OBSERVATIONS ON THE EFFECT OF ANOXÆMIA UPON HEART AND CIRCULATION.

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Starting from the observation that heart dilatation sometimes occurs at high altitudes Takeuchi(1) recently correlated the degree of dilatation of the heart with the oxygen content of the arterial blood in cats. He recorded the changes in heart size by using the cinematograph method. Prof. Barcroft suggested that we should repeat the experiments cardiometrically.

Methods. In order to vary the oxygen content in the air breathed we devised an arrangement for mixing air with nitrogen.

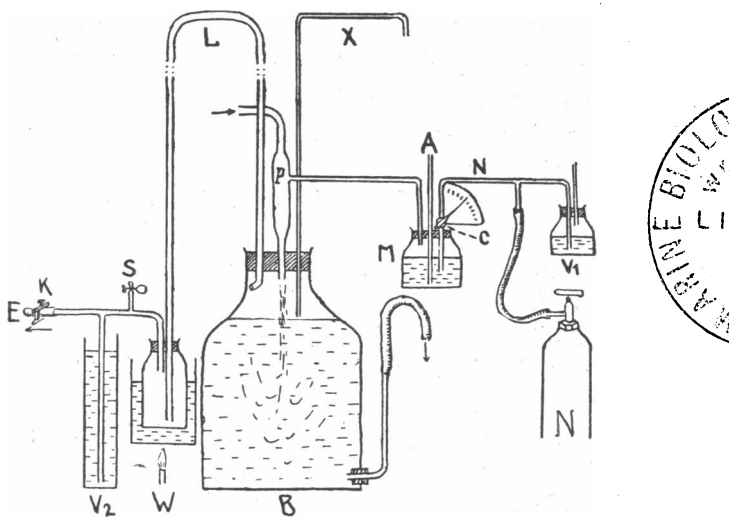

Fig. 1.

P is a filter pump. *M* is a mixing bottle with about 5 cm. of water at the bottom. *A* is a straight glass tube opening to the air and ending about 4 cm. under the surface of the water. *N* is a similar glass tube reaching about 2 cm. under the water surface, and provided with a cock *C*. The other end of it is connected by means of a T-tube with a nitrogen cylinder with a fine adjustment valve and a safety valve V_1 which regulates the nitrogen pressure to about 2 cm. of water.

If the filter pump is turned on and cock C is fully open, pure nitrogen will be sucked through, the pressure of nitrogen being 2 cm. of water higher than the pressure of the air in tube A. If now cock C is gradually closed and the nitrogen supply to M diminished, air will bubble from the lower end of A into M, the proportion of mixture between air and nitrogen being dependent on the position of cock C, which can be read on a scale calibrated empirically. The mixture is driven by the filter pump into the large bottle B, from which the water escapes from the outlet at the bottom through a rubber tube whose end can be adjusted at a variable height. The gas mixture leaves B by tube L, a tall band of compo-pipe reaching almost to the ceiling, and passes into a small warming bottle W. This arrangement is adopted in order to prevent droplets of water from being carried over to the animal. X is a small glass tube of about 5 mm. bore and 50 cm. height, which reaches about 8 cm. into the bottle B. If more gas mixture is driven into the bottle B then leaves it at L, the surplus will escape through X. S is an outlet for taking samples of inspired air and V_2 is a safety-valve regulating the pressure of inspired air as required. E is connected with Takeuchi's (2) revolving cock. The tap water on its way through the pump gives up part of its dissolved gases to the gas mixture, which in this way acquires a constant CO_2 content of ·7 p.c., but this in any case cannot be but advantageous to the animal. Some oxygen is added out of the water and this together with the oxygen content of the commercial nitrogen makes it impossible to obtain mixtures with less than 2–3 p.c. of oxygen. From this point up to 21 p.c. of oxygen any intermediate oxygen concentration can be quickly supplied as required in the course of the experiment.

We used cats and rabbits; since we could not employ volatile anæsthetics we gave in most experiments a large dose of urethane (about 1·5 grm. per kg.), but in some also chloralose or luminal.

We used Rothberger's cardiometer with Starling's (3) rubber cuff, and a piston recorder for registration of the heart volume. Both vagi and phrenic nerves were cut. The blood-pressure was taken from the carotid artery and blood samples from the femoral artery (each sample about 1·5–2 c.c.) with a pipette moistened with a concentrated sodium oxalate solution containing a trace of sodium fluoride. The blood samples were kept under paraffin. The oxygen percentage saturation was determined with Barcroft's differentiometer, the volume percentage CO_2 in the blood with Van Slyke's constant volume apparatus using ·2 c.c. for each determination. Inspired and expired air was analysed with Haldane's apparatus.

The experiments were conducted in the following way: the required concentration of oxygen was turned on, samples of inspired air, blood and expired air taken as soon as changes in the tracings occurred; or, at the higher values of oxygen content which had no apparent effects, after a corresponding time. With low oxygen concentration, when the heart began to fail, we switched over to ordinary air as quickly as possible in order to enable repeated tests to be made. Therefore our limits are threshold limits in acute anoxæmia.

Respiratory conditions and blood gases. The respiratory conditions of

our experiments are illustrated by three examples in Tables I–III (see Appendix). Figs. 2, 4 and 5 show the percentage oxygen saturation of the blood corresponding to the oxygen tensions of inspired and expired air. From Fig. 2 it will be seen that the curve lies somewhat lower than

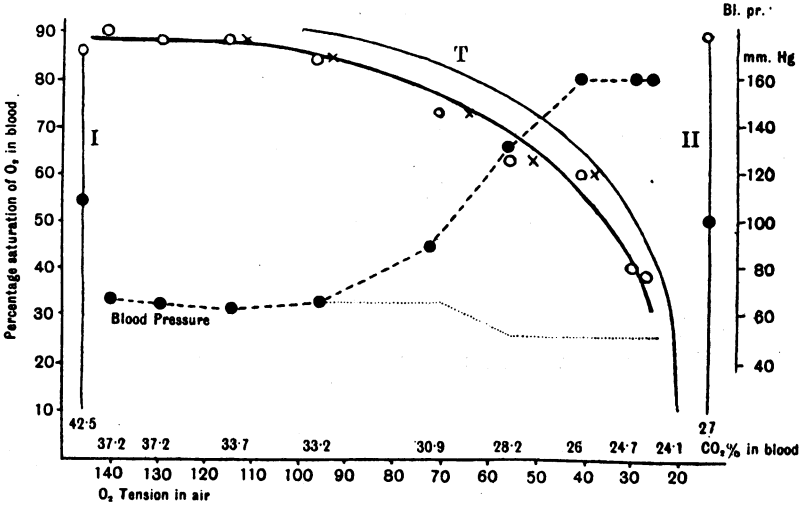

Fig. 2. Rabbit, urethane narcosis, chest unopened, vagi cut. Relation between oxygen pressure in inspired air ○ and expired air × and oxygen percentage saturation in the arterial blood and the blood-pressure ● - - - ●; the ..... line signifies the blood-pressure in the intervals between the anoxæmic periods. The volume p.c. CO_2 are noted under the respective points of the curve. *I* and *II* give the values with natural respiration before and after the period of artificial respiration. *T*, dissociation curve of rabbit's blood at 36° C. and about 40 mm. $HgCO_2$ pressure (Barcroft and King (4)). It should be observed that the figure does not give any information on the sequence of the different observations but only the values obtained in the different tests in the course of the experiment.

the oxygen dissociation curve of rabbit's blood obtained *in vitro* by Barcroft and King(4) (at a CO_2 pressure 40 mm.), but it should be observed that the percentage saturation is not plotted against the alveolar oxygen tensions as it was not possible to determine these. But throughout the experiment the pressure of inspired air and the rate of breathing were constant, and as the vagi were cut, the dead space can be regarded as constant for each experiment. A further circumstance which tends to depress the curve will be mentioned in the remarks at the end of this paper.

The CO_2 content in the expired air is comparatively low as a result of the inevitable over-ventilation with artificial respiration. Corre-

spondingly, the volume p.c. of CO_2 in the blood drops with the onset of the artificial respiration, the degree of acapnia varying in the different experiments; but the extent of acapnia increases regularly towards the end of the experiment. (Decreasing CO_2 production, emptying the CO_2 stores (Haldane(5)), appearance of acid products.) This acapnia has to be taken into account in considering the question of the oxygen utilisation by the heart.

The hæmoglobin content of the blood, and consequently its total oxygen capacity, decreases as a rule in the course of the experiment. These changes can be related to the loss of blood by the taking of the samples and to the general low blood-pressure.

Blood-pressure. The blood-pressure was generally low in our experiments (70–80 mm. Hg). From Fig. 2 can be seen that with the onset of the artificial respiration the blood-pressure drops from 110 to 75 mm. This is doubtless due to the depressing influence of artificial respiration and acapnia upon the vaso-motor centre (Yandell Henderson(6), Dale and Evans(7)), for when the artificial respiration was stopped after three-quarters of an hour the blood-pressure rose again as high as 100 mm.

The response of the vaso-motor centre to anoxæmia in Fig. 2 is a considerable rise of blood-pressure beginning at an oxygen percentage saturation between 85 and 73, and becoming maximal at 60 p.c. saturation.

In the above experiment the chest was closed but in experiments with open chest and cardiometer the anoxæmic reaction of the vaso-motor centre is somewhat different. The rise of pressure is either much smaller or entirely absent or is replaced by a fall. In 9 out of 13 experiments the former was the case, in 4 a fall of blood-pressure was observed at such degrees of anoxæmia as produced rise of blood-pressure in the 9. This occurred before the heart began to be impaired (as shown by the cardiometer curves), indicating that the fall of blood-pressure was of central origin.

The state of the centres is very much impaired by the conditions necessarily involved in the method employed, namely, hæmorrhage, cooling (which cannot be avoided perfectly in cardiometer experiments of long duration), muscle injuries, heavy doses of non-volatile narcotics, and so on, all factors which—as is known—depress the bulbar centres. We tried to test the general excitability of the vaso-motor centre by stimulating the femoral nerve and the central end of the vagus at the beginning of each experiment and could evoke indeed only a very moderate rise of blood-pressure with very strong stimuli. Our experi-

ments confirm the view of Mathison(8) that paralysis of the vaso-motor centre occurs very early in asphyxia (Fig. 3), and this is quite

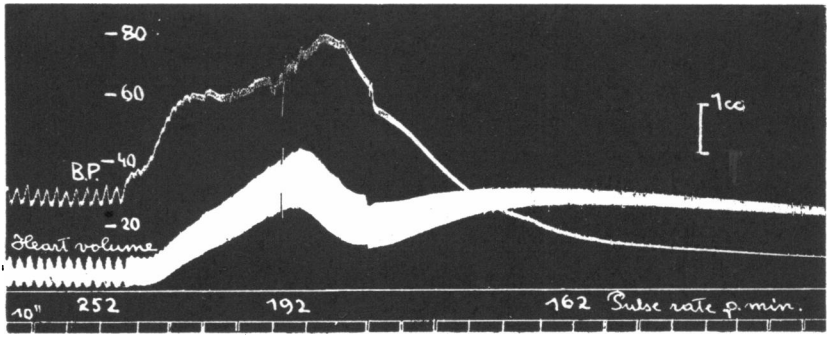

Fig. 3. Shows conclusively that in asphyxia the vaso-motor centre becomes paralysed, before the heart fails. On the end of an experiment (cat, under urethane) the artificial respiration was stopped. The heart volume first increases, then decreases, corresponding to the rise and fall of blood-pressure. The failure of the heart is signified by a fresh increase of heart volume.

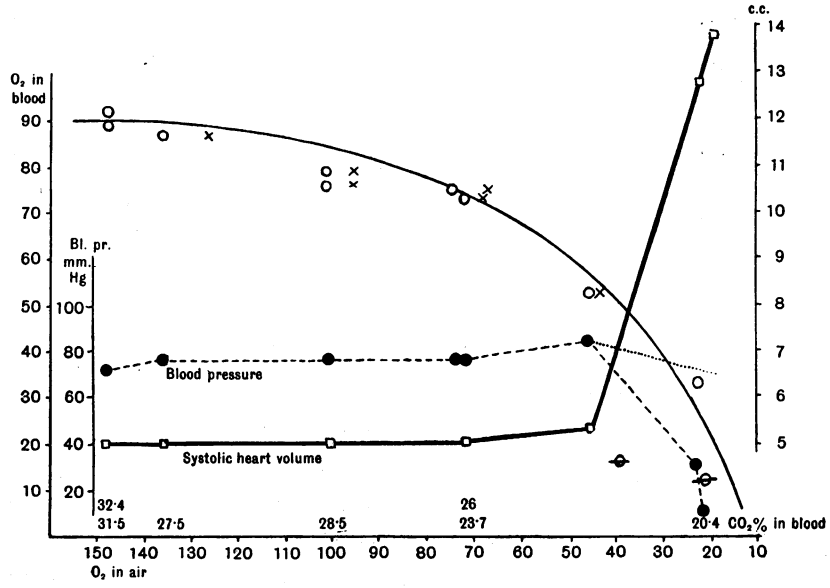

Fig. 4. Relation between oxygen pressure in inspired air ○ and expired air ×, and oxygen percentage saturation in the arterial blood and the blood-pressure ● - - ● - -. The ..... line signifies the blood-pressure in the intervals between the anoxæmic periods. □———□ signifies the systolic heart volume.

intelligible as the percentage utilisation of oxygen in the blood is very much lower with nervous tissue than with muscle tissue (L. Hill and Nabarro(9)). The tendency for paralysis of the vaso-motor centre was greater in cats than in rabbits.

Heart volume. Since the heart volume depends upon the blood-pressure we may consider it as a fortunate event for our purpose, that the vaso-motor centre did not play a more prominent part.

For simplicity's sake we have given in Fig. 4 an experiment where no rise of blood-pressure occurred. The heart volume does not alter before the percentage saturation has fallen below 60 p.c. With about 50 p.c. saturation acute dilatation of the heart sets in, the heart volume rushing up, the blood-pressure dropping rapidly. Quick administration of air restored it to its previous state. With 40 p.c. saturation the disaster was precipitated. Fig. 5 gives an example where a percentage

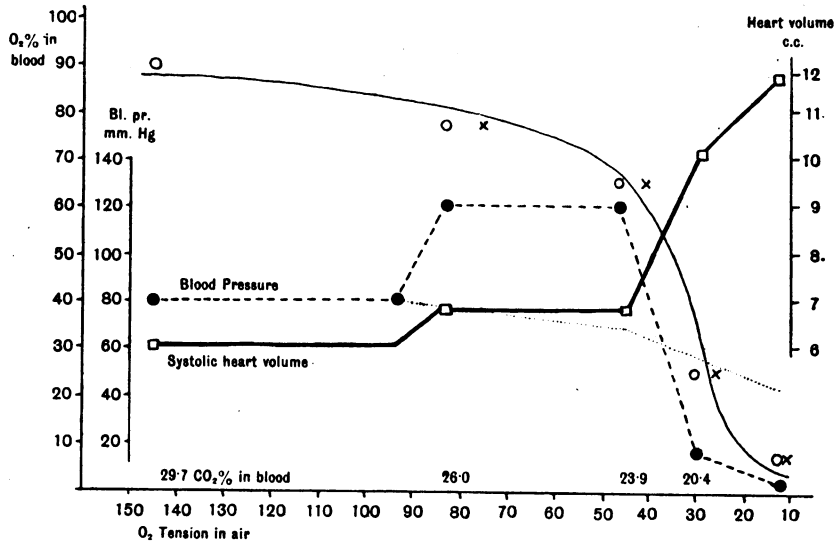

Fig. 5. ○, ×, ●- - ● - -, ..., □——□. As Fig. 4.

saturation of 77 and 65 caused a rise of blood-pressure, with a consequent increase of the heart volume. The disastrous dilatation of the heart only occurred with a further decrease of oxygen supply.

In another experiment in which the blood-pressure was low and responded with further fall to anoxæmia, the result was the same in principle, but dilatation occurred earlier, *i.e.* when the oxygen content of the blood was not reduced so much. The tracing showed that this

dilatation occurred later than the fall of blood-pressure. It is obvious that any reduction of the coronary circulation due to low blood-pressure —the oxygen percentage being already low—must impair the oxygen supply to the heart muscle and thus produce heart failure.

This leads us to consider the mechanism which produces complete failure of the heart in our experiments, as soon as the heart dilates beyond the mere compensatory dilatation corresponding to the rise of blood-pressure, showing that the heart muscle itself is affected. Obviously we have here a vicious circle establishing itself, namely, that the heart as soon as it becomes weaker impairs its own oxygen supply, multiplying the initial cause of its failure.

Our experiments therefore show that there is a definite critical degree of anoxæmia up to which the heart is not affected and beyond which complete failure of the heart, ending in death, occurs. This critical limit lies at 60 to 50 p.c. saturation and the available oxygen is still less, due to the Bohr effect as a result of the accompanying more or less pronounced acapnia. This limit appears to be somewhat higher in cats than in rabbits. Green and Gilbert(21) find as the critical limit of the O_2 content in the inspired air 3·26 p.c.; they diminished the O_2 contents of the inspired air gradually and observed the blood-pressure and electrocardiogram. These results agree quite well with our observations.

Pulse rate and amplitude. The pulse rate (on the average about 220 per minute, vagi cut) is comparatively little affected by anoxæmia. Degrees of anoxæmia which produce heart failure decrease the pulse rate about 15-20 p.c. or may leave it unchanged or may even slightly increase it.

Since the pulse rate is scarcely altered the discussion of the amplitude is simplified. We find the amplitude somewhat increased during anoxæmia with rise of blood-pressure. Patterson, Piper and Starling(10) proved this to be the consequence of an increased coronary flow which is added to the ordinary inflow and outflow of the heart when the blood-pressure rises. Besides which there acts in the sense of increasing the coronary flow the tendency of any tissue to open its channels in response to the call for oxygen; in the case of the heart Barcroft and Dixon(11) could measure directly the increase of coronary flow in anoxæmia. If the anoxæmia causes vaso-motor paralysis and the circulation as a whole fails, then of course the amplitude of the heart beat diminishes. Table IV gives the corresponding values for every 20th second of an anoxæmic period with 45 mm. O_2 tension in the inspired air and 45 p.c. saturation of the blood.

TABLE IV.

Blood-pressure (mm. Hg)	Amplitude* c.c.	Heart volume* increase in c.c.	Pulse rate per 20″
92	2·47	0	54
92	2·47	0	50
94	2·47	0·2	55
109	3·07	0·24	62
98	3·07	0·4	66
83	2·93	1·07	56
80	2·53	1·2	51
74	2·05	1·73	52
51	1·87	2·53	53
43	1·84	3·07	48
34	1·73	3·43	44

* Calculated from the calibration curve of the piston recorder.

Conclusions. It can be deduced from our experiments that the acute dilatation and failure of the heart under want of oxygen already described by Kaya and Starling (12), and Mathison (l.c.) occurs when the percentage saturation was lowered to about 60 to 50 p.c. In agreement with that, heart failure occurred in the experiments of Barcroft and Dixon (11) when they let the animal breathe an oxygen-nitrogen mixture containing about 4 p.c. of oxygen. The heart seems, therefore, to be very resistant to lack of oxygen in such acute experiments provided that there is adequate elimination of its metabolites. The heart goes on beating even if perfused with oil (Sollmann (13), Guthrie and Pike (21)) or indifferent gases such as nitrogen or hydrogen (Magnus (14)).

Taking into account the conditions of our experiments the actual resistance of the heart muscle ought to be estimated yet higher: (1) The pericardium has been removed, which in itself tends to increase the oxygen need of the heart as proved by Evans and Matsuoka (15), and to decrease its resistance towards factors leading to dilatation (Yas Kuno (16)). (2) The comparatively low blood-pressure due to the impaired action of the vaso-motor centre lessens the efficiency of the important self-regulation protecting the heart, namely the fact that the asphyxic stimulation of the vaso-motor centre raises the blood-pressure by constricting the systemic vessels whilst the coronary vessels dilate, thus increasing the oxygen supply at the most important spot. This is the reason why in the experiments quoted above (Fig. 2) high blood-pressure was maintained at percentage saturations which in the cardiometric experiments were far beyond the critical limit.

Now we should like to suggest why our researches differ from the work of Takeuchi (1), who found the chief changes in heart size to occur at the less extreme ranges of anoxæmia. The low pulse rate of his experiments seemed to us to prove that the vagi had not been cut, which is

of importance for the reaction of the heart under anoxæmic conditions, as was shown by Green and Gilbert(20). We therefore made an experiment with vagi intact to test the influence of the vagus reflexes upon the course of the experiment. (Artificial respiration, tracheal cannula, anoxæmic stimulation of vagus centre.) In this experiment we found, as the only one out of 15, a rise of blood-pressure already with 15·8 p.c. oxygen in the inspired and 14·15 p.c. oxygen in the expired air, while the percentage saturation was 72 (this latter value being in agreement with our other experiments as regards the critical limit for the excitation of the vaso-motor centre). Since we had immediately before with 20·9 p.c. oxygen in the inspired and 18·7 p.c. oxygen in the expired air, a percentage saturation of 90, and immediately afterwards with 14·8 p.c. oxygen in the inspired and 12·7 p.c. in the expired air (without any vaso-motor reaction), 80 p.c. saturation, the only possible explanation is that it was caused by bronchiospasm due in some incontrollable way to the vagus nerve. Further complications arose from irregularities, caused by heart block. If in Takeuchi's film the heart was caught in just such a state, the average value for the heart size will appear to be increased, since by omission of heart beats the size of the heart is increased abnormally during the prolonged diastole.

The dilatation of the heart due to anoxæmia is of the type of paralysis such as Socin(17) produced with depressing drugs, and cannot be applied to the question which arose from the observation of increased heart size in man at high altitudes. This observation may better be approached from the standpoint of the problem of the tone of the heart. A possible analogy to the observations in Peru may be found in the greatly increased hearts of soldiers returning from the mountain front which did not show signs of serious heart muscle weakness; these enlarged hearts decreased in size with short rests only, or quicker after digitalis treatment (Kaufmann and H. H. Meyer(18)).

Remarks on the relations between oxygen percentage saturation of the blood and state of general circulation. Whilst limiting the critical oxygen percentage saturation for the heart, we tested in one and the same experiment several times the same oxygen concentration in the inspired air. We found, without any exception, that the corresponding oxygen percentage saturation of the blood was lower later on in the experiments, the general conditions of the circulation as indicated by the lower average arterial pressure being impaired. The correspondence between oxygen percentage saturation and blood-pressure appeared in one experiment in which the blood-pressure was rising spontaneously from 42 to 90 mm.,

and the percentage saturation correspondingly rose from 82 to 90 p.c. (breathing ordinary air with ·7 p.c. CO_2). Looking for an explanation why the slowing down of the circulation tends to depress the oxygen saturation curve of the blood, one has to remember that the tissues under anoxæmic conditions may pour into the blood acid metabolites which render the blood meionectic (Barcroft and Orbeli(19)), and that the regulating function of the kidney is very much impaired under the same conditions.

Summary.

1. A gas mixing apparatus is described which delivers mixture of nitrogen and oxygen in any required proportion between 21 and 3 p.c. of oxygen.

2. In cats and rabbits the relation between the oxygen percentage saturation in the arterial blood and the oxygen content in inspired and expired air was determined.

3. The vaso-motor centre responds when the percentage saturation is lowered to about 75 p.c. Usually, rise of blood-pressure then occurs, but sometimes fall of blood-pressure was observed.

4. Down to 60 to 50 p.c. saturation the heart itself is not affected under the conditions of our acute experiments (*i.e.* with vagi cut). At this critical limit acute dilatation and failure of the heart is imminent.

5. Impairment of the circulation decreases the amount of oxygen in the arterial blood.

We wish to thank Prof. Barcroft for suggesting this work to us and for his kindly interest during its progress. To Prof. Langley our thanks are due for offering us the hospitality of his laboratory. We are indebted to Mr T. R. Parsons for reading our manuscript.

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APPENDIX.

Tables I–III are examples to illustrate the respiratory conditions and blood gases. The figures—as far as breathing with 20·9 p.c. of oxygen—are such as given by Takeuchi (2) for optimal conditions for artificial respiration with chest open.

TABLE I. Rabbit; urethane narcosis.

Inspired air		Expired air		Oxygen percentage saturation (blood)	Volume CO_2 p.c. (blood)	Oxygen capacity of blood
O_2 p.c.	CO_2 p.c.	O_2 p.c.	CO_2 p.c.			
20·94*	0·03	—	—	93·0	—	13·7
11·74	0·62	10·54	1·54	75·0	29·74	13·6
6·63	0·70	6·00	1·05	65·0	26·02	13·7
5·48	0·71	3·88	1·14	25·2	23·94	13·4
20·93	0·70	—	—	95·0	20·04	13·2
1·91	0·75	1·70	1·07	7·0	—	13·2

TABLE II. Rabbit; urethane narcosis.

Inspired air		Expired air		Oxygen percentage saturation (blood)	Volume CO_2 p.c. in arterial blood	Total oxygen capacity (c.c. of 100 c.c. of blood)
O_2 p.c.	CO_2 p.c.	O_2 p.c.	CO_2 p.c.			
20·95*	0·03	—	—	92·2	32·5	—
20·93	0·70	—	—	89·0	31·5	—
19·20	0·76	17·80	1·95	86·8	27·6	17·5
14·50	0·65	13·50	1·82	79·4	28·5	17·1
14·45	0·70	13·50	1·50	76·0	—	16·6
10·51	0·72	9·60	1·61	77·2	26·0	19·3
10·16	0·78	9·82	1·17	73·1	23·8	19·3
6·75	0·67	6·25	1·02	53·0	—	16·5
2·92	0·63	2·15	1·19	33·3	20·5	15·5
5·50	0·65	—	1·19	15·8	—	15·0
3·12	0·70	—	—	12·5	—	13·5

* Natural respiration, before opening the chest.

TABLE III. Cat; urethane narcosis.

Inspired air		Expired air		Oxygen percentage saturation (blood)	Volume CO_2 p.c. (blood)	Oxygen capacity (total)
O_2 p.c.	CO_2 p.c.	O_2 p.c.	CO_2 p.c.			
20·94*	0·03	—	—	80·0	33·85	12·8
20·80	0·70	17·85	2·23	85·0	32·70	12·4
17·15	0·73	15·96	2·25	74·9	30·98	11·1
14·50	0·74	11·50	2·24	71·9	31·85	10·7
10·05	0·72	9·50	1·82	66·0	29·89	10·5
7·56	0·69	6·80	1·40	46·0	25·25	9·8

* Natural respiration, before opening the chest.