THE RESPIRATORY RESPONSE TO ANOXÆMIA.

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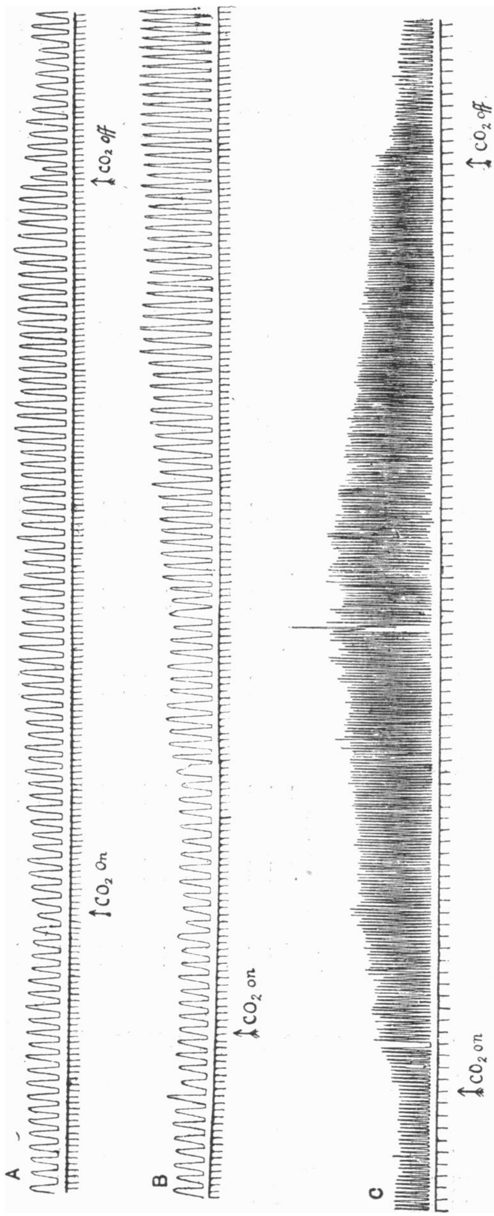
IT has been recognised for some time that ordinarily the respiration is regulated with the utmost delicacy in correspondence with the CO_2 tension of the blood passing through the respiratory centre[1] and it is now generally agreed upon that what the centre actually responds to is increased hydrogen ion concentration.

Fig. 1 shows quantitative records of the breathing taken by means of an apparatus which will be described in the subsequent paper on shallow breathing. In each case the subject of the experiment was sitting at rest while breathing from the apparatus. The tracings show the records obtained when breathing air containing (*a*) 3·28 p.c., (*b*) 4·29 p.c. CO_2. Study of these tracings brings out clearly the following points. Firstly the characteristic effect of CO_2 is increased in depth of respiration accompanied by only slight quickening of the rate. In this connection we may refer to the well known "air hunger" of diabetic coma. Here also the deep protracted breaths constitute the response of the respiratory centre to increased hydrogen ion concentration in the arterial blood caused by the state of "acidosis." Secondly it also appears that when the breathing of air containing added CO_2 had been continued for some time the depth of the respirations and the total ventilation of the lungs per minute showed a tendency to diminish. For example in the tracing taken when breathing 4·29 p.c. of CO_2 the depth of respiration and ventilation per minute steadily increase for about seven minutes and then progressively fall off again. The fall is probably connected with fatigue and perhaps also with the process of adaptation discovered by Yandell Henderson[2], who found that the CO_2 capacity of the blood of dogs increased when they were made to breathe air containing an added amount of CO_2. Thirdly it is evident from the tracings that

[1] Haldane and Priestley. This *Journal*, **32**. p. 225. 1905.

[2] Henderson and Haggard, *Journ. of Biol. Chem.* **33**. p. 333. 1918.

as long as the breathing of the CO_2 is continued there is a definite, though not very great, increase in the rate of respiration, which shows no tendency to diminish with the decreasing volume.



This and subsequent curves are read from left to right. Inspiration being the upstroke.

Fig. 1. Subject J. S. H.

(*a*) Breathing 3·28 p.c. CO_2. Time marker = 2 seconds,
(*b*) " 4·29 p.c. CO_2. Time marker = 2 seconds,
(*c*) " 4·29 p.c. CO_2. Time marker = 10 seconds.

Table I gives the numerical data deduced from the tracings.

TABLE I.

Subject / Mixture breathed		J. S. H. Air + 3·28 % CO_2			J. S. H. Air + 4·29 % CO_2			J. S. H. Air + 4·29 % CO_2			J. G. P. Air + 4·38 % CO_2		
	Time in succ. half mins.	Rate of resp. per min.	Vol. per resp. c.c.	Vol. per min. litres	Rate of resp. per min.	Vol. per resp. c.c.	Vol. per min. litres	Rate of resp. per min.	Vol. per resp. c.c.	Vol. per min. litres	Rate of resp. per min.	Vol. per resp. c.c.	Vol. per min. litres
Prelim. control period breathing air	—	—	—	—	—	—	—	18	563	10·12	15·5	344	5·34
	—	14	534	7·47	—	—	—	18	555	9·98	14	351	4·91
	—	14	543	7·60	15	523	7·85	18	550	9·90	15	398	5·97
	—	14	568	7·96	15·5	537	8·32	—	—	—	16·5	376	6·20
Period of experiment breathing mixture	1	14	559	7·83	15·5	510	7·90	19·5	682	13·30	14·5	463	6·71
	2	15	640	9·60	15	541	8·12	16	921	14·74	16	617	9·87
	3	14·5	747	10·84	16	684	10·95	21	983	20·66	17	767	13·04
	4	15·5	746	11·56	16	733	11·73	22	1003	22·03	18·5	879	16·26
	5	15·0	803	12·04	18	877	15·78	22	1229	27·06	19	648	12·31
	6	15	856	12·84	17	1024	17·41	23	1265	29·11	18	635	11·43
	7	15	850	12·75	17	1194	20·30	24	1288	30·91	18	628	11·30
	8	15·5	830	12·87	18	1153	20·77	23	1319	30·33	18	720	12·96
	9	—	—	—	19	1211	23·03	24	1386	33·27	17·5	608	10·64
	10	—	—	—	21	1238	26·01	24	1457	34·99	18·5	662	12·25
	11	—	—	—	—	—	—	25	1464	36·61	17·5	885	15·49
	12	—	—	—	—	—	—	24	1511	36·28	18	675	12·15
	13	—	—	—	—	—	—	24	1655	39·71	18	760	13·68
	14	—	—	—	—	—	—	23	1511	34·77	17	727	12·36
	15	—	—	—	—	—	—	24	1655	39·71	16	776	12·42
	16	—	—	—	—	—	—	22	1614	35·52	18	836	15·05
	17	—	—	—	—	—	—	23	1605	36·93	19·5	847	16·52
	18	—	—	—	—	—	—	24	1493	35·85	18	796	14·33
	19	—	—	—	—	—	—	24	1462	35·10	17·5	733	12·83
	20	—	—	—	—	—	—	24	1444	34·67	—	—	—
	21	—	—	—	—	—	—	25	1315	32·87	—	—	—
	22	—	—	—	—	—	—	24	1243	29·84	—	—	—
	23	—	—	—	—	—	—	25	1207	30·19	—	—	—
	24	—	—	—	—	—	—	24	1162	27·91	—	—	—
	25	—	—	—	—	—	—	24	1100	26·50	—	—	—
	26	—	—	—	—	—	—	24	1055	25·33	—	—	—
	27	—	—	—	—	—	—	25	970	24·26	—	—	—

So far we have only considered the effects of altering the CO_2 percentage of the air breathed. It next becomes of interest to study the effects, if any, of altering the proportion of oxygen in the inspired air.

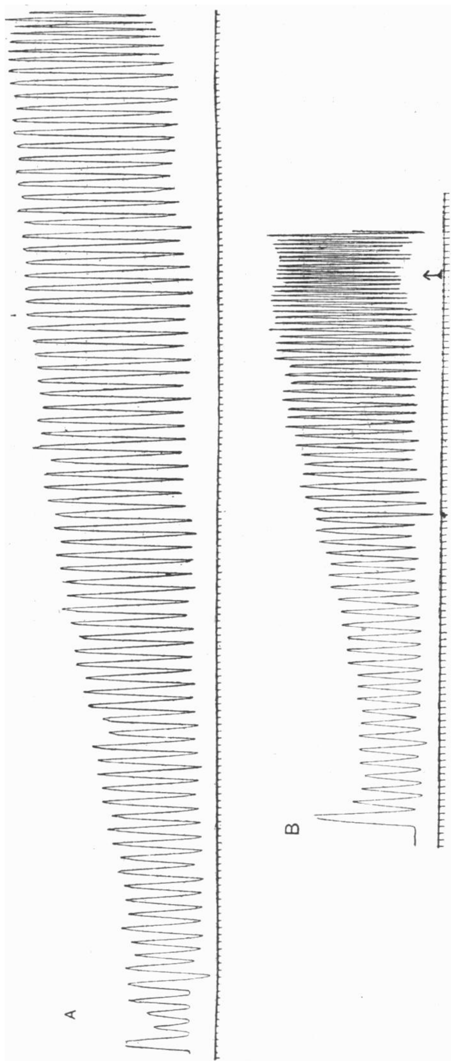


Fig. 2. Subject Cpl. M.

(*a*) Rebreathing—Concertina filled with oxygen—CO_2 accumulating,
(*b*) " " " air " "
Time marker = 2 seconds. Arrow shows point where lips were distinctly blue.

Fig. 2 shows the records of a subject rebreathing from the recording "concertina." Thus only about 4 litres of air were available and the rise of CO_2 percentage and the fall of oxygen percentage were rapid—with such a small volume of air the oxygen percentage falls more quickly

TABLE II.

Name		Initial mixture	Rates and volumes at successive half minutes														
Capt. F.	Rate per min.	Air	12	12	12	14	18	—	—	—	—	—	—	—	—	—	—
		Oxygen	12·5	10	10	12	12	14	14	17	17	—	—	—	—	—	—
	C.c. per resp.	Air	670	960	1150	1290	1610	—	—	—	—	—	—	—	—	—	—
		Oxygen	740	820	930	870	1000	1340	1310	1350	1700	—	—	—	—	—	—
	Litres per min.	Air	8·05	11·49	13·77	18·07	29·02	—	—	—	—	—	—	—	—	—	—
		Oxygen	9·21	8·23	9·26	10·46	12·04	18·74	18·34	22·99	28·89	—	—	—	—	—	—
Capt. McC.	Rate per min.	Air	10	14	16	22	28	32	—	—	—	—	—	—	—	—	—
		Oxygen	12	11	11	12	12	13	14	15	16	19	21	22	24	24	25
	C.c. per resp.	Air	1410	1370	1470	1850	2200	2790	—	—	—	—	—	—	—	—	—
		Oxygen	1170	1120	980	1180	1190	1510	1550	1510	1830	1850	1710	1990	2140	2380	2370
	Litres per min.	Air	14·13	19·23	23·43	40·7	61·7	89·4	—	—	—	—	—	—	—	—	—
		Oxygen	14·0	12·3	10·7	14·2	14·3	19·7	21·6	22·7	29·3	35·1	36·0	43·8	51·4	57·2	59·3
Corp. M.	Rate per min.	Air	16	17	18	23	29	48	—	—	—	—	—	—	—	—	—
		Oxygen	14	15	15	15	15	15	15	15	15	18	—	—	—	—	—
	C.c. per resp.	Air	1090	1440	1820	1930	2510	2240	—	—	—	—	—	—	—	—	—
		Oxygen	1260	1300	1830	1880	2490	2330	2880	2710	2990	2780	—	—	—	—	—
	Litres per min.	Air	17·4	25·2	32·8	44·4	72·7	107·7	—	—	—	—	—	—	—	—	—
		Oxygen	17·7	19·5	27·4	28·1	37·3	34·9	43·2	40·6	44·9	50·0	—	—	—	—	—
Capt. V.	Rate per min.	Air	20	22	20	23	29	—	—	—	—	—	—	—	—	—	—
		Oxygen	22	24	22	24	26	29	30	—	—	—	—	—	—	—	—
	C.c. per resp.	Air	560	870	1610	2560	3060	—	—	—	—	—	—	—	—	—	—
		Oxygen	690	750	1270	2070	2200	2390	2310	—	—	—	—	—	—	—	—
	Litres per min.	Air	11·3	19·2	32·2	58·9	88·6	—	—	—	—	—	—	—	—	—	—
		Oxygen	15·1	18·0	27·9	49·6	57·3	71·3	69·4	—	—	—	—	—	—	—	—
Capt. P.	Rate per min.	Air	28	29	32	—	—	—	—	—	—	—	—	—	—	—	—
		Oxygen	19·5	20·5	19·5	21·5	26	29	—	—	—	—	—	—	—	—	—
	C.c. per resp.	Air	920	2000	3210	—	—	—	—	—	—	—	—	—	—	—	—
		Oxygen	540	850	970	1490	1950	2730	—	—	—	—	—	—	—	—	—
	Litres per min.	Air	25·8	57·9	102·8	—	—	—	—	—	—	—	—	—	—	—	—
		Oxygen	10·6	17·5	19·0	32·1	50·8	79·2	—	—	—	—	—	—	—	—	—
J. S. H.	Rate per min.	Air	14	16	24	48	66	—	—	—	—	—	—	—	—	—	—
		Oxygen	14	14	16	18	20	25	30	—	—	—	—	—	—	—	—
	C.c. per resp.	Air	1000	1400	1850	1970	1980	—	—	—	—	—	—	—	—	—	—
		Oxygen	880	1220	1720	2210	2460	2680	2690	—	—	—	—	—	—	—	—
	Litres per min.	Air	14·0	22·3	44·4	94·3	130·7	—	—	—	—	—	—	—	—	—	—
		Oxygen	12·3	17·1	27·5	39·8	49·2	67·1	80·6	—	—	—	—	—	—	—	—

than the CO_2 percentage rises. The reason of this temporary inequality between the amount of oxygen used up and the amount of CO_2 given out is to be found in the fact that the body possesses very considerable storage capacity for CO_2 while it has practically none for oxygen.

Two series of records were taken with the concertina filled with (*a*) air, (*b*) oxygen at the start.

Table II gives the figures deduced from this and similar tracings.

They show (1) the effect of want of oxygen in lowering the threshold for CO_2, and (2) that on the whole the result of low oxygen percentage in the air inspired is to cause ultimately quickening of the rate and diminution of the depth of respiration.

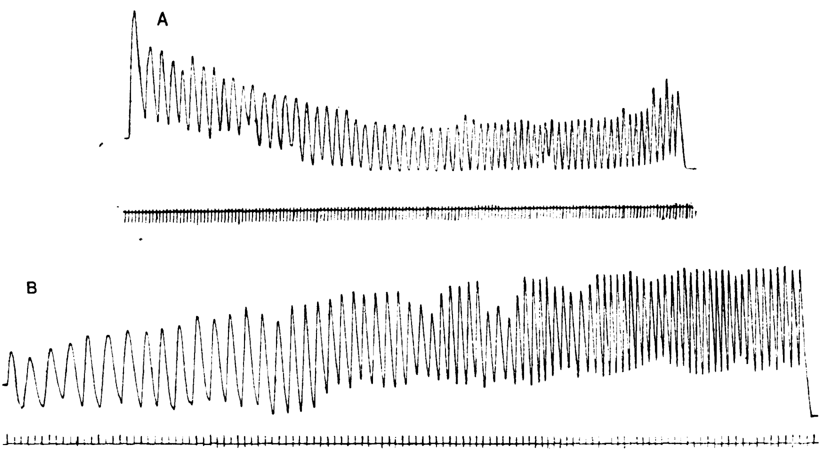


Fig. 3. Rebreathing through soda-lime from concertina. Time marker = 2 seconds. (*a*) Subject Cpl. M. (*b*) Subject J. S. H.

Records were obtained by breathing in and out of a large galvanised iron cylinder attached to a different recording apparatus. Tracings were taken (*a*) when the cylinder was filled with almost pure oxygen to start with; (*b*) when the cylinder was filled with air. In each case the breathing is affected by the gradually increasing proportion of CO_2 in the air inspired but in the one case the oxygen supply remains at least equal to ordinary air throughout the experiment while in the other case the oxygen percentage is continually decreasing below the normal. The fall however is not enough to produce any marked anoxæmia. On measuring up the tracings it is found that the effect of the diminishing oxygen percentage is to lower the threshold of the respiratory centre for CO_2, and consequently the depth of each respiration and the ventilation per minute increase more rapidly when the cylinder contains air than when it is filled with oxygen at the beginning of the experiment.

The measurements of the tracings are given in Table III.

TABLE III.

Time in successive 2 min. periods	Air: Rate per min.	Air: Vol. per resp. c.c.	Air: Vol. per min. litres	Oxygen: Rate per min.	Oxygen: Vol. per resp. c.c.	Oxygen: Vol. per min. litres
1st	13	1460	18·9	13	1540	19·6
2nd	14	1940	27·1	13	2090	29·2
3rd	14	2540	35·0	14	2310	32·9
4th	14	3100	43·3	16	2320	36·5
5th	14	4120	57·7	15	2810	42·2
	—	—	—	17	3610	60·2

Fig. 3 shows the tracings taken with two of the same subjects and the same apparatus as in the last experiment except that a soda lime purifier was inserted in the respiratory circuit. The result therefore was to obtain records of the effect of diminishing oxygen without any accumulation of CO_2.

Table IV gives the results of measuring these and similar tracings.

These results as compared with the CO_2 results, show that the effect of want of oxygen is to increase the rate of respiration rather than the depth, while CO_2 increases the depth rather than the rate. Some of them also show the production of periodic breathing at certain stages of the oxygen want.

Figs. 4 and 5 show tracings taken when breathing for a longer period from the recording "concertina" air containing a constant low percentage of oxygen.

Table V gives the numerical data corresponding to these and similar tracings.

These records differ remarkably from the records of the effect of increased CO_2. It will be seen that the first result of diminution in the oxygen percentage is increase in the depth of respiration owing to lowering of the threshold exciting value of CO_2[1]. There then comes a point at which the breathing becomes periodic. The subject of periodic breathing was fully investigated by Haldane and Douglas[2]. They proved that the essential cause of the periodicity is the much quicker action of want of oxygen as compared with that of increase of CO_2. Owing to the great solubility of CO_2 in the body fluids changes of amount of CO_2 only slowly produce effective changes of tension. The result of

[1] Haldane and Poulton. This *Journal*, **37**. p. 404. 1908.
[2] Haldane and Douglas. *Ibid.* **38**. p. 401. 1909.

TABLE IV.

Name		Rates and volumes in consecutive half minutes											
J. G. P.	Rate per min.	18	16	16	16	16	15	16	18	22	34	—	—
	Vol. per resp., c.c.	430	440	505	580	645	750	795	835	1195	1415	—	—
	Vol. per min., litres	8·0	7·0	8·0	9·5	10·5	11·5	12·5	15·0	26·5	48·0	—	—
Capt. F. I	Rate per min.	8	9	9	10	10	9	9	9	9	10	12	15
	Vol. per resp., c.c.	885	775	725	735	765	1015	715	875	685	940	1135	815
	Vol. per min., litres	7·0	7·0	6·5	7·5	7·5	9·0	6·5	8·0	6·0	9·5	13·5	12·5
Capt. F. II	Rate per min.	8	8	10	10	8	10	9	8	7	10	11	—
	Vol. per resp., c.c.	680	700	660	780	1080	585	865	1030	1010	590	790	—
	Vol. per min., litres	5·5	5·5	6·5	8·0	8·5	6·0	8·0	8·0	7·0	6·0	9·0	—
Capt. McC.	Rate per min.	11	9	9	9	7·5	8	12	—	—	—	—	—
	Vol. per resp., c.c.	960	1015	1250	985	1265	1510	1795	—	—	—	—	—
	Vol. per min., litres	10·5	9·0	11·5	9·0	9·5	12·0	21·5	—	—	—	—	—
Cpl. M. I	Rate per min.	12·5	13·75	13	12·5	13	14	13·5	13·5	15·5	15·5	—	—
	Vol. per resp., c.c.	1065	705	960	920	865	995	1060	1205	1335	1645	—	—
	Vol. per min., litres	13·5	10·5	12·5	11·5	11·0	14·0	14·5	16·5	20·5	25·5	—	—
Cpl. M. II	Rate per min.	10	10	10	10·5	11	10·5	13·5	16	15	16	—	—
	Vol. per resp., c.c.	1110	1025	870	1105	730	900	770	795	925	995	—	—
	Vol. per min., litres	11·0	10·0	8·5	11·5	8·0	9·5	10·5	12·5	14·0	16·0	—	—
J. S. H. I	Rate per min.	14	15	17	19·5	25·5	28	32	40	—	—	—	—
	Vol. per resp., c.c.	745	860	870	1020	945	995	990	905	—	—	—	—
	Vol. per min., litres	10·5	13·0	14·0	20·0	24·0	28·0	31·5	36·0	—	—	—	—
J. S. H. II	Rate per min.	15	16	17	21	26	29	36	—	—	—	—	—
	Vol. per resp., c.c.	680	730	625	795	795	795	890	—	—	—	—	—
	Vol. per min., litres	10·0	11·5	10·5	16·5	20·5	23·0	32·0	—	—	—	—	—
J. S. H. III	Rate per min.	11·5	12	14	18·5	22	25	29	31	—	—	—	—
	Vol. per resp., c.c.	1050	1405	1720	1575	1510	1740	1615	1780	—	—	—	—
	Vol. per min., litres	12·0	17·0	24·0	29·0	33·5	43·5	47·0	55·0	—	—	—	—

this is that the respiration can adapt itself to changes in the proportion of CO_2 in the air breathed without overshooting the mark. In the case

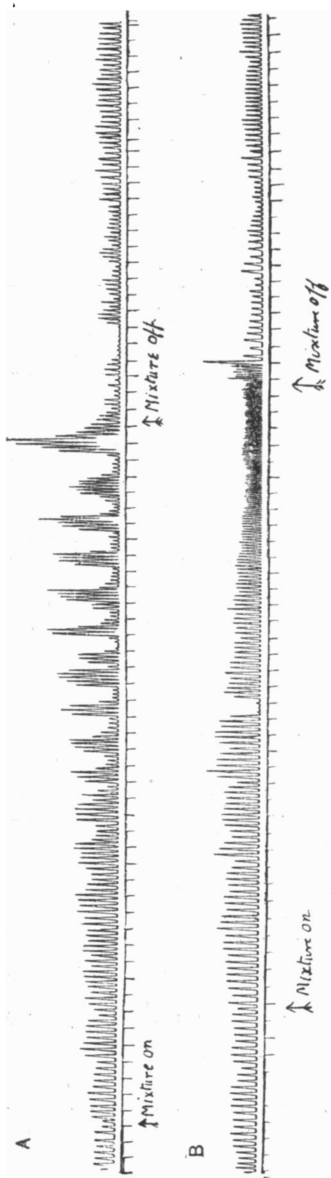


Fig. 4. Subject J. G. P. Time marker = 10 seconds.
(*a*) Breathing 10·33 p.c. oxygen, (*b*) Breathing 9·59 p.c. oxygen.

of oxygen however where the solubility is so much less, changes of tension occur with great rapidity after changes of amount and hence the local effect of want of oxygen on the respiratory centre is very rapid and the consequent result is periodicity of the breathing.

Where the proportion of oxygen is still further reduced this last

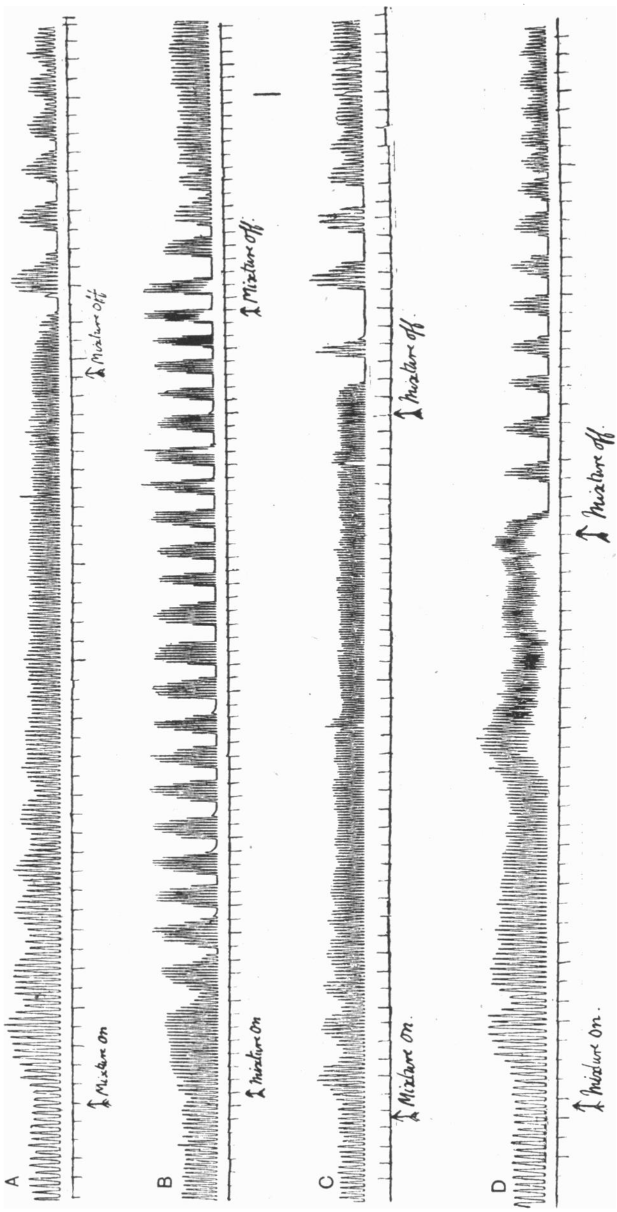


Fig. 5. Subject J. S. H. Time marker = 10 seconds. (*a*) Breathing 11·19 p.c. oxygen, (*b*) Breathing 11·05 p.c. oxygen + 0·7 p.c. CO_2, (*c*) Breathing 10·64 p.c. oxygen, (*d*) Breathing 9·84 p.c. oxygen.

TABLE V.

	J. S. H. 11·19 % O_2			J. S. H. 10·64 % O_2			J. S. H. 9·84 % O_2			J. G. P. 9·59 % O_2		
	Rate per resp. per min.	Vol. per resp. c.c.	Vol. per min. litres	Rate per resp. per min.	Vol. per resp. c.c.	Vol. per min. litres	Rate per resp. per min.	Vol. per resp. c.c.	Vol. per min. litres	Rate per resp. per min.	Vol. per resp. c.c.	Vol. per min. litres
Prelim. control	—	—	—	—	—	—	15	559	8·39	—	—	—
period breath-	16	496	7·94	20	465	9·30	17	599	10·18	15	420	6·30
ing air	18	514	9·25	21	452	9·45	16	568	9·09	15	407	6·11
	17	519	8·82	23	443	10·18	17·5	563	9·85	16	438	7·01
Period of experi-	16	653	10·45	23	626	14·40	18	877	15·79	15·5	541	8·39
ment breath-	18	839	15·09	27	604	16·30	20	881	17·62	16	644	10·30
ing mixture	20	693	13·86	29	563	16·33	26	863	22·44	16	555	8·88
	22	716	15·74	32	590	18·88	30	792	23·76	18	608	10·94
	23	648	14·91	35	541	18·94	36	680	24·48	18	689	12·40
	25	568	14·20	38	492	18·30	36	783	28·19	18	501	9·02
	26	563	14·65	40	510	20·40	42	653	27·43	20	546	10·92
	28	548	15·35	42	474	19·91	50	568	28·40	20	470	9·40
	30	523	15·70	44	425	19·80	52	528	27·46	26	443	11·52
	34	537	18·25	44	443	19·49	—	—	—	37	349	12·91
	35	496	17·37	43	447	19·22	—	—	—	54	282	15·23
	36	479	17·23	44	443	19·49	—	—	—	68	313	21·28
	38	465	17·67	45	465	20·93	—	—	—	—	—	—

effect is replaced by another. This is seen in the tracings which show that the periodicity of the breathing is succeeded by a very rapid, shallow type of respiration. The serious nature of this result will become apparent after consideration of the paper on the effects of shallow breathing, and it will be sufficient to mention here the main conclusion reached in that paper, which is that shallow breathing in itself is a cause of anoxæmia. Thus a very dangerous vicious circle tends to be set up. Want of oxygen in the inspired air causes shallow breathing, which in turn intensifies the anoxæmia.

In seeking for an explanation of this effect of want of oxygen one must bear in mind (1) the effect of fatigue, which will be discussed in a later paper, (2) the great sensitiveness of the tissues to want of oxygen. The body is unable to store oxygen to any appreciable extent and hence the effects of low oxygen percentage in the inspired air are immediately felt by the tissues and their functional activity is greatly impaired by any interference with the oxygen supply. The grave effects of interrupting the circulation for a short time through such an organ as the kidney are well known, and it appears probable that the quickening and shallowing of the respiration when low oxygen percentages are breathed is due to impairment of the vitality of the respiratory centre, which is unable to perform its function adequately when starved of oxygen.

The above description of the respiratory effects of want of oxygen applies to the results observed on the whole. There are however individual differences. In some subjects the lowering of the threshold for CO_2 and consequent hyperpnœa is a more conspicuous result than in others. In such cases the dangerous effects of want of oxygen will tend to be somewhat postponed owing to the increased efficiency of the lung ventilation and consequent efficient use of such oxygen as is present in the air breathed.

This fact would seem to afford an explanation of the much greater liability of some people than others to mountain sickness. Those who react to want of oxygen pre-eminently by shallow breathing will be more seriously affected under conditions of lowered barometric pressure than those whose reaction involves a great alteration of CO_2 threshold.

Finally the tracings also show well the onset of periodic breathing when normal air is substituted for the low oxygen mixture breathed. The explanation of this phenomenon is evidently that given by Haldane and Douglas for Cheyne-Stokes breathing after forced breathing.

We wish to acknowledge the assistance we have received from the Medical Research Committee.

SUMMARY.

1. The respiratory response to anoxæmia is in three stages.

(*a*) Increased depth of respiration, and increased ventilation per minute owing to lowered CO_2 threshold.

(*b*) Periodic breathing unless the anoxæmia is considerable.

(*c*) Frequent and correspondingly shallow breathing.

2. Excess of CO_2 (increased hydrogen ion concentration) causes a considerable and persistent increase in depth of respiration and relatively slight increase in frequency. This response is in marked contrast to the response to want of oxygen.

3. The maximum increase in lung ventilation is obtained when excess of CO_2 and anoxæmia are both present.