FURTHER OBSERVATIONS ON OXYGEN ACCLIMATISATION.

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MOST previous observations on animals under altered O_2-pressures in the air have been of comparatively short duration. In a recent paper (1) some observations dealing with prolonged exposures of rabbits to increased and to decreased O_2-pressure in the inspired air were considered. In the present paper, this research has been extended, employing monkeys, cats, cavies, mice and rats in addition to rabbits.

Technique. Most of the details of technique will be found in the paper (1) mentioned above; here we refer briefly to certain modifications. Nine experiments (see Table I) were performed, employing three different chambers. One of them, called "ordinary small" in Table I, was the same as that used in the previous research and had a capacity of about 169 litres; another termed "ordinary large" was on the same principle, but about four times as large. In both these chambers all the experiments (Nos. 1 to 8) were carried out under normal barometric pressure. In the remaining experiment, No. 9, a cylindrical decompression chamber about 6 ft. in height and 4 ft. in diameter was used at the premises of Messrs Siebe Gorman, Marine Engineers, London; in this experiment the barometric pressure was lowered by gradual stages to about 260 mm. Hg, equivalent to an altitude of 30,000 ft., and a group of 30 animals—6 rabbits, 6 rats, 6 cavies and 12 mice—were exposed day and night to these changes for a total period of 33 days. The animals were enclosed in their usual cages which were placed in the decompression chamber. For purposes of feeding the animals and cleaning the cages, this chamber had to be opened about every 4 days, but the necessary manipulations were carried out rapidly so that the animals were exposed to ordinary air for a total period of about 300 minutes only of the whole 33 days; during the last 7 days under barometric pressure 260 mm. Hg the chamber was not opened at all because the animals did not require fresh food, as they had lost their appetites and had not eaten the food last supplied to them. The same principle for feeding and cleaning was followed in all experiments with rabbits, rats, cavies and mice. In the case of cats and monkeys, the chambers had to be opened more frequently, that is, every 2 days instead of every 4 days; by having two sets of trays, cages etc., these manipulations required only a short time, in fact a couple of minutes; if samples of blood etc. had to be taken from the animals, an extra 5 or 10 minutes' time was expended.

TABLE I. Outline of Experiments.

Exp. ref. No.	Chamber used	Animals employed	Barometer mm. Hg	Av. O_2-pressure in inspired air mm. Hg	Av. O_2-pressure in inspired air p.c.	Approx. altitude corresponding to O_2-pressure ft.	Duration days
1	Ordinary small	2 cavies, Nos. I and II	745	141	20·1	Sea-level	8
			745	330	47·1	—	24
			745	433	61·9	—	33
			745	141	20·1	Sea-level	14
2	Ordinary small	1 cat, No. II	745	140	20·0	Sea-level	7
			745	287	41·0	—	16
3	Ordinary large	3 cats, Nos. I, II and III	745	326	46·6	—	11
		3 cats, Nos. I, III and IV	745	376	53·7	—	7
			745	140	20·0	Sea-level	24
4	Ordinary small	6 rats and 6 mice	745	140	20·0	Sea-level	10
			745	297	42·4	—	14
			745	424	60·6	—	21
5	Ordinary large	2 monkeys, Nos. I and II	745	138	19·7	Sea-level	6
			745	311	44·4	—	18
			745	371	53·0	—	11
			745	140	20·0	Sea-level	14
6	Ordinary small	2 cavies, Nos. I and II	745	82	11·7	15,000	10
			745	72	10·3	20,000	7
			745	67	9·5	22,500	7
7	Ordinary large	3 cats, Nos. I, III and IV	745	141	20·1	Sea-level	6
			745	86	12·3	15,000	14
			745	64	9·1	25,000	15
8	Ordinary large	1 monkey, No. II	745	137	19·6	Sea-level	4
			745	95	13·6	13,000	12
			745	76	10·9	18,000	7
			745	70	10·0	20,000	6
			745	147	21·0	Sea-level	20
9	Decompression	6 rabbits, 6 rats, 6 cavies, 12 mice	600	116	16·6	7,000	3
			440	85	12·1	15,000	7
			400	77	11·0	18,000	1
			375	72	10·3	20,000	6
			320	62	8·8	25,000	7
			290	56	8·0	27,500	1
			260	50	7·1	30,000	8

The temperature inside the chambers was kept about 15–20° C. They were well lighted with electric light or daylight by means of large windows of glass and the animals could thus be kept under observation.

In all cases the animals were enclosed in the cages to which they had been accustomed in the laboratory. As they had lived for considerable periods in these cages before the experiments commenced, the experiments did not involve any sudden diminution of space for movement. The monkeys (*Macacus rhesus*) about 2 kilos in weight had plenty of room to climb about in their cage which measured 67 cm. × 61 cm. × 61 cm. In two of the experiments, Nos. 3 and 7, three cats were placed in their separate cages in the large chamber, so that they could see one another and had the company of one another; they slept most of the time and when awake, took an interest in what was going on in the laboratory, which they could see through the glass window.

For food, monkeys received bananas, apples, oranges, lemons, potatoes, green stuff, tinned milk, biscuits (Spratts), nuts and cod-liver oil; cats received raw and cooked meat, boiled fish and fresh milk; rabbits received hay, oats and cabbage; rats were given oats, barley, bread and milk, and green stuff; mice received much the same as the rats; cavies had bran, grain, hay and greenstuff. A very liberal supply of water was placed in all the cages and chambers to prevent dryness; the bedding was kept clean by use of a large amount of sawdust as in the previous research (1).

In five of the experiments, No. 1 to 5, the animals were exposed to increased O_2-pressure in the air, the maximum amounting to about 200 p.c. above normal; in the other four experiments the animals—in some cases the same individuals as used for high O_2-experiments—were exposed to lowered O_2-pressure in the air, the minimum being about 60 p.c. below normal. The general outline of the experiments is given in Table I; to take an example, in Exp. No. 1 two cavies were exposed in the ordinary small chamber at normal barometric pressure, to 140 mm. Hg of O_2 in the inspired air—that is about normal O_2-pressure —for 8 days; then for the next 24 days they were exposed to increased pressure of O_2 at a level averaging about 330 mm. Hg; this was immediately followed by 33 days exposure to O_2 at 433 mm. Hg, whilst for the last 14 days in the chamber the animals were again under almost normal O_2-pressure for the purpose of control results. Exp. No. 3 followed immediately after Exp. No. 2 without any break, the change involving increase in the number of cats used and also increase in the size of the chamber employed.

Frequent analyses of the air in the decompression chamber and daily analyses of the air in the ordinary chambers were made, the same precautions being observed as in the previous research(1); O_2-consumption, blood changes and tissue CO_2- and O_2-tensions were estimated by the same methods described in the paper referred to. Blood samples were taken from an ear vein in all animals except rats and mice when a tail vein was used.

Effects of altered O_2-pressure in the air upon blood. The increase of Hb p.c. and of red cells which normally occurs on exposure to lowered O_2-pressure in the air was observed in all my animals except cats Nos. III and IV (see Table II and Fig. 1). We are concerned here chiefly with the new results with the opposite condition namely increase of O_2-pressure; I found previously(1) in rabbits a marked decrease of Hb p.c. and of red cells under increased O_2-pressure and Bornstein(2) obtained somewhat similar results in a monkey and some dogs in the Elbe tunnel under increased barometric pressure (+ 2 atmospheres). The present experiments (see Table III and Fig. 1) established the general truth of the statement that Hb p.c. and red cells are decreased

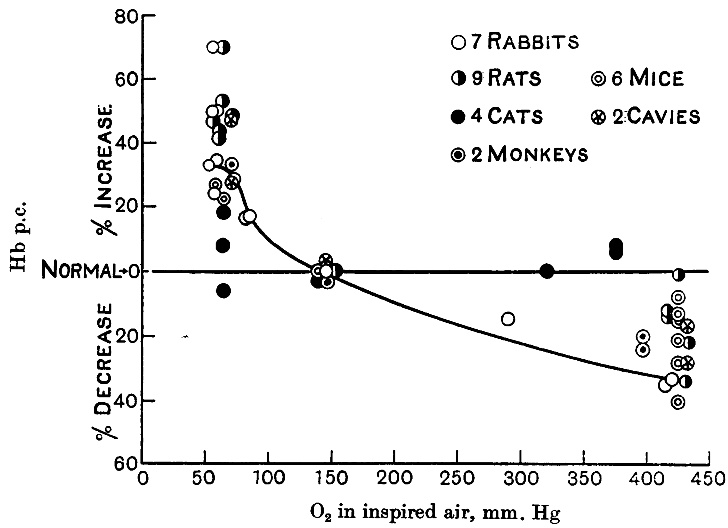

Fig. 1. Relations between Hb p.c. and O_2-pressure in the inspired air during prolonged exposures. The curve is drawn through points taken from one and the same animal, Rabbit No. 2 (1).

by increased O_2-pressure in the air; it will be seen that this was so for rats mice, monkeys, and cavies as well as rabbits; cats were the only

TABLE II. Average figures for blood changes under decreased O_2-pressure.

Exp. ref. No.	Animals	Red cells mills. p.c. mm. Normal	Under low O_2	Hb p.c. Normal	Under low O_2	Colour index Normal	Under low O_2	Reticulated red cells; per thousand red cells Normal	Under low O_2	White cells; thousands p.c. mm. Normal	Under low O_2
9	5 rabbits	4·9	9·3	76	110	1·00	0·76	25	57	9·6	9·0
	6 rats	7·8	13·2	92	138	1·00	0·88	26	62	14·6	17·4
	2 mice	9·2	13·7	96	120	1·00	0·84	12	65	10·5	13·0
8	1 monkey, No. II	5·5	8·0	75	100	1·00	0·91	15	35	14·0	12·2
6	Cavy No. I	7·5	9·0	100	127	1·00	1·06	20	60	9·0	12·5
	,, No. II	6·0	8·5	90	132	1·00	1·03	22	50	12·0	12·0
*	1 rabbit, No. II	5·5	9·5	90	120	1·00	0·77	—	—	7·2	10·2
	Averages	6·6	10·1	88	121	1·00	0·89	20	55	10·9	12·3
7	Cat No. I	8·7	11·5	85	100	1·00	0·88	—	—	10·7	18·0
	,, No. III	7·5	8·0	80	87	1·00	1·02	—	—	16·0	15·0
	,, No. IV	7·5	8·0	85	80	1·00	0·89	—	—	14·0	18·0
	Averages	7·9	9·2	83	89	1·00	0·92	—	—	13·6	17·0

* Previous result; see reference (1).

TABLE III. Average figures for blood changes under increased O_2-pressure.

Exp. ref. No.	Animals	Red cells mills. p.c. mm. Normal	Under high O_2	Hb p.c. Normal	Under high O_2	Colour index Normal	Under high O_2	Reticulated red cells; per thousand red cells Normal	Under high O_2	White cells; thousands p.c. mm. Normal	Under high O_2
1	Cavy No. I	7·5	4·2	100	72	1·00	1·28	20	10	9·0	12·0
	,, No. II	6·0	4·5	90	75	1·00	1·11	22	10	12·0	12·0
5	Monkey No. I	5·9	4·4	72	58	1·00	1·07	10	5	10·9	10·3
	,, No. II	5·5	3·8	75	57	1·00	1·10	15	5	12·2	14·0
4	6 rats	8·2	6·7	97	82	1·00	1·03	23	17	17·3	15·6
	6 mice	9·7	7·1	94	74	1·00	1·07	27	29	12·2	17·7
*	2 rabbits	5·7	3·0	87	57	1·00	1·25	—	—	8·6	10·0
	Averages	6·9	4·8	88	68	1·00	1·13	19	11	11·7	13·1
2, 3	Cat No. I	8·7	8·5	85	90	1·00	1·09	—	—	10·7	12·5
	,, No. II	7·0	7·5	82	85	1·00	0·96	—	—	9·5	20·0
	,, No. III	7·5	9·0	80	87	1·00	0·90	—	—	16·0	25·0
	Averages	7·7	8·3	82	87	1·00	0·98	—	—	12·1	19·2

* Previous results; see reference (1).

animals tested which failed completely to follow the general rule although there were one or two exceptions also amongst the rats and mice (see Fig. 1).

Some of the rats and rabbits showed striking increases (70 p.c. and more) of Hb and of red cells under low O_2-pressure whilst some of the mice, rats and rabbits exhibited marked decreases (40 p.c.) under high O_2-pressure (see Fig. 1); it was possible by alteration of O_2-pressure in the air to produce nearly three-fold variations in the Hb p.c. and red cells.

The changes I observed, both under low and high O_2-pressure, were produced gradually and passed off again gradually on return to normal O_2-pressure, several weeks being required as shown previously for rabbits(1); this seemed to exclude simple changes in concentration of blood or in storage of red cells. Again Barcroft(3) and others(4) have shown that the reticulated red cells are markedly increased by low O_2-pressures which is regarded as evidence of new red cell formation. I obtained a similar increase in the reticulated red cells (see Table II). Moreover, under high O_2-pressure I observed the opposite change, namely a decrease in reticulated red cells (see Table III) in all animals tested except mice. It is possible also that there was an increase in rate of destruction of red cells under high O_2-pressure. Muir and Dunn(5) showed that in hæmolytic anæmia where there was a rapid destruction of red cells, there was a marked increase in iron content of the liver, spleen and kidney. Boycott and Douglas(6) showed that this was observed only in the spleen when the rate of destruction of red cells was slower. I carried out a series of tests with five animals (rats and mice) which had been exposed to high O_2-pressure, using a set of normal rats and mice as controls; I found with the Prussian blue reaction and also by microscopic examination—for remnants of Hb pigment —a greater content of pigmented material in the spleens of the experimental animals than in those of the controls.

Some of the changes in colour index were interesting. There was an increase of 25 p.c. in colour index of some rabbits and a cavy (see Table III) under high O_2-pressure and a decrease of colour index of about 24 p.c. under low O_2-pressure (see Table II). Change in colour index indicates of course a change in the Hb-content of each red cell. It was unlikely that a change in value of Hb-content from 0·75 to 1·25 was produced merely by change in concentration of blood.

As in the previous research(1) I found no connection whatever between changes in Hb p.c. and changes in body weight.

It has been stated above that the increase of Hb p.c. under low O_2-pressure passed off in a few weeks after return to normal O_2-pressure, so that any increase of Hb produced by residence at a high altitude soon loses, after a few weeks residence at sea-level, any advantage it may have offered.

The leucocyte counts did not show any constant changes (see Tables

II and III); under low O_2-pressure cats Nos. I and IV and under high O_2-pressure the mice and cats II and III exhibited marked increases in the number of white cells of the blood; there was no evidence of infection and no rise of body temperature to explain these increases.

The differential counts for leucocytes under low O_2-pressure (see Table IV) gave an increase in polymorphonuclear leucocytes as was observed before(1); under high O_2-pressure no great change was observed (see Table V) except in cats II and III where there was the polymorphonuclear leucocytosis mentioned above.

TABLE IV. Average differential counts for leucocytes under decreased O_2-pressure.

		Normal				Under low O_2			
Exp. ref. No.	Animals	Poly-morphs	Small lympho-cytes	Large lympho-cytes	Mono-nuclears	Poly-morphs	Small lympho-cytes	Large lympho-cytes	Mono-nuclears
9	5 rabbits	32	32	23	13	57	32	6	5
	6 rats	17	51	23	9	27	39	26	8
	2 mice	18	33	37	12	28	46	19	7
8	1 monkey, No. II	39	35	14	12	75	12	9	4
6	2 cavies	22	45	28	5	30	43	15	12
7	3 cats	40	38	17	5	60	23	10	7

TABLE V. Average differential counts for leucocytes under increased O_2-pressure.

		Normal				Under high O_2			
Exp. ref. No.	Animals	Poly-morphs	Small lympho-cytes	Large lympho-cytes	Mono-nuclears	Poly-morphs	Small lympho-cytes	Large lympho-cytes	Mono-nuclears
1	2 cavies	26	33	32	9	27	43	24	6
5	2 monkeys	36	29	24	11	27	51	16	6
4	6 rats	25	62	10	3	23	57	10	10
	6 mice	23	59	12	6	18	62	15	5
*	2 rabbits	23	66	5	6	15	69	6	10
2, 3	3 cats	60	27	8	5	81	7	4	8

* Previous results; see reference (1).

Effects of altered O_2-pressure upon tissue O_2- and CO_2-tensions. The tissue O_2- and CO_2-tensions were estimated as before(1) by injection of N_2 under the skin and into the abdominal cavity and estimating the CO_2- and O_2-tensions in this gas after constancy was established. Cats and monkeys were employed to compare with the previous experiments(1) with rabbits. The monkeys were rather small and only small quantities, 100 c.c., of N_2 were injected. Under high O_2-pressure as noted previously the gas was absorbed very rapidly so that frequent injections were made. It has been found that if an animal be injected with N_2 in the evening, samples may be withdrawn the next day for experiments provided that previously the animals had several small daily injections for about a week to enable the tissues to become accustomed to the presence of the gas.

In Figs. 2 and 3 the results for O_2-tensions have been plotted to

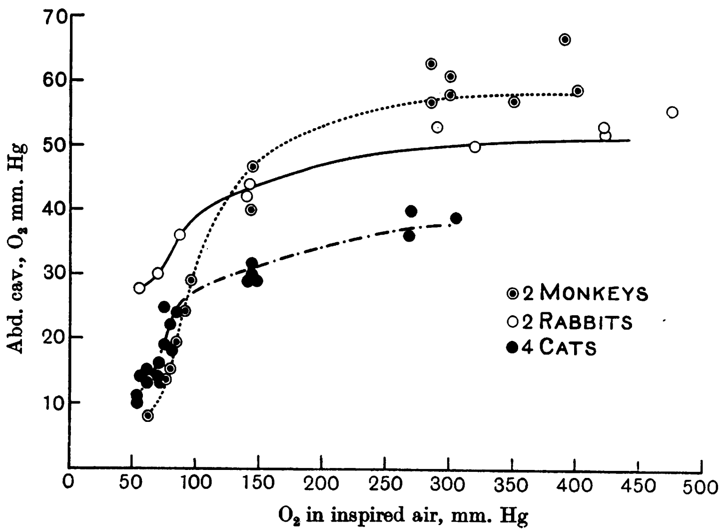

Fig. 2. Relations between O_2-tensions in the abdominal cavity and O_2-pressure in the inspired air during prolonged exposures.

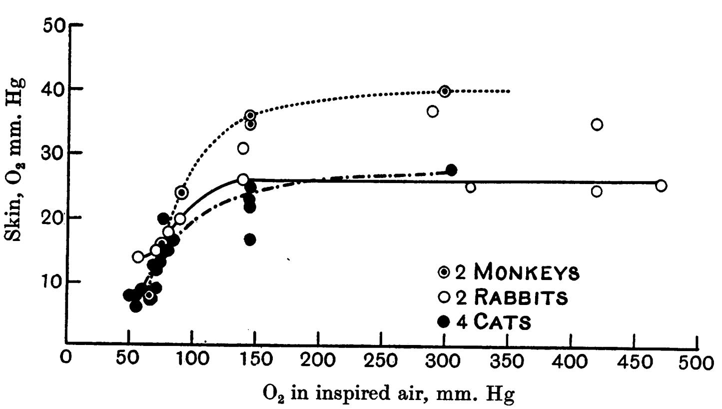

Fig. 3. Relations between O_2-tensions under the skin and O_2-pressure in the inspired air during prolonged exposures.

show their relationships with O_2-pressure in the air. Fuller details are given in Tables VI and VII.

TABLE VI. Tissue gas tensions under decreased O_2-pressure.

Exp. ref. No.	Animal	No. of days since beginning of exposure to low O_2	O_2-pressure in inspired air mm. Hg	CO_2-tensions in tissues mm. Hg		O_2-tensions in tissues mm. Hg	
				Skin	Abd. cav.	Skin	Abd. cav.
7	Cat, No. I	—	146	46	46	23	32
		14	84	37	36	17	24
		6	78	34	31	15	22
		2	75	35	32	15	19
		27	68	31	29	9	16
		22	60	27	25	9	15
		29	56	28	27	6	10
		17	54	23	23	8	12
7	Cat, No. III	—	146	42	43	25	30
		7	75	27	26	20	25
		23	68	28	28	13	14
		20	52	22	22	8	13
7	Cat, No. IV	—	146	46	42	17	29
		8	76	31	28	13	19
		24	68	29	29	13	14
		16	62	27	27	8	13
8	Monkey, No. II	—	140	39	42	37	40
		7	97	—	38	—	29
		9	91	38	40	24	24
		23	84	—	37	—	19
		5	78	32	37	15	15
		18	74	—	35	—	15
		14	73	—	33	—	14
		16	63	30	33	8	8

Table VII. Tissue gas tensions under increased O_2-pressure.

Exp. ref. No.	Animal	No. of days since beginning of exposure to high O_2	O_2-pressure in inspired air mm. Hg	CO_2-tensions in tissues mm. Hg		O_2-tensions in tissues mm. Hg	
				Skin	Abd. cav.	Skin	Abd. cav.
2	Cat, No. II	—	146	46	46	23	29
		2	274	46	48	21	36
		4	306	46	48	28	39
		8	269	42	41	35	40
5	Monkey, No. I	—	145	47	43	35	47
		18	300	—	43	—	63
		25	400	—	46	—	67
		29	300	—	47	—	61
5	Monkey, No. II	—	145	50	39	37	38
		4	301	48	—	40	—
		17	300	—	46	—	59
		25	400	—	55	—	59
		26	348	—	56	—	57

The chief results with rabbits Nos. II and III of the previous research are shown in Figs. 2 and 3 for purposes of comparison. It will be observed that with all animals the O_2-tensions in the tissues increased as the O_2-pressure in the air increased; the curves for the different types of animals showed on the whole a resemblance in shape but those for the abdominal cavity (Fig. 2) were rather more separated from one another than those for the skin (Fig. 3). Monkeys and rabbits had normally—that is when breathing O_2 at about 140–150 mm. Hg—higher O_2-tensions in the tissues than cats as was shown previously (7).

The shape of the curves depended in the main on the O_2-dissociation curve for blood. The points for the rabbit at very low O_2-pressures exhibited a striking difference from those for the cats and the monkey, the former occupying a much higher level than the latter. Thus under O_2-pressure in the air about 50–60 mm. Hg, the O_2-tensions in the abdominal cavity of the rabbit were about 28–30 mm. Hg (Fig. 2), whilst those for the monkey and the cats were about 8–10 mm. Hg; the O_2-tensions under the skin (Fig. 3) showed similar but less marked differences. The cats and the monkey were much weakened and very drowsy, whilst the rabbit seemed very much better; the heart was obviously much less affected in the rabbit than in the other animals and circulation was maintained better.

Another feature of importance was that the points followed the curves quite independently of the duration of exposure to altered O_2-pressure (Tables VI and VII). The O_2-tensions in the tissues were not brought back to normal level by prolonging the exposure, in other words by acclimatisation; if this had been so the relationships, at least for rabbit No. II which acclimatised well (Figs. 2 and 3), should be represented by almost straight lines and not by curves. My experiments proved that acclimatisation to low O_2-pressure was not due to improvement in O_2-tensions in the tissues but to the fact that the tissues became accustomed to the low O_2-tensions surrounding them. Rapid acclimatisation is due evidently to the fact that the vital organs, particularly the heart, can tolerate low O_2-tension. Similarly under high O_2-pressure in the air, the O_2-tensions (Fig. 2) were not reduced to normal by prolonging the exposure and acclimatisation to high O_2-pressure is due to the tissues becoming accustomed to the high O_2-tensions in their immediate environment.

The CO_2-tensions in the tissues on the whole increased as the O_2-pressure in the air increased (Fig. 4, Tables VI and VII). The points, for both CO_2-tensions under the skin and in the abdominal cavity, for all animals were fairly close together. The CO_2-tensions in the case of the monkey did not fall to such a striking degree under low O_2-pressure

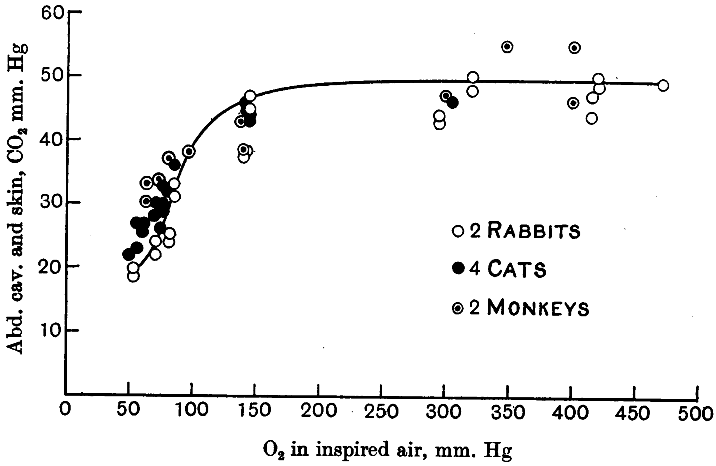

Fig. 4. Relations between CO_2-tensions in the tissues and O_2-pressure in the inspired air during prolonged exposures. The curve is drawn through points taken from Rabbit No. 2 (1).

as did those for cats and rabbits; this agrees with the fact that in some men low O_2-pressure does not depress the alveolar CO_2-tension to the same extent as in others (8).

Since the values for CO_2-tensions in the tissues were much the same in the cats and rabbits, CO_2-tensions—and therefore breathing—did not play the chief part in acclimatisation because the rabbits acclimatised well and the cats did not acclimatise at all.

Acclimatisation to low O_2-pressure. No great difference was observed in the behaviour of the animals under low O_2-pressure produced by decompression and low O_2-pressure produced by presence of a large quantity of N_2. Rarefied air did not possess any advantage as is sometimes suggested.

Perhaps the simplest indication of acclimatisation is the possession of normal appetite, capable of maintaining normal weight and normal O_2-consumption. Table VIII shows the changes in weights and metabolism. There was a distinct loss of weight in all experiments under low O_2-pressure, indicating that the animals were not fully acclimatised to the lowest pressures of O_2 tested. The loss of weight was underestimated in some cases because the animals were young and growing; young animals were used since they are stated to acclimatise better than older animals. The O_2-consumption was not quite so good a guide as the weight; it was estimated over practically the whole period of the experiment but was not for basal conditions since it included effects of feeding and movement. The figures were most useful and important

TABLE VIII. Average figures for metabolism and weight under decreased O_2-pressure.

Exp. ref. No.	Animals	Duration of exposure to low O_2 days	O_2-consumed c.c. per min. per animal: Normal	Under low O_2	Alteration p.c.	Weight per animal gm.: Normal	Under low O_2	Alteration p.c.
9	5 rabbits	33	—	—	—	2486	1864	-25·0
	6 rats	33	—	—	—	131	104	-20·6
	2 mice	33	—	—	—	21	16	-23·8
8	1 monkey, No. II	25	24·3	18·5	-23·9	1720	1430	-16·8
6	2 cavies	24	13·7	9·5	-30·6	827	685	-17·1
9	6 cavies	17	—	—	—	304	260	-14·0
*	1 rabbit	43	28·5	27·1	- 4·8	2750	2400	-12·7
7	Cat No. I	29	21·9	14·2	-35·1	2710	1670	-38·3
	„ No. III	22				2730	1480	-45·7
	„ No. IV	28				2200	1120	-49·1

* Previous results; see reference (1).

since they fully confirmed the changes in weight; the animals did not appear to change their habits of feeding and movement to any degree from time to time. Where there was a loss of weight under altered O_2-pressure, the experiment was continued in the chamber under normal O_2-pressure to prove that living in the chamber was not responsible for this loss of weight; under normal O_2-pressure the fall of weight soon ceased and there was a gradual return to normal appetite and weight whilst still in the chamber. There was no evidence that animals accustomed to laboratory life were affected adversely by mere enclosure in the chambers used and for the durations tested.

Although it was proved that none of the animals became acclimatised to O_2-pressure about 50 mm. Hg, that is equivalent to the O_2-pressure at the top of Mount Everest, nevertheless 5 rabbits, 6 rats and 2 mice, after a certain degree of training, survived 7 days' continuous exposure to 50 mm. Hg pressure of O_2 (see Exp. 9, Table I). It was obvious then that some mammals can exist for at least a week under O_2-pressure similar to that on Mount Everest; the animals had lost their appetites and were deteriorating rapidly although the rats and mice exhibited activity at infrequent intervals, climbing about their cages. The rate of breathing was increased slightly, in some cases about 30 p.c., but there was no obvious respiratory distress. The survivors certainly looked more vigorous and capable of movement than did similar animals which were exposed suddenly to low O_2-pressure at about 50 mm. Hg for 6 hours, without any previous training. In this sudden decompression, the animals were exceedingly weak and drowsy exhibiting marked hyperpnœa, yet all except one survived the 6 hours test; 2 cats, 2 finches, 5 rabbits, 6 rats, 6 cavies, and 12 mice constituted the survivors, 1 rabbit dying.

It was observed in the prolonged experiments that some rabbits, rats and mice maintained their appetites and weights at 70 mm. Hg pressure of O_2 (20,000 ft.) and seemed to have become acclimatised to that pressure; but the cats and the monkey lost their appetites completely before this level and could not tolerate such a low pressure of O_2, losing weight rapidly; cavies also fared badly. Dr J. S. Haldane informed me that cats cannot live even on Pike's Peak (14,000 ft.).

We have already seen (Figs. 2 and 3) that the O_2-tensions in the tissues of the monkey and the cats were much lower than those of the rabbit No. II, during the exposure to very low O_2-pressure in the air and it is considered that heart failure in the monkey and cats was responsible. The differences between the animals existed from the first days of exposure and were not at all dependent on the length of time of exposure. These differences were not connected in any way with the powers to increase Hb; thus rabbit No. II (1) and monkey No. II exhibited similar increases (about 33 p.c.) in Hb p.c. after several weeks' exposure to low O_2-pressure yet rabbit No. II tolerated the change better than any other animal tested whilst monkey No. II was the least able to withstand it, exhibiting great weakness.

As was proved before with rabbits (1) increase of Hb p.c., when it did occur, produced no improvement in tissue O_2-tension under low O_2-pressure in the air. Thus cat No. I showed an increase of nearly 20 p.c. in Hb p.c. and of 32 p.c. in red cells whilst cats Nos. III and IV showed much smaller changes, yet in all three cats the changes in tissue O_2-tensions were much the same under very low O_2-pressure (see Table VI). What then was the value of the increase in Hb p.c.? Obviously it allowed the blood to carry more O_2 per c.c. and this in itself would relieve the vital organs, heart, etc., in their efforts to supply the necessary O_2; cat No. I was definitely more resistant than cats Nos. III and IV. It was obvious that the absolute value of O_2-tension in the tissues did not decide the issue since all three cats had the same O_2-tensions in the tissues (see Table VI). It is suggested that the deciding factor was the ability of the heart of cat No. I to continue to function under the low O_2-pressure; undoubtedly in this case the extra Hb was of value.

Haldane(9) pointed out some years ago that acclimatisation often occurs rapidly and long before there is any change either in Hb or in certain other factors often credited with much importance. Somervell(10) found that some native porters with low values of Hb p.c. were more efficient at high altitudes than European members of the expedition with much higher Hb p.c. Again if we take loss of weight as an indicator of the powers of acclimatisation to low O_2-pressure we shall see that changes in Hb p.c. had no connection with acclimatisation; thus in six rabbits the losses of weight in percentages were 13, 14, 19, 30, 30 and 32 respectively whilst the percentage increases in Hb p.c. were 33, 22, 50, 50, 34 and 71 respectively. All the evidence thus suggests that increase of Hb p.c. is merely a consequence or symptom connected with prolonged exposure to low O_2-pressure and although of value was not the factor invariably controlling acclimatisation.

Barcroft(11) has reviewed the evidence regarding the adverse effects of low O_2-pressure upon the efficiency of the heart. That the heart was the chief organ concerned in the power of the body to tolerate very low O_2-pressure in my experiments was evident from post-mortem examination of the organs of 2 cats, 1 rabbit, 7 cavies and 5 mice. Nerve cells were but little changed from normal. The heart in all cases showed definite evidence of failure, being dilated, flabby and exhibiting in varying degree a degeneration similar to the fatty change described for cavies by Rosin(12). Degenerative and necrotic changes in the liver and kidney indicated lessened circulation due to heart failure, as did the general state of marked congestion of the organs. Why the heart in some animals was more efficient under low O_2-pressure was not obvious; none of the present theories of acclimatisation solved the problem; some inherent quality of the muscle fibre must be searched for.

An interesting change was observed perhaps indicating a physiological adaptation; the tunica muscularis of the branches of the pulmonary artery were markedly hypertrophied (see Fig. 5) in the cats; also the plain muscle fibre in the interalveolar septa was greatly increased. The condition was not observed in normal cats but it was noted in a cat suffering from O_2-deficiency due to broncho-pneumonia. It is possible that the change represented an adaptation to increased pressure in the pulmonary circulation due to inefficiency of the left ventricle, or perhaps the increase of muscular tissue aided the onward flow of blood through the lungs by rhythmical contraction. Whatever the explanation it was evident that tissue reproduction could occur at very low O_2-tensions.

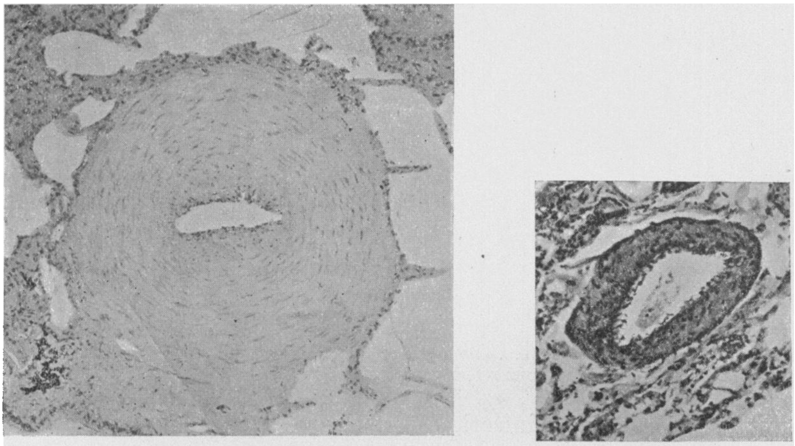

Fig. 5 A. Fig. 5 B.

Fig. 5. (A) Transverse section of branch of pulmonary artery of cat No. III showing hypertrophy of tunica muscularis, after exposure to low O_2-pressure. H. and E. $\times 125$.

(B) Transverse section of similar artery from a normal cat. H. and E. $\times 125$.

Acclimatisation to increased O_2-pressure. Lorraine Smith[13] and others[14] have proved that animals die from a type of pneumonia if suddenly exposed for any length of time to O_2-pressure at or above 490 mm. Hg (70 p.c. of an atmosphere). I[1] found that rabbits survived very prolonged exposures to somewhat lower pressures, namely 420 mm. Hg (60 p.c. of an atmosphere). About the same time Barach[15] obtained similar results with rabbits. In the present experiments it was proved that monkeys, cavies, rats and mice also tolerated O_2-pressure at 420 mm. Hg for prolonged periods without great loss of weight (Table IX). Monkey No. I, one of the rats and five of the mice gained in weight; but one of the rats and one of the cavies lost considerable weight. Most of the above animals showed no great loss of appetite but a striking difference was observed with cats; they did not appear to tolerate O_2-pressure at 300 mm. Hg (about 40 p.c. of an atmosphere), losing their appetites and becoming exceedingly sleepy; the loss of weight was great (see Table IX) but apart from general weakness and drowsiness there was no obvious symptom; body temperature was normal until the O_2-consumption had fallen greatly, then the body temperature also fell

TABLE IX. Average figures for metabolism and weight under increased O_2-pressure.

Exp. ref. No.	Animals	Duration of exposure to high O_2 days	O_2-consumed c.c. per min. per animal: Normal	Under high O_2	Alteration p.c.	Weight per animal gm.: Normal	Under high O_2	Alteration p.c.
1	Cavy No. I	59	13·5	10·2	−24·4	850	670	−21·1
	„ No. II	59				670	630	− 6·0
5	Monkey No. I	29	27·7	23·0	−16·9	2210	2220	+ 0·4
	„ No. II	29				1985	1890	− 5·0
4	6 rats	35	35·9*	36·6*	+ 1·9	193	179	− 7·2
	6 mice	35				26·8	30·7	+14·5
†	2 rabbits	31	28·7	26·5	− 7·3	2875	2625	− 8·7
2, 3	Cat No. I	18	29·7	18·7	−37·0	3050	2300	−24·6
	„ No. II	27				3100	1570	−49·3
	„ No. III	18				3220	1570	−51·2

* Total c.c. per min. for 6 rats and 6 mice.
† Previous results; see reference (1).

definitely; there was no infection in the blood and no obvious injury to the organs except the lungs which exhibited some collapse and congestion and the presence of a few catarrhal cells. Although there was no definite evidence it might be conceived that some poison was formed by the action of the high O_2-pressure upon the lung epithelium and general poisoning resulted; the cats for some reason could not antagonise this "poison" so well as rabbits, rats, mice, monkeys and cavies. Perhaps the diet was concerned. The absolute values of the O_2-tensions in the tissues (Figs. 2 and 3) under increased O_2-pressure in the air did not control the powers of toleration, since the tissue tensions were much higher in the monkeys and rabbits than in the cats, and yet the cats were so much more sensitive to the change.

The changes in Hb p.c. were no accurate guide to the powers of acclimatisation to high O_2-pressure as judged by general appearance, change in weight, etc. Thus one of the mice showed scarcely any decrease in Hb p.c. yet its increase (25 p.c.) in weight was greater than that of any other mouse or any other animal tested. Changes in Hb p.c. under increased O_2-pressure were possible consequences and not the essential factor controlling acclimatisation. Acclimatisation to high O_2-pressure in the air is due to the tissues becoming accustomed to the effects of the abnormally high O_2-tension in their immediate environment; even when the Hb was greatly decreased in the rabbits and the monkeys the O_2-tensions were still abnormally high (see Tables III and VII and also previous results (1)).

SUMMARY.

1. Some mammals—rabbits, rats and mice—after a certain degree of acclimatisation can exist in a decompression chamber for at least 7 days under continuous exposure to low O_2-pressure equivalent to that at the top of Mount Everest; the animals exhibited some activity but were deteriorating rapidly. Cats, a monkey and cavies tested could not tolerate such a low O_2-pressure for such a time.

2. Unlike most animals cats could not tolerate prolonged exposure to high O_2-pressure at 420 mm. Hg (about 60 p.c. of an atmosphere). They lost appetite and deteriorated rapidly, general weakness being the only obvious change and a general poisoning being suspected; it is suggested that the poison is formed in the lungs although the lungs showed only some collapse and congestion.

3. Decrease of Hb p.c. and of red cells occurs as a rule under exposure to increased O_2-pressure in the air with normal barometric pressure, in monkeys, rabbits, rats, cavies and mice, but was not observed in any of the cats tested. The general rule that Hb p.c. decreases as the O_2-pressure in the air increases and *vice versa* is thus established. It is possible to produce nearly three-fold variations in the Hb p.c. and red cells by alteration in O_2-pressure in the air. Any change produced by altered O_2-pressure in the air passes off again, after a few weeks' exposure to normal O_2-pressure.

4. Changes in Hb p.c. are not essential to acclimatisation to changes in O_2-pressure in the air and should be regarded only as possible consequences; they are of value to the heart when they do occur, at least under low O_2-pressure.

5. Contrary to prevailing views acclimatisation to lowered O_2-pressure in the air is not due to improvement in tissue O_2-tension; what really occurs is that the tissues become accustomed to the low O_2-tension in their immediate environment. Rapid acclimatisation is due to the ability of the vital organs, particularly the heart, to continue to function under a low O_2-tension; in all animals affected by low O_2-pressure heart failure was the most constant phenomenon.

6. Acclimatisation to increased O_2-pressure in the air is due chiefly to the tissues becoming accustomed to the effects of an abnormally high O_2-tension in their immediate environment; tissue O_2-tension is not reduced to normal.

7. An hypertrophy of the tunica muscularis of the branches of the pulmonary artery was observed under exposure to low O_2-pressure.

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