The Rate of the Assumption of Chloroform by the Blood during Anæsthesia.

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Although it is obvious that the essential condition of anæsthesia is one in which chloroform is associated with the cells of the body, and among these the cells of the central nervous system, the gradual storing-up of the drug must depend upon the supply available in the blood, the red corpuscles of which are, as we have shown, the chief agents for the transport of chloroform either from or to the pulmonary alveoli.

A definite threshold-value for the percentage of chloroform in arterial blood must be reached in order that anæsthesia shall occur, and the state be maintained. The drug, as Tissot, Nicloux, and ourselves have found, is eliminated at first rapidly, and subsequently more slowly, on the cessation of the administration of chloroform. During anæsthesia the drug does not simply accumulate, since the processes of intake and output go on side by side. Though chloroform is eliminated at first with great rapidity, the last traces of the drug take a long time to slowly leak out of the tissues, but apart from this fact the elimination of a high percentage of chloroform in the blood takes place nearly as rapidly, and perhaps at times even as rapidly, as the assumption of a high percentage.

The following scheme probably represents what occurs during anæsthesia :—

A. Mixture of chloroform vapour and air, constantly supplied in excess.

- B. Portion which does not reach the alveoli, but is expired.
- C. Portion which reaches the alveoli and enters the blood.
  - D. Portion which is associated by the tissues.
  - E. Portion which is eliminated at the pulmonary epithelium.

The relative amounts of B and C will, for a given percentage of chloroform, depend upon the rate and depth of the respiratory movements. This

is modified as the anæsthetic state progresses to asphyxia, owing to the increasing feebleness of the respiratory centres or to the gradual effect of the drug on the muscles concerned in respiration, a factor which probably is of small importance, since Sherrington has shown that striped muscles, unlike the heart, are not readily poisoned by chloroform. In the case of cats, during the very early stages of anæsthesia by chloroform, the rate of respiration diminishes, and is followed by a marked increase. This variation of respiratory movement would no doubt affect the relative proportions of B and C. Of the chloroform passing inwards by the pulmonary epithelium and which is carried by the blood, part is associated by the cells, D, and a part is eliminated, E. As anæsthesia progresses D will be a decreasing factor, while E will be an increasing factor, owing to the augmentation of chloroform in the blood returning to the lungs. The rate of elimination, E, may be even greater than the rate of assumption, C, though the total amount of C exceed that present in the returning blood. Although the rate at which chloroform is tending to pass out may be greater than the rate at which it tends to pass in, the actual amounts going either way will depend, other things being equal, on the mass of the chloroform on either side of the pulmonary epithelium. If, therefore, the nerve centres remained unaffected, we should expect that with a constant normal type of respiration a condition of equilibrium would be reached between factors A and B and C and E, with any given percentage of chloroform inhaled, which would effect a perfect anæsthesia and not rapidly kill.

During the progress of anæsthesia the nerve centres become paralysed, but not necessarily in a regular order, as we have often noticed that various reflexes vanish or reappear in different sequence in animals of the same species. We should expect, therefore, that the curves indicating the variations of the percentage of chloroform in blood with time would not necessarily be smooth.

The determination of the amount of chloroform which is present in the anæsthetised animal has been attempted in three different ways: (1) By ascertaining the percentage of chloroform in the blood of animals anæsthetised or killed by chloroform. (2) By determination of the amount of chloroform in the blood and various organs of the body *post mortem*.* (3) More frequently by reckoning the difference between the amount of chloroform in the inspired and expired air. Waller,† Vernon Harcourt,‡ Collingwood,§ and

* Nicloux, 'Comptes Rend.,' 1906, vol. 60, p. 206.
† Waller, 'Lancet,' November 28, 1903.
‡ Harcourt, 'Brit. Med. Journ.,' June, 1906.
§ Collingwood, 'Physiol. Soc. Proc.,' vol. 28, 1905.

Brodie and Widdows* have published the results of work undertaken on the third line, and the last observers have ascertained that the assumption of chloroform is much more rapid in the earlier than in the later stages of anæsthesia. We believe that by this method only a very limited amount of information can be gained as to the physiological processes which are concerned in anæsthesia. With the desire of throwing further light on this question, we have undertaken a number of experiments on the chloroform-content of the blood during the stages of anæsthesia. A very large number of experiments have been made, of which we quote three of the most detailed ones, which are typical of the whole.

Mode of Experiment.

The general mode of the experiment has been described in detail in a former paper.† The method we have now followed is similar, except that nitrous oxide was used instead of ether as the first anæsthetic. The effect of this gas was allowed to pass off and then chloroform was administered. We found some difficulty in maintaining the chloroform-content of the inspired air absolutely constant. The best mode of attaining this is by means of goldbeater's skin bags filled with a definite percentage of chloroform vapour by means of the Dubois apparatus, and this was the method adopted in some of the experiments. The apparatus gives fairly good results within the limits for which it is constructed, *i.e.*, up to percentages of 2, but above this value it is difficult to obtain constantly good results. It is also necessary that the goldbeater's skin bags shall be new and made of fresh skin, as it was found that with old bags, even if these were perfect, the contents became gradually weaker in chloroform, and direct experiments showed that this was due to the absorption of chloroform vapour by the material. With fresh goldbeater's skin this did not occur.‡ All the tubes used in making connection with the bags or cannula in the trachea should also be of wide bore, not less than $\frac{3}{4}$ inch, and rubber

* Brodie and Widdows, 'Brit. Med. Journ.,' June, 1906.

† 'Roy. Soc. Proc.,' B, vol. 78, p. 422.

‡ Aspiration of a mixture of chloroform vapour and air from an old goldbeater's skin bag. Weight of chloroform determined densimetrically.

In one experiment the weight of chloroform progressively fell in three-quarters of an hour from 0·045 to 0·032, and with a larger bag the progressive fall was from 0·023 to 0·01 in 20 minutes. 1·1 grammes of the skin of this bag, suspended in air containing chloroform vapour, increased in weight 0·026 gramme, while a similar control in air increased only 0·0015. An experiment with fresh skin showed practically no change in weight. A new bag, 36 inches in circumference, the content of which was analysed at regular intervals, showed no variation in an hour, though a slight decrease in the amount of chloroform took place on prolonged standing.

junctions should be avoided as far as possible. In other experiments a Woulff's bottle of the following description was used instead of bags. Capacity of the bottle 580 c.c.; volume of chloroform 170 c.c.; surface area 43 sq. cm.; volume of air-space 410 c.c.; diameter of inlet-tube, which was surrounded by a water jacket of the same temperature as the main bath, 2·5 cm.; diameter of outlet-tube 1·5 cm. The bottle was placed in a large bath so that it could be kept at any desired temperature. The apparatus was so arranged that the distance of the lower end of the inlet-tube from the surface of the chloroform could be varied at will. The outlet-tube was connected with the Chauveau-valve apparatus by means of a densimeter bulb 250 c.c. in capacity. By this means the percentage of chloroform in the inspired air could be ascertained. This apparatus proved in many respects satisfactory; not the slightest drag on the respiratory movements was noticed, a matter of great importance in any experiment of this kind, and particularly so when the duration of an experiment is prolonged. We have found that when the normal movements of respiration were mimicked by means of a bellows apparatus, which aspirated a mixture of air and chloroform vapour from the Woulff's bottle, considerable variations, amounting to as much as 50 per cent. of the higher values, were noticed when the rate or amplitude or both were varied. Actual experiments on cats showed that the variations which occur during anæsthesia were much less marked. Thus, during one experiment lasting 20 minutes, the following percentages were obtained: 1·8, 2·1, 2, 1·6, 1·7. In another experiment of 24 minutes' duration, the values at intervals were as follows: 4·1, 3·6, 4·5, 3·1, 2·95, 3·8, 3·75. For the first experiment the average was 1·8 and for the second 3·8.

In the experiment (No. I), asphyxial convulsions began within a minute of the cessation of respiration, and with the continued inhalation of chloroform the convulsions recurred at intervals until 4.23. The heart ceased to beat at 4.28.

The data obtained from this table are given in a graphic form in Curve I, while in Column 7 of the table the type and frequency of the respirations, at the time each sample was taken, are given.

In the experiment (No. II), chloroform was commenced at 2.20 P.M., but before the end of the first minute the animal ceased to breathe. The inhalation was at once stopped, the animal recovered and the experiment restarted at 2.45, by which time the chloroform would have been eliminated. This early and sudden cessation of respiration we have repeatedly noticed with cats, and it is not a mere holding of the breath, as in other experiments it was often found necessary to use artificial respiration in order that the animal should recover. After this has happened, under apparently precisely similar

Experiment I.—In this experiment a Cat weighing 4 kilogrammes was used, and 2-per-cent. chloroform administered by bags. The results obtained are given in the following table. The respiratory movements were recorded by a tambour on the chest.

Time.	Anæsthetic.	Weight of samples of blood taken.	Weight of AgCl found.	Percentage of chlorine.	Differences in percentage of chlorine, reckoned as $CHCl_3$.	Type and frequency of respirations. Number per minute.	Remarks.
1.20	N_2O						
1.40	,,	3·2787	0·0448	0·3378	—	—	Control sample
1.55	$CHCl_3$, 2 per cent.	—	—	—	—	Average depth; 84	
1.56	,,	2·5603	0·0355	0·3428	0·0056		
1.58	,,	2·8968	0·0404	0·3448	0·0078	Twice as deep; 61	
2.1	,,	2·9232	0·0416	0·35186	0·0157	Depth as above; 63	
2.6	,,	2·6256	0·0377	0·355	0·0193	Below average; 45	Reflexes (eye) just gone
2.11	,,	2·6288	0·0388	0·3649	0·03	Average depth; 57	
2.25	,,	3·4286	0·0499	0·3598	0·0247	,, 57	
2.35	,,	2·9925	0·0444	0·3668	0·0325	Below average; 95	Stepping movements began
2.45	,,	2·6117	0·04	0·3787	0·0458		
2.55	,,	2·7168	0·044	0·364	0·0294	Average depth; 63	
3.10	,,	2·8223	0·0429	0·3758	0·0426	,, 56	
						During this time average 69	
4.15	,,	3·7013	0·0574	0·3834	0·0512	,, 49 to 34	Respiration ceased

Experiment II.—Weight of Cat, 3·2 kilogrammes. Chloroform administered by a Woulff's bottle. Percentage of chloroform vapour about 2 per cent. Respiratory movements recorded as in Experiment I.

Time, in minutes.	Anæsthetic.	Weight of samples of blood.	Weight of AgCl found.	Percentage of chlorine.	Differences in percentages of chlorine, reckoned as $CHCl_3$.	Type and frequency of respirations per minute.	Remarks.
—	N_2O	3·4226	0·0473	0·3417	—	—	Control sample
0	$CHCl_3$, 2 per cent. on						
1	,, ,,	2·3853	0·0341	0·3535	0·0132	Slightly above normal; 180	
3	,, ,,	3·4803	0·0512	0·3637	0·0247	Average depth; 91	
4	,, ,,	—	—	—	—	—	Eye reflexes gone
6	,, ,,	3·2651	0·0479	0·3627	0·0236	Slightly below average; 77	
10	,, ,,	3·2084	0·0483	0·3722	0·0342	Average depth; 97	
15	,, ,,	3·5437	0·0518	0·3614	0·022	,, 110	
20	,, ,,	2·9433	0·044	0·3696	0·0313	,, 66	
30	,, ,,	3·0934	0·0463	0·37	0·0318	,, 92	
40	,, ,,	3·1379	0·0486	0·3829	0·0463	,, 107	
50	,, ,,	3·3724	0·0513	0·376	0·0386	,, 107	
75	,, ,,	—	—	—	—	Constant depth and frequency	
81	,, ,,	2·8224	0·0438	0·3837	0·047	Average depth; 96	
93·3	,, ,,	4·6549	0·0729	0·3872	0·0511	—	Respiration ceased at 93; blood difficult to get; animal squeezed
95	,, ,,	—	—	—	—	—	Asphyxial convulsion

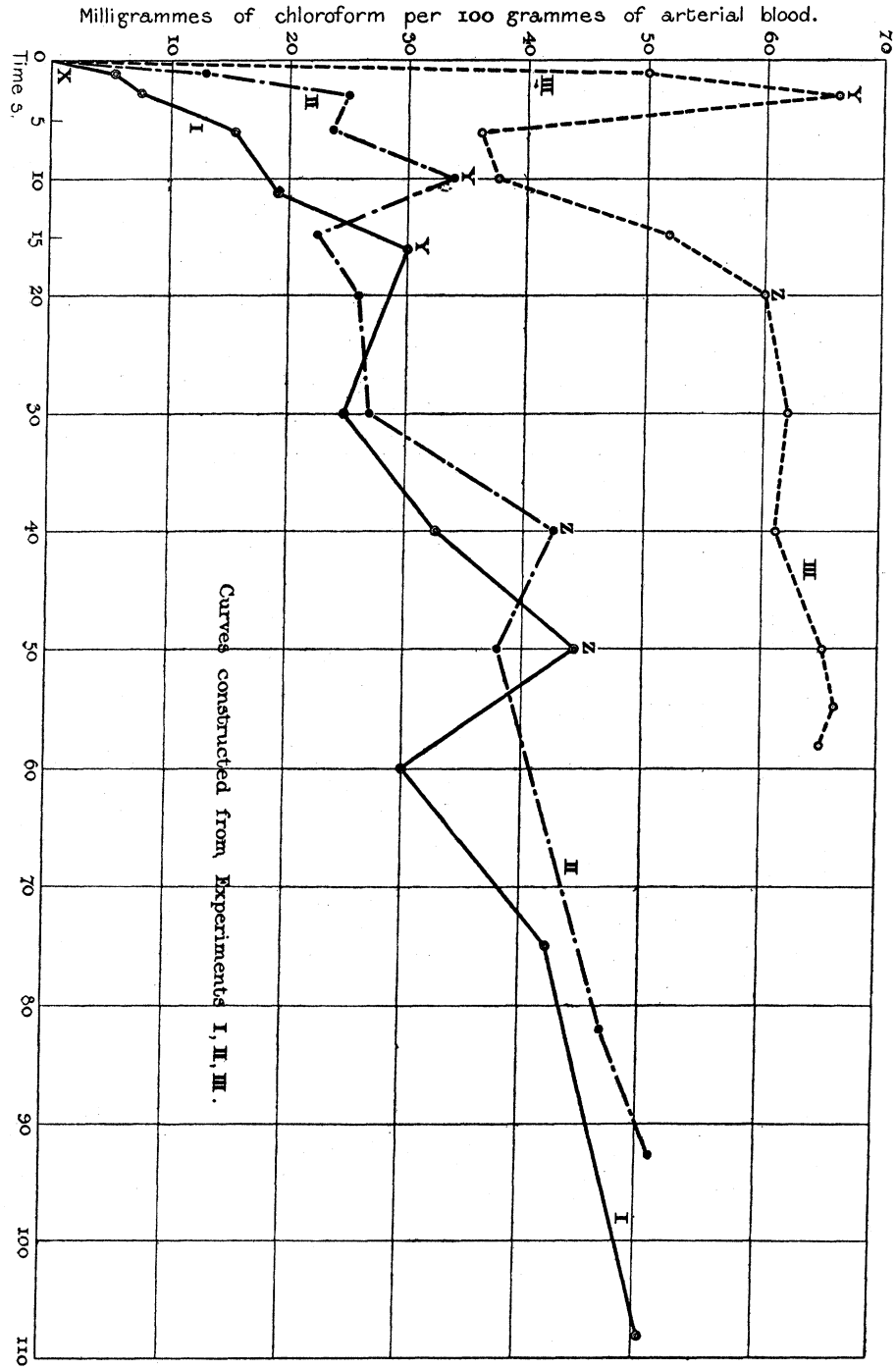
conditions, with the same percentage of chloroform the subsequent anæsthetisation will generally proceed in a perfectly normal manner for a prolonged period of time. We consider this is a fact of much importance which will be subsequently considered.

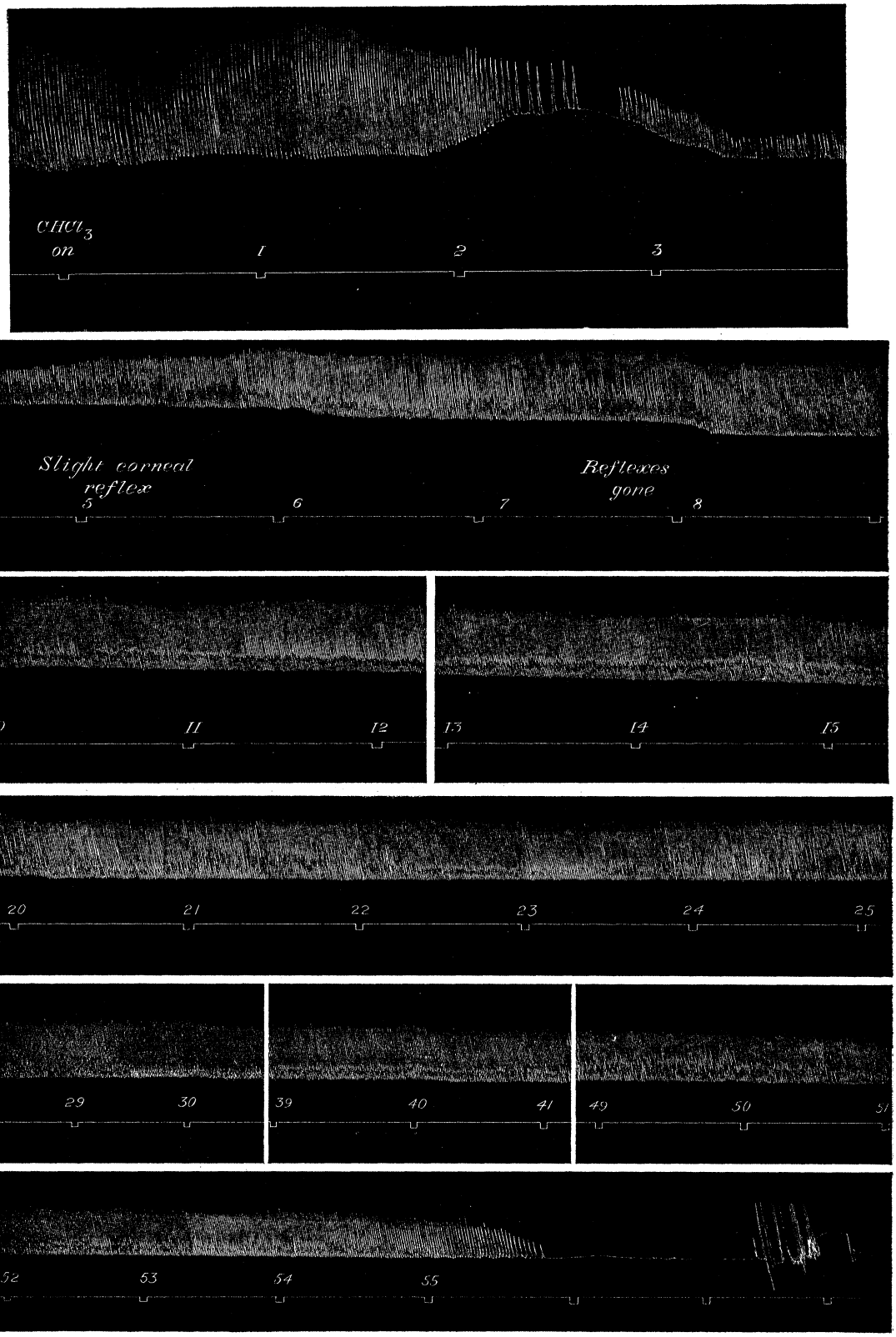
The results of this experiment are shown in Curve II. The type and frequency of the respirations at the times the samples were taken are given in Column 7 of the table.

Experiment III.—Cat. Weight 3·5 kilogrammes. Chloroform, between 3 and 4 per cent., administered by a Woulff's bottle. This experiment is of a special interest, as the early cessation of respiration mentioned in connection with the last experiment took place, but the animal recovered naturally, without it being necessary to discontinue the chloroform.

Time.	Anæsthetic.	Weight of sample of blood taken.	Weight of AgCl found.	Percentage of chlorine.	Differences in percentages of chlorine, reckoned as $CHCl_3$.	Remarks.
12. 15	N_2O on					
12. 32	,,	3·3454	0·0456	0·337	—	Control
12. 40	Chloroform 3–4 per cent.					
12. 41	,,	2·444	0·0377	0·3814	0·0498	
12. 43	,,	2·4221	0·0388	0·3961	0·066	
2. 44	,,	—	—	—	—	Slight eye reflexes
2. 46	,,	3·3243	0·0497	0·3696	0·0366	Reflexes gone
2. 48	,,	—	—	—	—	
2. 50	,,	2·4079	0·0361	0·3707	0·0378	
2. 55	,,	2·8451	0·0441	0·3832	0·0519	
1. 0	,,	2·954	0·0467	0·3909	0·0604	
1. 10	,,	2·7349	0·0434	0·3923	0·0621	
1. 20	,,	2·7826	0·0441	0·3918	0·0615	
1. 30	,,	2·9142	0·0466	0·3954	0·0655	
1. 35½	,,	2·4282	0·0389	0·3961	0·0663	Respiration ceasing
1. 38	,,	1·8758	0·03	0·3954	0·0656	1st asphyxial convulsion

In Curve III the results of this experiment are illustrated graphically, and we append a portion of the respiration tracing:—


Milligrammes of chloroform per 100 grammes of arterial blood.
10
20
30
40
50
60
70
Time s.
0
5
10
15
20
30
40
50
60
70
80
90
100
110
X
Y
Z
I
II
III
Curves constructed from Experiments I, II, III.



Respiratory Tracing of Experiment III.

Conclusions.

From the tables and curves that have been given, we consider that the views expressed in the earlier part of the paper, which were based on a much larger number of experiments undertaken with various other objects, and with which this paper does not deal, are justified. The chloroform-content of the blood rises in the initial stages of anæsthesia with great rapidity to a value which approaches a maximum. During this period the quantity of chloroform in the blood appears to affect particularly the respiratory centres, so that breathing becomes slower and often ceases during the first few minutes of anæsthesia, and it is necessary to resort to artificial respiration in order to prevent the animal dying. With the percentages of chloroform that have been employed, we have never noticed failure of the heart at this stage. The cessation or slowing of respiration at this stage is, as might have been expected, more liable to occur with high than with low percentages of chloroform. Sudden failure of the heart's action has never been noticed by us in cats under the conditions of our experiments, where no percentages of chloroform above 5 have been employed. We have found that a definite danger-point occurs in the first few minutes of anæsthesia, owing to paralysis of the respiratory nervous mechanism.

If the animal naturally passes this stage, which is marked on the curves between X and Y, as in Experiment III, or is restored either by stopping the chloroform inhalation or by artificial respiration, then on continuing the anæsthetic the amount of chloroform in the blood quickly rises again towards a maximum value. An equilibrium between the factors which determine the amount of chloroform in the blood subsequently appears to be obtained, the processes of intake and output at the surface of the lung going on side by side. This stage extends from point Z onwards.

This state of equilibrium is reached, and may persist for a considerable length of time. The exact length of this period differs with different individuals, and even in the same individual in different experiments. During this period the animal may die at any moment should any disturbing influences come into play, and therefore the state is not one of safety. During this period the animal can always be killed with chloroform, even though the percentage of chloroform in the blood rises only very slowly. We would emphasise the point that the difference between the amount of chloroform in the blood throughout this anæsthetic stage and death is very minute. It will be noticed that the difference between the percentages of chloroform in the blood at the point where the corneal reflexes vanish and the maximum values attained are by no means large in actual value,

but are relatively so, averaging, in the experiments quoted, about 50 per cent. After the corneal reflexes have vanished, even though the percentage of chloroform administered be kept absolutely constant, there is no criterion other than analysis by which we can judge of the progress of anæsthesia in these animals.

In our experiments, death always occurred by failure of the respiration succeeded by asphyxia. Under the conditions of our experiments undertaken on a very large number of cats, we have never noticed death by heart failure preceding cessation of respiration.

We take this opportunity of expressing our thanks to the Government Grant Committee of the Royal Society for assistance in carrying out this work; and also our appreciation of the valuable assistance of Mr. G. W. Ellis, who has helped in a large number of the laborious analyses.