·9*	*55·0*	*1340*	*493*	*2·84*
	,, latter 3 day periods	*38·2*	*16·6*	*23·8*	*5·8*	*8·8*	*59·8*	*1205*	*446*	*2·83*
A. M. K.										
Controls at atmospheric pressure	Table I 4 periods (3 night, 1 day)	53·3	25·2	36·6	11·9	17·7	60·0	843	412	6·04
	,, II 4 night periods	47·1	32·5	46·2	13·9	20·0	59·4	1168	510	5·55
	,, ,, 6 day periods	57·3	30·4	43·1	13·6	20·7	60·9	1052	526	5·69
At reduced pressure	*Table I 4 day periods*	*60·5*	*7·1*	*19·1*	*4·1*	*11·2*	*73·0*	*826*	*479*	*3·30*

were collected over similar "night" and day periods, and the meals were made as far as was practicable the same in time and character as those taken during the experiments. The results of these observations (in all 26 controls and 8 experiments) are summarised in Table III. The following points are evident:

1. *Titratable acid.* In J. S. H. the hourly rate of secretion is reduced to one-half (from 18 to 9 c.c. 0·1 N acid per hour). If the first experiment (April 23rd), in which there was only a slight reduction of pressure, and J. S. H. reacted but slightly, be excluded from the average, the reduction is to one-third. In A. M. K. the acid falls to less than one-third (from 13 to 4 c.c. 0·1 N per hour)[1].

2. *Ammonia.* The hourly rate is lowered in J. S. H. to about two-thirds (from 16 to 10 c.c. 0·1 N), and in A. M. K. to nearly one-half (from 19 to 11 c.c.). Thus A. M. K. reacts to reduced pressure more than does J. S. H. as regards both acid and ammonia.

3. *Ratio of ammonia to acid.* This rises, as is shown by the figures under "NH_3 per cent. of acid + NH_3" in Tables. This change would in any case be expected in experiments of short duration, since the kidney can alter the acidity of the urine immediately, whereas the normal ammonia content of the blood and tissue-fluids must first be lowered by excretion before the full lessened production of the base will be apparent in the urine.

4. *Ammonia-nitrogen per cent. of total nitrogen.* This percentage falls, and it is evident from the figures given that this is not due to an increase in the total nitrogen. In A. M. K. the mean hourly rate of total nitrogen is practically the same at normal and at reduced pressure (489 mg. and 479 mg.). In this respect, therefore, our experiments confirm completely those of Hasselbalch and Lindhard. It may be noted also that so far as can be judged from their determinations of hydrogen ion concentration in the earlier stages of their long experiment, our results as regards acid excretion are in accord with theirs.

These results provide an illustration of the buffer-capacity of the blood which is of some interest. In A. M. K., the excretion of acid was reduced by, in round numbers, 9 c.c. 0·1 N per hour for 8 hours, giving a total of 72 c.c. 0·1 N. One may add to this the diminution in ammonia, namely 8 c.c. 0·1 N per hour for the same time, giving a total of 72 + 64 = 136 c.c. 0·1 N. This might seem at first sight a somewhat formidable

[1] In the second preliminary experiment mentioned above, the hourly excretion of acid was reduced in A. M. K. to the very low figure of 2·9 c.c., as against 17·7 c.c. of 0·1 N during the preceding period.

amount; it is one-sixth of the acid + ammonia produced normally by A. M. K. in a day (about 800 c.c.). But it is very small in comparison with the total "alkaline reserve" or "buffer-capacity" of the body.

Discussion of the results.

Symptoms observed at low pressures. The symptoms observed were in general such as have already been described in connection with high balloon ascents and the experiments of Paul Bert and others in steel chambers; but various special points emerge more definitely than before.

In the first place it appears that in no case were the durations of exposure to the low pressures sufficient to produce in the subjects observed the ordinary symptoms (nausea, vomiting, diarrhœa, and extreme depression) of mountain sickness. Only a certain degree of headache was observed after the more severe exposures. In J. S. H. mountain sickness was produced after the first eight hours on Pike's Peak (14,100 feet), and has often been caused by exposure of several hours to sufficient carbon monoxide to produce symptoms of want of oxygen; but in all these cases the exposure was either more prolonged, or more severe, than in the present experiments. On the other hand it seems certain that in some individuals mountain sickness is produced more easily than in any of the subjects of the present experiments. For instance, in the experiments, already referred to, of Boycott and Haldane, the former suffered from severe and prolonged mountain sickness after an exposure of about an hour (along with J. S. H., who remained immune) to a pressure of 356 mm. in the chamber.

The general symptoms of anoxæmia were very characteristic, and exemplify clearly certain of the special dangers associated with CO-poisoning or high balloon or aeroplane ascents. Thus in the second preliminary experiment J. S. H. became the subject of a fixed idea that it was necessary to remain at 320 mm. Similarly, balloonists usually become possessed at very high altitudes of the fixed idea of going higher, or miners when suffering from carbon monoxide poisoning cannot be diverted from rescue operations, exploring, or fire-fighting work, and often violently resist anyone who tries to make them desist. These fixed ideas often take very strange forms. The tendency to singing (observed in J. B. S. H.) and to various forms of uncontrolled emotion is often observed in CO-poisoning.

Loss of the power of memory was also prominent in the experiments. There appeared to be no real loss of consciousness; but the mental registration of events was quite ineffective, so that a blank remained.

In connection with the anoxæmia caused by lung-irritant gases used in warfare the same loss of memory was often observed, sufferings which at the time were only too evident, being just as completely forgotten afterwards as were conversations and other definitely perceived events.

A further point which appeared quite definitely was that the symptoms of anoxæmia did not coincide in the different subjects with the degree of blueness of the face. The contrast in this respect between A. M. K. and J. S. H. was very marked. The former was always much bluer than the latter, but was otherwise much less affected, and retained his faculties when the latter was helpless. It may be noted in this connection that A. M. K. is one of the class of persons who do not become apnœic on forced breathing, and in whom periodic breathing cannot easily be produced.

Increased frequency of breathing was a far more prominent symptom in J. B. S. H. than in any of the other subjects. In nearly all of them, however, increased depth and frequency of breathing and increased frequency of pulse were very evident at first, but became less marked within a few minutes, except perhaps at very low pressures. This falling off in breathing was doubtless related to washing out of preformed CO_2 from the blood by the increased breathing. It seems probable that the diminution in pulse-rate was due to a similar cause, or perhaps to a gradual coming into play of active secretion of oxygen inwards by the lung epithelium. The lasting increase of frequency was out of normal proportion to the comparatively slight increase of alveolar ventilation, and must be regarded as a sign of partial failure or fatigue of the respiratory centre in consequence of the anoxæmia (5).

Where the reduction of pressure was moderate, as in the first preliminary experiment, the symptoms of anoxæmia seemed to diminish distinctly with time during the period of observation. This was doubtless due to acclimatisation factors (increased oxygen secretion and diminished alkaline reserve of the blood) coming into play. But with a greater diminution of pressure the symptoms increased with time, as in the second preliminary experiment, or in the case of J. B. S. H. in the third acclimatisation experiment. The inevitable ill effects of continued serious anoxæmia were evidently making themselves felt in spite of attempts at adaptation, and probably the respiratory centre and heart were gradually failing.

Other things being equal the alveolar oxygen pressure at a barometric pressure of 380 mm. would be the same as if air were breathed at ordinary atmospheric pressure and contained only 9·8 p.c. of oxygen. Nevertheless

the effects of a pressure of 380 mm. on J. S. H. seemed definitely less than those produced by breathing from a bag air containing 9·8 p.c. of oxygen at ordinary pressure. The results of various experiments on J. S. H. with air of about this composition are given by Haldane and Poulton (6), and a special experiment in which exactly 9·8 p.c. of oxygen was breathed with a maximum of resistance had a similar result, twitching of the limbs becoming very marked. The difference in favour of the air at low pressures may possibly depend to some extent on the slight resistance when air is breathed from a bag, but is probably mainly due to the fact that at low pressures the diffusion of oxygen molecules within and into the lung alveoli is much more free at the low pressure. The reason why diffusion of oxygen is so slow in air in comparison with the enormous velocities at which the individual molecules are moving is that the mean free path of the oxygen molecules is so small. Thus the oxygen molecules cannot reach the alveolar epithelium freely because in their passage towards it they are so frequently deflected by collisions with molecules of nitrogen, CO_2, and H_2O. When the atmospheric pressure is reduced the concentration of nitrogen molecules is correspondingly reduced. Hence with a given concentration, or partial pressure, of oxygen, diffusion is much more free, and the oxygen reaches the alveolar epithelium more rapidly. In so far, therefore, as defective saturation of the blood with oxygen is due simply to the slow rate at which oxygen reaches the alveolar epithelium, a given alveolar oxygen pressure will be more effective in saturating the blood when the barometric pressure is greatly lowered than when it is normal. This physiological advantage at low barometric pressures must be taken into account in considering the effects of low barometric pressures and the possibilities of acclimatisation through increase in the secretory activity of the alveolar epithelium.

It is evident that a striking degree of acclimatisation was actually obtained, as on the fourth day J. S. H. could easily carry on with gas analyses, etc., and even work on the ergometer, whereas in the second preliminary experiment he was quite helpless at the same pressure. On the fourth acclimatisation day the symptoms at 360 mm. seemed also to be less than on the third day. Nevertheless the acclimatisation was a failure in certain very important respects, for not only did the hæmoglobin percentage fail to rise (since in both subjects it was lower on the fourth than the first day), but there was no lasting lowering of the alveolar CO_2 pressure, which was almost as high on the morning of the fourth day as on that of the first day. When acclimatisation is produced in the ordinary way by a lasting exposure to low atmospheric pressure,

not only does the hæmoglobin percentage rise, but there is a lowering of the alveolar CO_2-pressure (and consequent increase in the breathing), most of which lasts for long after a return to ordinary pressure. This was first fully brought out in an experiment in which Dr Ogier Ward remained 24 hours in the chamber ((4), p. 367) and in experiments by him in an expedition to Monte Rosa (7), and was confirmed by the Pike's Peak expedition and subsequent observations.

Want of oxygen causes, of course, an immediate increase in the breathing, and consequent fall in alveolar CO_2-pressure and rise in alveolar oxygen pressure. As, however, Haldane and Poulton pointed out (6), the alveolar CO_2-pressure still regulates the breathing, though in consequence of the anoxæmia a lower CO_2-pressure now suffices to excite the centre. After a few minutes, during which there is a considerable washing out of preformed CO_2 from the blood, and corresponding great increase of the breathing, the breathing settles down to correspond with the lowered threshold of alveolar CO_2-pressure. But the lowered threshold, and doubtless also the higher pulse-rate, depend on the stimulus of a very serious want of oxygen. This want of oxygen is partly due to imperfect saturation with oxygen of the blood leaving the lungs, but partly also to the fact that the CO_2-pressure in the systemic capillaries is lowered in consequence of the increased breathing. As a result of this, as was shown by Bohr and his pupils, the dissociation curve of the oxyhæmoglobin is altered, so that oxygen is given off less readily by the red corpuscles. There may in this way be considerable anoxæmia, although the colour of the blood as shown in the lips is almost normal. Where, as in A. M. K., the lips are blue without very marked other symptoms of anoxæmia, it seems probable that owing to vaso-constrictor or other control of the circulation the fall of CO_2-pressure in the systemic capillaries is to a large extent avoided, so that oxygen is given off more easily from blood which has a bluish colour than from blood which is much less blue but with a lower CO_2-pressure. In this way it is possible to account for the fact that in different individuals the symptoms of anoxæmia are not necessarily proportional to the degree of blueness of the blood; also that apnœa is much less readily produced in some persons than in others.

In fully acclimatised persons the dissociation curve of the oxyhæmoglobin when in presence of the existing alveolar CO_2-pressure remains normal, in spite of the lowered CO_2-pressure, as was first shown by Barcroft in the Teneriffe expedition (8). He has also shown that it is in virtue of its acid properties that carbonic acid affects the dissociation

curve of oxyhæmoglobin. In acclimatised persons part of the normal effect of carbonic acid in raising the hydrogen ion concentration of the blood is produced by other acids retained in the blood, or rendered superfluous by withdrawal of alkali. The hydrogen ion concentration of the blood then appears by the existing methods of measurement to be the same as at normal barometric pressure, although, as will be shown below, it is not exactly the same.

The results of the urine analysis indicate that during the exposure to lowered pressures the kidneys were retaining within the body more acid, or excreting more alkali. This would tend to reduce the available alkali in the body. Since the excretion of ammonia salts was diminished, it is also clear that a smaller proportion of NH_3 was being formed within the body, and this would act in the same direction. The progressive fall in alveolar CO_2 pressure, and coincident amelioration of symptoms and fall in pulse-rate, as shown in some of the experiments, indicate also that the available alkali in the blood was diminishing, so that the increased breathing could be maintained without such excessive stimulus from want of oxygen. The process had, however, to be started almost afresh each day, as since the previous day the blood had almost returned again to its normal alkalinity. This was shown by the alveolar CO_2-pressure observed before entering the chamber each morning.

It is difficult to attribute the progressive acclimatisation actually observed on successive days to much else than an increasing power of secreting oxygen inwards in response to the stimulus of oxygen want. For the direct experimental evidence in favour of secretion we may refer to the paper by Douglas and Haldane(9), and to the report of the Pike's Peak expedition. As, however, our object in the present investigation was not specially to investigate oxygen secretion, but acclimatisation as a whole, we do not propose to discuss oxygen secretion further at present. It is of course possible that the power of rapidly reducing the alkaline reserve of the blood may have been increased by the repeated exposures to low pressures. The urine analyses do not show this, but the changes in acid secretion by the kidneys may not be a direct measure of the changes in the alkaline reserve of the blood.

The present experiments show that while a considerable degree of acclimatisation can be obtained by repeated intermittent exposures of a few hours' duration to low atmospheric pressures, the acclimatisation is much less complete than that obtained by gradually increasing but continuous exposure, as, for instance, always occurs in ascending to great heights in the Himalayas. In the experience of one of us (A. M. K.)

ordinary mountain sickness has never been experienced, either in himself, or among the native carriers accompanying him, at heights up to 23,180 feet in the Himalayas. This is an extraordinary contrast to common experiences in the Andes, or at such places as Pike's Peak (14,100 feet). Thus nearly everyone who came for more than a few hours to Pike's Peak was more or less mountain sick after a short time. It is of course true that persons in good physical training become mountain sick less easily than others. This is, however, attributable to the fact that their powers of actively secreting oxygen inwards have been increased by use during muscular exertion. The ordinary function of oxygen secretion by the lungs is to supplement diffusion during the enormously increased oxygen intake of muscular exertion; and the increased powers of oxygen secretion in a man in good physical training will of course be utilised at low atmospheric pressures. His acclimatisation is, however, still as imperfect as that which we attained during the present experiments.

On account of the imperfection in the type of acclimatisation obtained in these experiments, they do not answer the question as to what height it is possible by means of maximum acclimatisation, and without oxygen apparatus, to live at without mountain sickness, or other disabling consequences. As yet there is no definite reason for assuming that owing, merely, to the rarity of the air, the highest peaks in the Himalayas could not be reached by persons breathing ordinary air, although unacclimatised persons die of asphyxia at such altitudes, as was shown clearly by the deaths of the balloonists Sivel and Crocé-Spinelli at a maximum diminution of pressure to 263 mm. (30,000 feet).

The observations made during work at a pressure corresponding to 25,000 feet showed clearly that with the apparatus used the addition of as little as 1 litre of oxygen a minute was an enormous help in doing work. The light cylinder fitted up for the trial under the direction of the R.A.F. Technical Department would give this supply for six hours, and could be carried quite easily for use during the harder climbing work.

We may now attempt to interpret the changes in renal excretion during acclimatisation to low atmospheric pressure, in view of the fresh light thrown on the subject by the present experiments and others published since the report of the Pike's Peak expedition. The subject, it may be remarked, has now a very wide importance in practical medicine in view of war experiences of anoxæmia in gas-poisoning and other cases, and the recent demonstration by Haldane, Meakins and Priestley that anoxæmia is easily produced by defects in the nervous regulation of

breathing or by commonly occurring hindrances to even expansion of the lungs (10).

When the partial pressure of oxygen in the inspired air is diminished, there is, of course, other things being equal, a corresponding diminution in the partial pressure of oxygen in the alveolar air. If this latter diminution were only moderate, and we looked only to its *average* amount as shown by analyses of the mixed alveolar air, we should conclude from the dissociation curve of the oxyhæmoglobin in blood that there would only be an almost inappreciable diminution in the saturation of the arterial blood with oxygen, and that there would be no need for appreciable adaptive changes. As a matter of fact, however, the experiments of Miss FitzGerald (11) have shown that even a very small change in partial pressure evokes very appreciable adaptive responses in both the amount of air breathed and the percentage of hæmoglobin in the blood. The experiments of Haldane, Meakins and Priestley have furnished the key to this anomaly. They have shown that the average alveolar oxygen pressure (as determined by analysis of the mixed alveolar air) or the average oxygen pressure of the blood leaving the alveoli (as determined by the carbon monoxide method of Haldane and Lorrain Smith or Douglas and Haldane) does not correspond to the oxygen pressure of the *mixed* arterial blood (as determined by the aerotonometer method). The reason for this is that the distribution of oxygen in the alveolar air is more or less uneven, with the result that on account of the shape of the dissociation curve of oxyhæmoglobin in blood the saturation of the mixed arterial blood tends to be lower than corresponds to the *average* partial pressure of the blood leaving the alveoli. In this way we can now account for the fact that the carbon monoxide and aerotonometer methods give different results, and that appreciable anoxæmia exists and has to be compensated for, even though there is only a slight diminution in the partial pressure of oxygen in the inspired air. The experimental proof, by the carbon monoxide method, of the existence of oxygen secretion as a response to anoxæmia remains, however, completely unimpaired, and the whole of the phenomena relating to the physiological response to anoxæmia become much more easily intelligible than before.

We are now in a position to form a comprehensive idea of what normally happens when the partial pressure of oxygen in the inspired air is reduced, as by a diminution in barometric pressure. The first effect of such a diminution will be (in consequence of the uneven distribution of oxygen in the alveoli) to produce an *appreciable* diminution in the

percentage saturation of the arterial blood with oxygen. The respiratory centre, as clearly appears in connection with the phenomena of periodic breathing, and of voluntary holding of the breath (Hill and Flack, and others), is extremely sensitive to even slight anoxæmia, and immediately responds with increased breathing. The effect of this is, however, to wash out more CO_2 than usual from the arterial blood, and so diminish its hydrogen ion concentration and rapidly check the increased breathing, as was pointed out by Haldane and Poulton. The body then settles down for the time into a condition in which there is both a slight diminution of hydrogen ion concentration in the blood and a slight anoxæmia. It is very important to realise that anoxæmia cannot be compensated for by mere increase in the breathing. The advantage gained by higher saturation of the blood with oxygen in the lungs is counteracted by the alkalosis produced, through the fact that, as Bohr found, the dissociation curve of oxyhæmoglobin is shifted in consequence of the diminution in CO_2. Owing to this the hæmoglobin not only combines more readily with oxygen in the lungs, but also holds on more tightly to it in the tissues, so that their oxygen supply is not much improved, though the blood is redder. Barcroft showed that this effect is due to diminished alkalinity. Even, therefore, if the diminished hydrogen ion concentration with increased breathing did not automatically diminish the increased breathing, there would (unless the anoxæmia was extreme) be little gained by the increased breathing, except just at first, before the hydrogen ion concentration in the tissues had time to equalise itself with that of the blood. *Mutatis mutandis* the same considerations apply to increase in the circulation rate. Neither increase in circulation rate nor increase in breathing can by itself compensate for the want of oxygen; and the fallings off in the initial increases of breathing and pulse-rate after a state of anoxæmia is produced are indices of this. At first sight it might seem that mere increases in the breathing and circulation would be the natural response to reduced atmospheric pressure; but these responses would be ineffective for the reasons just given.

We are thus left in face of the fact that in spite of any mere increases in the breathing or circulation (such as might be continued permanently without the slightest strain on the powers of the respiratory apparatus or heart) a condition of anoxæmia remains, along with a slight diminution in the hydrogen ion concentration of the blood. That this condition is in itself a harmful one is shown clearly by the phenomena of mountain sickness and the serious effects of long-continued anoxæmia in cases of illness. In our experiments we purposely avoided mountain sickness by limiting

the periods of exposure to anoxæmia; but nothing is more significant than the ease with which a long-continued very slight anoxæmia produces mountain sickness, or the corresponding phenomena in slight CO-poisoning. To avoid mountain sickness it is absolutely necessary to give time for true acclimatisation to come into play. To what extent mountain sickness is due directly to anoxæmia, or to the secondary diminution in the hydrogen ion concentration of the blood ("alkalosis"), it is impossible at present to say; but in any case the two causes are closely bound up with one another, and the present experiments seem to enable us to follow out in some detail the response, more particularly, to the alkalosis.

As shown both by the preliminary short experiments and by the longer ones summarised in Table I, an immediate response to anoxæmia is a very great diminution in the total acid normally excreted in the urine. At the same time the ammonia salts excreted are also diminished, so that there is a decreased conversion of nitrogenous material into ammonia. The net result must be a diminution in the abnormal alkalinity of the body caused by the increased breathing. Hence the breathing can be still further increased without hindrance from an increase in the alkalosis. The *ultimate* cause of the increased breathing is still, however, the stimulus of anoxæmia, while the immediate stimulus leading to decreased elimination of acid and diminished production of ammonia is the alkalosis caused by increased breathing. The decreased excretion of acid with diminished "alkaline reserve" of the blood, and presumably also of the body generally, is thus indicative, not of an acidosis for which there would be no explanation, but of an alkalosis of which the physiological stimulus is quite evident. The whole of the facts seem to fit in naturally and simply with this mode of explanation.

One of us (J. S. H.) was largely responsible for the current view that slight anoxæmia produces a slight acidosis, evoking an increase in the breathing. The causes of this acidosis were first sought in excessive production of lactic acid, and when this theory was found to be untenable, in a lowering of the threshold of alkalinity to which the kidneys and liver regulate the hydrogen ion concentration of the blood[1]. The latter theory seems now to be quite unnecessary, as the phenomena can be explained without the assumption that there is any change in the normal functions of the kidneys and liver in regulating the reaction of the blood.

It now seems evident that the kidneys and liver on the one hand, and the respiratory centre on the other, regulate with a delicacy which is as

[1] This theory was put forward in the Pike's Peak report; pp. 301, 302.

yet far in excess of the delicacy of existing physical or chemical methods of measurement(12), the reaction of the blood. Of these regulators, the respiratory centre appears to do the rough and immediate work necessitated by the rapidly varying production of CO_2 within the body. The kidneys and liver, on the other hand, act far more slowly, but also more exactly. In addition, the kidneys appear to regulate the normal proportions of the alkaline salts of the blood, just as they regulate the normal proportions of sodium chloride and other crystalloid constituents. In this way only can we account for the fact that the alveolar CO_2-pressure during rest, the capacity of the blood for combining with CO_2(13), and its composition generally, remain so astoundingly steady as they do, under ordinary conditions. The changes in the "alkaline reserve" of the blood during acclimatisation is only slow because the kidneys and liver are slow in getting level with the very considerable amount of work which they are called on to perform. As L. J. Henderson(14) has so clearly pointed out, a very large amount of alkali must be withdrawn from the body in order to alter its reaction appreciably. Hence the kidneys and liver can only perform their work slowly; and acclimatisation, in so far as the blood-reaction is concerned, takes a considerable time. Conversely, it must take a considerable time for the alkali in the body to return to normal when the anoxæmia is removed. Hence the alveolar CO_2-pressure remains low for some time.

A balance must finally be struck between the stimulus of anoxæmia which by increasing the breathing produces alkalosis and the reaction of the liver and kidneys in diminishing the alkaline salts in the body and so tending to neutralise the alkalosis and diminish the want of oxygen in the systemic capillaries. A balance is struck because the alkaline salts are normal constituents of the body, and their removal is accordingly resisted. The excretion of acid will thus tend to reach a normal standard again when acclimatisation is established; and it appears from the determinations by Hasselbalch and Lindhard, of the hydrogen ion concentration of the urine after acclimatisation was established, that this is the case. On the other hand, they found that the excretion of ammonia remains abnormally low so long as the stay at lowered atmospheric pressure continues; and this is a clear indication that a slight degree of alkalosis still remains. Directly the anoxæmia is removed the excretion of ammonia rises to a normal standard and there is a corresponding sudden rise towards normal in the alveolar CO_2-pressure. This marks the end of the alkalosis, and it only remains to restore gradually the normal proportion of alkaline salts in the blood. During this process

there will, of course, be some diminution in the alkali excreted by the urine. Hasselbalch regards diminished formation of ammonia as the cause of the hypothetical acidosis of anoxæmia, and assumes that this acidosis lasts for some days after an acclimatised person returns to normal atmospheric pressure. The interpretation which we now give seems, however, to be much simpler and more satisfactory. In this connection we may point out that electrometric or other measurements of the hydrogen ion concentration of fully reduced blood at alveolar CO_2-pressure may be very misleading when the alkaline salts or percentage of hæmoglobin are abnormal, since reduction of the hæmoglobin acts like addition of alkali to blood, as Christiansen, Douglas and Haldane showed in the paper already quoted.

Our interpretation is, we think, greatly strengthened by recent experiments in which Yandell Henderson and Haggard(15) showed that the effect of continued excessive artificial respiration is to produce a very marked diminution in the "alkaline reserve" of the blood. The alkalosis which results from the excessive lung ventilation thus leads to a removal of alkali from the blood in an attempt at compensation. They also found that a converse effect is produced when a considerable excess of CO_2 is breathed. These important discoveries seem to suggest that the body has some rough and rapid means of varying the quantity of alkali in blood quite apart from the slow action of the liver and kidneys.

While this paper was passing through the press we received a copy of a lecture on the Physiology of Aviation, published by Yandell Henderson in *Science*, May 8, 1919. Referring to the supposed acidosis of anoxæmia he makes the following remarks. "Recent and as yet unpublished work by Dr Haggard and myself indicates that the process involved is almost diametrically opposite to that which has been hitherto supposed to occur, and that the result is not a true acidosis. Under low oxygen, instead of the blood becoming at first more acid with a compensatory blowing off of CO_2, what actually occurs is that, as the first step, the anoxæmia induces excessive breathing. This lowers the CO_2 of the blood, rendering it abnormally alkaline; and alkali passes out of the blood to compensate what would otherwise be a condition of alkalosis." It is thus evident that he has reached, though on independent grounds, similar conclusions to ours on this subject.

It is evident that the degree of acclimatisation brought about by diminution of the alkali in the blood does not help against deficient saturation of the blood with oxygen at the existing oxygen pressure in the lung alveoli. To help against this the other two responses to anox-

æmia come into play. In the first place the power of reacting by active secretion of oxygen inwards is increased, so that with a given pressure of oxygen in the alveolar air the percentage saturation of the hæmoglobin is increased, as was shown experimentally during the Pike's Peak expedition to be the case. The stimulus to secretion arises from the anoxæmia in the tissues, and this side of acclimatisation appears to be nothing more than an example of the familiar fact that the functioning of any organ tends to become more efficient with use, and particularly if the use is discontinuous, so that harmful fatigue effects are avoided. It is thus easy to understand why acclimatisation due to this response was most prominent in our experiments. The second response is that the percentage of hæmoglobin in the blood increases, as want of oxygen acts as a stimulus in this direction. The effect of the increased percentage is that with the circulation and lung-ventilation remaining the same, the partial pressure of oxygen in the systemic capillaries will be higher, and in this way anoxæmia will be diminished. In the present experiments this means of acclimatisation did not appear to have come into play at all, as the hæmoglobin percentage was rather lower on the fourth than the first day.

Summary.

1. The symptoms in different persons of the anoxæmia produced by different degrees of reduction of atmospheric pressure are described and discussed.

2. These symptoms appear to be less marked than when the alveolar oxygen pressure is reduced to the same extent by simply reducing the oxygen percentage in the air breathed.

3. In different individuals the severity of the symptoms is not always proportional to the blueness of the lips and face, and particular symptoms vary a good deal.

4. During the anoxæmia there is a very marked diminution in the acid excreted by the kidneys, and a less marked diminution in the excretion of ammonia.

5. Partial acclimatisation to reduced atmospheric pressure was obtained by discontinuous exposure to progressive diminutions of pressure; but this partial acclimatisation was apparently due almost entirely to increased inward secretion of oxygen by the lung epithelium.

6. The phenomena of anoxæmia and acclimatisation to low pressures are analysed more fully than before. It is pointed out that a mere increase in respiration or circulation cannot relieve the anoxæmia, and the

conclusion is drawn that the supposed slight acidosis of acclimatisation is in reality only an incomplete compensation of a continued alkalosis due to the increased breathing caused by the anoxæmia.

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