Function of the Red Corpuscles in Chloroform Anæsthesia.

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(From the Physiological Laboratory of the University of London.)

It has been conclusively shown by Pohl,* Nicloux,† Moore and Roaf,‡ and ourselves§ that when chloroform is associated with the blood, the bulk of the drug is held by the red corpuscles. It would appear, therefore, highly probable that in chloroform anæsthesia the transport from and to the surface of the lungs is a function of the red corpuscles. In order to throw more light on this point, we have investigated the effect of the variations in the volume of blood in circulation on the duration of anæsthesia and on the percentage of chloroform in the blood.

Removal of blood, other conditions being constant, should not alter the percentage of chloroform in the blood. Several causes might separately or together prevent the conditions being constant, and therefore bring about deviations from the above conclusion.

1. The gradual entrance into the blood of extra-vascular liquid. According to Starling,‖ "the fluids contained in the tissue spaces possess the same tonicity and the same composition in salts as the blood-plasma." If, therefore, the extra-vascular fluids entered the blood-stream instantly to an amount equal to that of the blood withdrawn, the percentage of chlorine in the blood would only be slightly raised, because the corpuscles contain a somewhat lower percentage of chlorine than the plasma.¶ The restoration of the volume after hæmorrhage is known to be a gradual process, and during the time and under the conditions of our experiments could not have taken place to any marked extent. Therefore the variations in the chlorine-content of the blood would be practically negligible, and well within the errors of experiment. This conclusion was repeatedly confirmed in the course of our experiments by analyses made at the beginning, before and after bleeding.

2. An entrance of red corpuscles into the blood-stream, consequent on

* 'Archiv f. exp. Path. u. Pharmak.,' vol. 28, 1890—1891.
† 'Comptes Rendus,' Nos. 2, 3, 7, 1906.
‡ 'Roy. Soc. Proc.,' vol. 73, 1904.
§ 'Roy. Soc. Proc.,' B, vol. 78, 1906.
‖ 'Journal of Physiology,' vol. 19, No. 4, 1896.
¶ Buckmaster and Gardner, 'Roy. Soc. Proc.,' B, vol. 78, 1906.

hæmorrhage, is known to be a very slow process, and one dependent upon the activity of the bone-marrow. The evidence which exists on this point, therefore, negatives the idea that any appreciable effect on the chlorine-content of the blood can be due to this cause.

3. Abnormal depth and frequency of respiration, combined with a high percentage of chloroform, might conceivably cause abnormality in any set of parallel experiments made before and after bleeding by the chloroform entering the plasma to an excessive amount.* The possibility of this factor coming into play necessitated a large number of experiments.

Finally, the peculiar nature of the anæsthetic process, to which we have drawn attention in another paper,† as an examination of the published curves will at once make clear, renders it unlikely that any definite conclusions could be drawn from a small number of experiments as to the effect produced by alteration in the volume of circulating blood. In the paper referred to we showed that the percentage of chloroform in blood rapidly rises to a point approaching a maximal value. When this point is reached, which may occur within the first few minutes of an experiment, the animal often ceases to breathe. This we have alluded to as the first danger-point of anæsthesia. When this point is passed naturally, the chlorine-content of the blood falls, but again rapidly rises. In most experiments, when breathing stopped at this point, we found it better to allow the animal to resume breathing and restart the experiment. In either case the maximal value was quickly reached again, when an equilibrium occurred between the intake and output of the drug. This state of equilibrium, when the percentage of chloroform only rose very slowly, was often maintained for a considerable period of time. During this period the respiration may stop at any moment from slight causes which cannot be controlled. This further rendered it necessary to make a large number of experiments.

The operative procedures for the administration of chloroform and for withdrawing blood were identical with those described in former papers.

Experiments in which the Asphyxial State was rapidly reached.

The percentage of chloroform used in these experiments was above 3 per cent. and under 5 per cent. Sometimes bags were used, sometimes a Woulff's bottle such as we have employed in experiments previously described, so that a slight drag on the respiratory movements was produced. These experiments may be fairly taken as representative of those in which death occurred at the first danger-point of anæsthesia.

* Buckmaster and Gardner, *ibid.*

† 'Roy. Soc. Proc.,' this volume.

The general plan of the experiment was to anæsthetise the animal with ether or nitrous oxide, allow the anæsthetic to be disengaged from the body, and then administer a known percentage of chloroform. The determination of the chloroform-content of the blood was made at the asphyxial point. The animal was then allowed to recover from the full effect of the chloroform, either naturally or by artificial respiration, and sufficient time was allowed for practically all the chloroform to be eliminated from the blood. One hour to one and a-half hours was usually sufficient for this, and it was generally necessary to give the animal a little ether or nitrous oxide in order to preserve unconsciousness. During this period the animal was bled from the carotid artery to a known amount. The quantity of blood withdrawn varied with the weight of the animal. Sometimes the whole amount was taken at once, but generally in successive small quantities. The animal was re-anæsthetised and another determination of the amount of chloroform in the blood made at the asphyxial point, but before re-anæsthetisation a sample of blood was always taken as a control. The details of the experiments are recorded in Table I.

These are the only experiments in which the respiration-curves definitely indicated that asphyxia occurred both before and after bleeding in the initial stage of anæsthesia. In five of the seven experiments, comparative determinations were made before and after bleeding. Of these, in two cases the percentages of chloroform found in the blood were practically identical. In two cases the percentage was higher after than before bleeding, and in one case lower. In the other two experiments in which values after bleeding were obtained, the figures are fairly normal.

Before bleeding the average percentage of chloroform in 100 grammes of blood was approximately 0·043 gramme and after bleeding 0·045 gramme. It would appear, therefore, that in the above experiments the percentage of chloroform in the blood is not altered by bleeding.

Experiments in which Asphyxia took place during the Second Stage of Anæsthesia.

In these experiments chloroform was inhaled from the Woulff's bottle described at length in a former paper "On the Rate of the Assumption of Chloroform by the Blood during Anæsthesia." In those cases where respiration stopped within the first few minutes, the animal was brought round artificially or allowed to recover naturally and the anæsthetic again administered continuously. In other respects the procedure was the same as in the first group of experiments. The details of the experiments are recorded in Table II.

Table I.—*Experiments in which the Asphyxial state was rapidly reached.*

No. of experiment.	Weight of cat in kilos.	First anæsthetic.	Percentage of $CHCl_3$ inhaled.	Chloroform apparatus.	Time to asphyxia in minutes.		Amount of blood withdrawn in c.c.	Percentage of chloroform in blood at asphyxia in grammes per 100 grammes blood.		Remarks.
					Before bleeding.	After bleeding.		Before bleeding.	After bleeding.	
I	2·6	Ether	3—4	Bag	14	10	18	0·053	0·063	Respiration curves show asphyxia at first danger-point. Asphyxial convulsions after bleeding at 12 minutes
II	3·3	Ether	3—4	Bag	—	11	30	—	0·037	Animal bled before experiment
III	2·4	Ether	4—5	Bag	4·5	4	13·5	—	0·0412	
			4—5	„	9	2·5	—	—	—	Re-done
			4—5	„	—	3	—	—	—	Re-done half hour later
			4—5	„	—	3	—	—	—	Re-done 8 minutes later
			4—5	„	—	3·5	—	—	—	Re-done 10 „
IV	3·2	Ether	5	Bag	29	20	18	0·0404	—	Sample before bleeding at asphyxial convulsions
			5	„	—	16—17	—	—	0·0413	Re-done after 1 hour
			5	„	—	16—17	—	—	—	Re-done 40 minutes later
						17	—	—	—	Re-done 30 „
V	2·3	Ether	4·5	Bag	11					
			4·5	„	14	11	19	0·0369	—	Re-done 30 „
			4·5	„	—	13	2	—	0·0369	Re-done 20 „
			4·5	„	—	10	—	—	—	Re-done 20 „
			4·5	„	—	12·5	—	—	—	Re-done 30 „
VI	2·2	Ether	3—4	Bag	4·5					
					3					
			3—4	„	—	—	—	0·0246	—	Re-done 10 minutes later; breathing shallow and abnormal after the first minute
							20			
			3—4	„	—	9				
			3—4	„	—	15	—	—	0·048	Re-done 1 hour later
VII	2·3	N_2O	3·5—4·5	Bottle	8					
					9	—	—	0·0605	—	Re-done 28 minutes later
							25			
						4	—	—	0·0488	Blood proved free from $CHCl_3$ before re-anæsthetisation

Table II.—*Experiments in which Asphyxia occurred during the Second Stage of Anæsthesia.*

No. of experiment.	Weight of cat in kilos.	First anæsthetic.	Percentage of $CHCl_3$ inspired.	Apparatus.	Time in minutes.		Blood withdrawn in c.c.	Percentage of chloroform in grammes per 100 grammes blood.		Remarks.
					Before bleeding.	After bleeding.		Before bleeding.	After bleeding.	
VIII	3·6	N_2O	3·5	Bottle	63	—	—	0·0499	—	Initial stage passed naturally, though respiration almost ceased
			3·5	,,	—	—	30	—	—	After interval of 1 hour, analysis showed blood free from chloroform
			3·5	,,	—	29—30	—	—	0·05	Sample from heart
IX	3·6	N_2O	4	Bottle	31	—	—	0·068	—	Asphyxial convulsions at time of sample. Rhythmical movement of hind limbs and tail during anæsthesia
			4	,,	—	18	30 —	—	0·0438	Sample from heart and body cavity
X	3·8	N_2O	3·5	Bottle	24	—	—	0·048	—	Stepping movements occurred
							35	—	—	Sample proved blood free from $CHCl_3$
			3·5	,,	—	20	—	—	0·052	Stepping movements occurred
XI	3	N_2O	3	Bottle	30	—	—	0·0476	—	$CHCl_3$ discontinued for short time after first minute. Time commences from re-anæsthetisation
				,,	—	53	26 —	—	0·052	Stepping movements more marked than before

XII	3·5	N_2O	2—2·5	Bottle	75	—	—	0·0532	—	Initial stage passed naturally, was well shown on tracing
						108	34	—	0·0489	After recovery from chloroform animal slept for some time. Analysis showed all $CHCl_3$ out of blood. No stepping movements
XIII	2·8	N_2O	2—2·5	Bottle	—	—	—	—	—	Initial stage recovered from naturally
								0·0405	—	30 minutes after commencement of $CHCl_3$
								0·0464	—	15 minutes later
					80	—	—	0·0482	—	Cessation of respiration. Slept after recovery
							32	—	—	Sample taken 80 minutes later showed only 0·001 chloroform
			2·5	,,	—	69	—	—	0·0548	Initial process passed naturally, subsequently slight stepping movements. First danger-point well marked
XIV	4	N_2O	2—2·5	Bottle	—	—	—	0·043	—	After 30 minutes from commencement of chloroform
					41	—	—	0·0355	—	11 minutes later, on cessation of respiration, which occurred very gradually
							39			1½ hours' elapse
			2·5	,,	—	—	—	—	—	Initial danger-point well marked
						55	—	—	0·0467	At asphyxia
										Experiment absolutely uncomplicated

It will be seen, therefore, that the average percentage of chloroform in the blood at the asphyxial point is 0·048 before and 0·051 after bleeding, or eliminating the first two figures in Column 9, quoted in Experiment XIII, and the first figure in same column in Experiment XIV, as these values were determined in samples taken considerably before asphyxia, the corrected averages are 0·05 before and 0·0497 after bleeding. In one experiment the figures were sensibly the same before and after withdrawal of blood, and in four experiments there was a slight increase after the withdrawal of blood. In the two remaining experiments a decrease was observed after a hæmorrhage.

In the following table (No. III), we quote two experiments in which the respiration tracings showed that asphyxia took place before bleeding in the second stage of anæsthesia, and after bleeding at the initial stage.

Experiments in which comparisons were made of the percentage of chloroform in the blood at the asphyxial stage after hæmorrhage and after the replacement of the blood which had been removed by the blood of another animal of the same species. All the observations were made in the second stage of anæsthesia.

The replacement of blood was effected in the following way:—A cat was anæsthetised with ether and a cannula placed in the carotid artery. The cannula was connected by a short rubber tube fitted with a clip, with the outflow end of a burette. This was warmed and smeared inside with olive oil, and before making connection with the cannula, the cannula, rubber tube and about an inch of the burette were filled with warm olive oil, so that the blood could be received from the animal without coming in contact with the air or glass, and without cooling to any serious extent. A small cannula had been previously placed in the femoral vein of the animal which was the subject of the anæsthetic experiment. This cannula was filled with a warm solution of sodium sulphate of a strength isotonic with that of blood plasma. The burette was now disconnected from the cannula in the carotid artery, and connected with the cannula in the femoral vein, care being taken that no air entered the circulation. The requisite amount of blood was then allowed slowly to flow during the course of two or three minutes into the animal. The whole transfer of blood was effected in less than four minutes. In none of our experiments did we notice any disturbing effects produced by the introduction of the blood. The animal was then re-anæsthetised with chloroform, after recovering from the first anæsthetic, precisely as in the first part of the experiment. Details of these experiments are recorded in Table IV.

In two out of the three complete experiments the percentage of chloroform in the blood at the asphyxial point after bleeding and after replacement

Table III.—*Asphyxia during the Second Stage of Anæsthesia before and during the First Stage after Bleeding.*

No. of experiment.	Weight of cat in kilos.	First anæsthetic.	Percentage of $CHCl_3$.	Apparatus.	Time in minutes.		Blood withdrawn in c.c.	Percentage of chloroform in grammes per 100 grammes of blood.		Remarks.
					Before bleeding.	After bleeding.		Before bleeding.	After bleeding.	
XV	2·6	N_2O	4·5	Bag	20	—	—	0·0409	—	Sample taken during asphyxial convulsions. Initial stage well shown in respiration curve
							18·5			85 minutes elapse so that chloroform may be eliminated
			4·5	Bag	—	8—9	—	—	0·0298	Respiration rapid and deep at first, and ceased between first and second stage
XVI	3·5	N_2O	4	Bag	30	—	—	0·0484	—	Second stage reached naturally, as shown by tracing. Stepping movements
							29			80 minutes elapse for chloroform to be eliminated
			4	,,	—	5	—	—	0·0776	Respiration deep and rapid, and tracing clearly showed that asphyxia occurred at initial stage. One hour elapses for $CHCl_3$ to be eliminated
			4·5	,,	—	3·5	—	—	0·0504	Asphyxia at initial stage, shown in tracing

Table IV.—*Experiments giving the Percentage of Chloroform in Blood at Asphyxial Stage, after Hæmorrhage and after Replacement of Blood.*

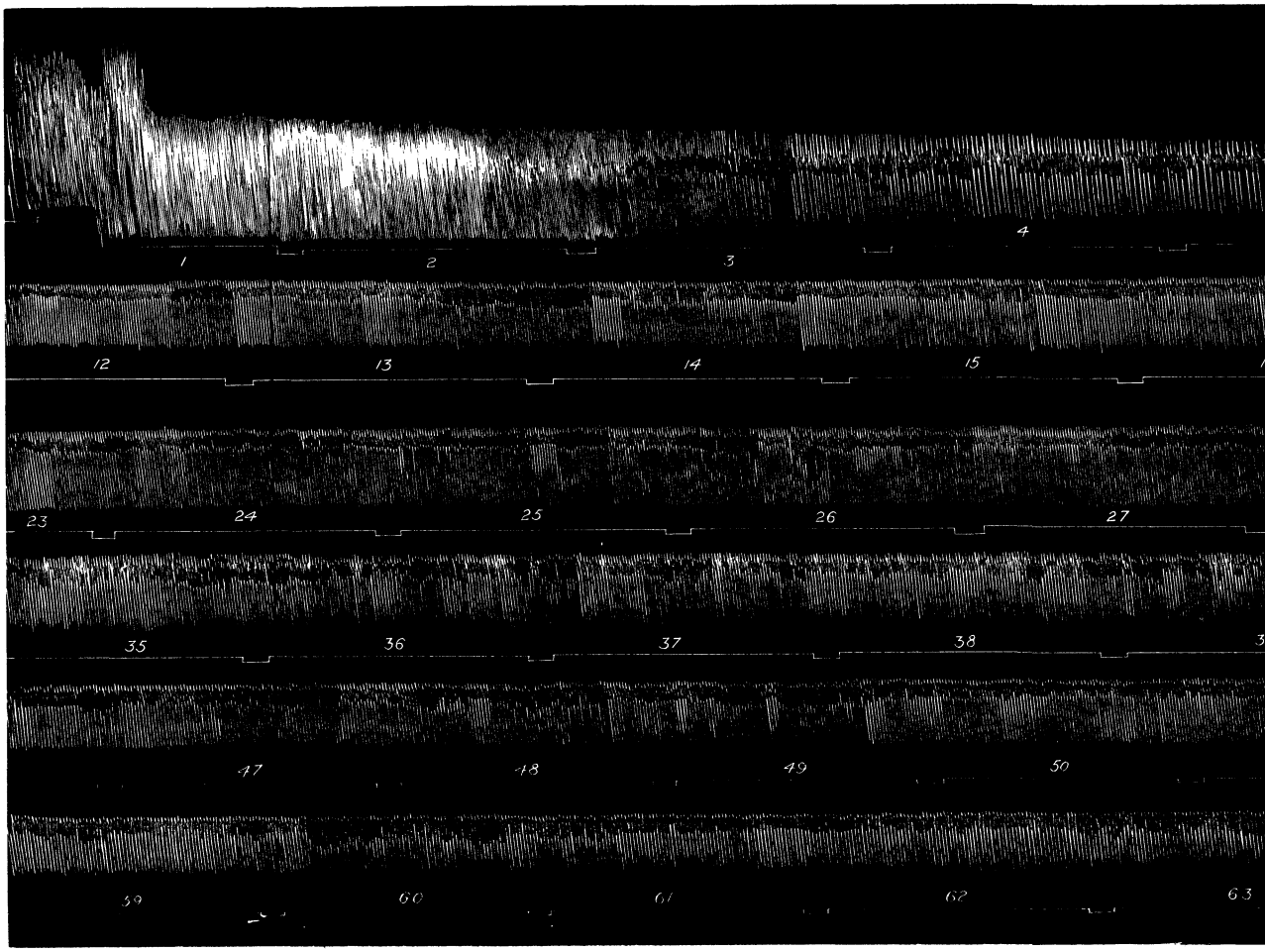
No. of experiment.	Weight of cat in kilos.	First anæsthetic.	Percentage of chloroform inhaled.	Apparatus.	Time in minutes.		Blood withdrawn in c.c.	Blood restored in c.c.	Percentage of chloroform in grammes per 100 grammes of blood		Remarks.
					After bleeding.	After restoration of blood.			After bleeding.	After restoration of blood.	
XVII	3·3	N_2O	—	—	—	—	32				
			2—3	Bottle	104	—	—	—	lost	—	Cessation of respiration in initial stage, and animal allowed to recover for half an hour. Time starts from this point. Stepping movements of hind limbs well marked
								38			80 minutes elapse to allow chloroform to be eliminated
			2—3	,,	—	19	—	—	—	0·061	
						54	—	—	—	0·0632	70 minutes elapse and experiment repeated
XVIII	4·0	N_2O	—	—	—	—	32				
			2	Bottle	126	—	—	—	0·0421	—	Animal ceased to breathe at initial stage, but was recovered by artificial respiration. Time starts from this point
								42			
			2	,,	—	153	—	—	—	0·0426	

XIX	3·5	N_2O	—	—	—	—	—	0·0437	—	Initial stage passed naturally. Stepping movements. Asphyxia very sudden
			2	Bottle	78	—	—	—	—	70 minutes elapse
							40			
			2	,,	—	103	—	—	0·0518	Breathing shallow. Initial stage passed naturally
XX	3·6	N_2O	—	—	—	—	32	lost	—	Initial stage passed naturally
			3·5—4	Bottle	44	—	—			
							38			
			3·5—4	,,	—	55	—	—	0·057	
XXI	3·2	N_2O	—	—	—	—	24	0·0768	—	Animal ceased to breathe at initial stage. Artificial respiration
			4—5	Bottle	52	—	—			90 minutes elapse
							30			
			4—5	—	—	52	—	—	0·0768	

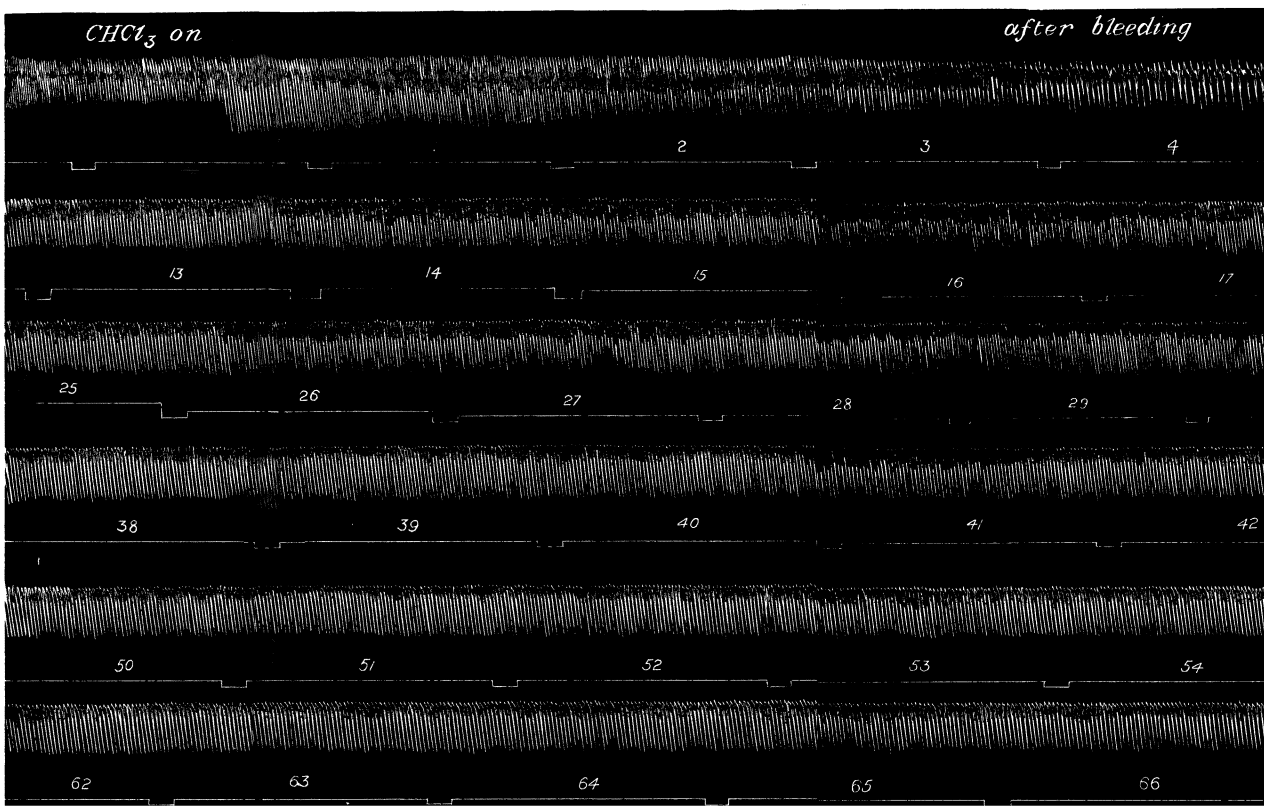
Table V.

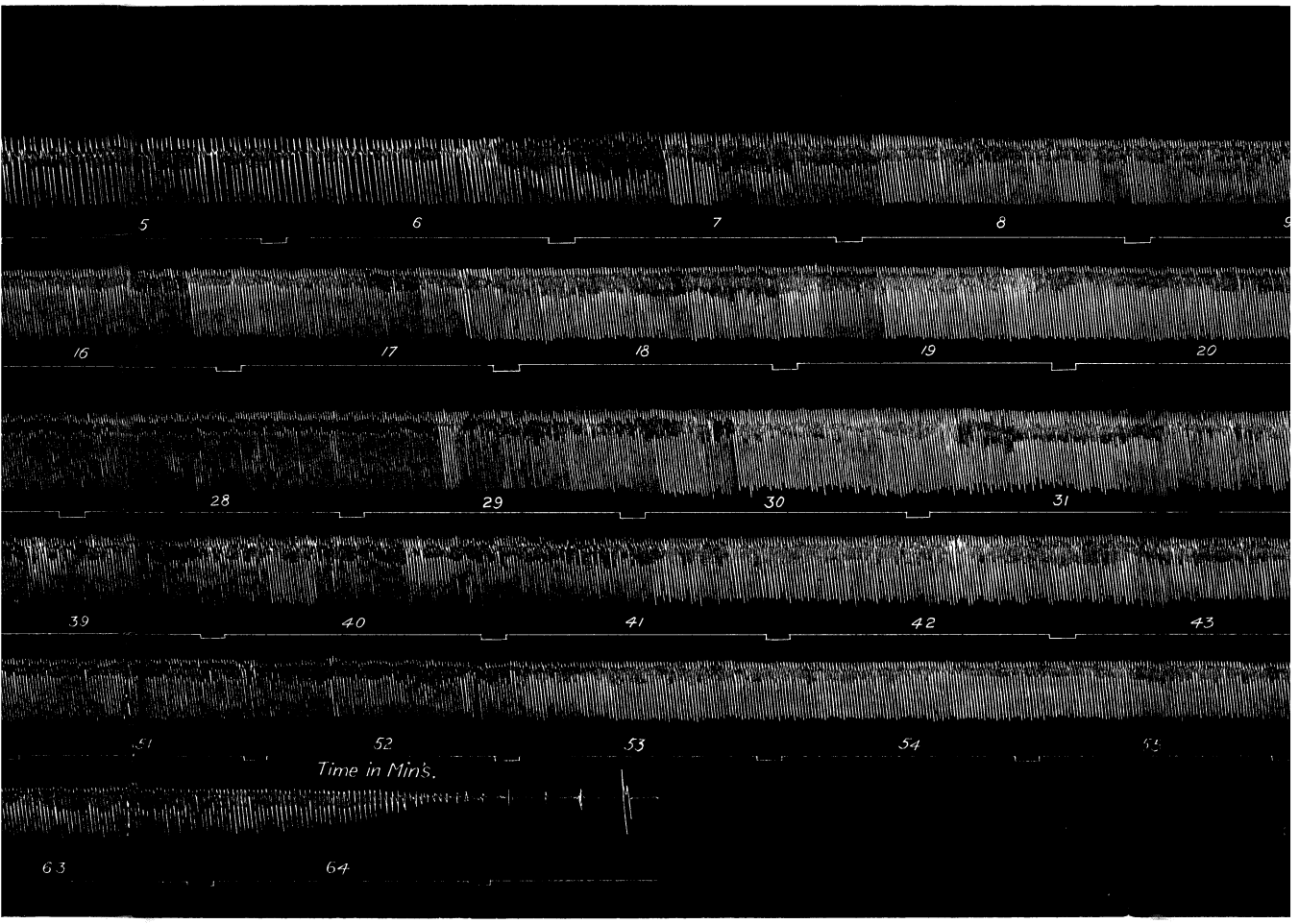
No. of experiment.	Weight of cat in kilos.	First anæsthetic.	Percentage of $CHCl_3$ inhaled.	Apparatus.	Time in minutes.			Blood withdrawn in c.c.	Blood replaced in c.c.	Chloroform in grammes per 100 grammes of blood.			Remarks.
					Before bleeding.	After bleeding.	After replacement of blood.			Before bleeding.	After bleeding.	After replacement of blood.	
XXII	3·1	N_2O	3	Bottle	19—20	—	—	—	—	0·0563			
								27					1 hour to recover. Sample showed chloroform had been completely eliminated
			4	,,	—	12	—	—	—	—	0·008*	—	*Respiration curve indicated that the animal had passed the first danger-point but respired so badly that the experiment was stopped and inhalation stopped. Blood obtained with difficulty and animal took a number of rapid deep respirations before the blood was obtained. Hence the low percentage of chloroform
									30				
			3—4	,,	—	—	11	—	—	—	—	0·02	Cheyne Stokes' respiration. Stepping movements. Respiration ceased at first stage, but revived naturally on stopping the anæsthetic
			4	,,	—	—	8	—	—	—	—	0·0365	After 40 minutes' interval re-anæsthetised by $CHCl_3$. After respiration ceased, syncope. Sample from chest cavity
XXIII	3·1	N_2O	2	Bag	39	—	—	—	—	0·0376	—	—	
								26					Transition from first to second stage scarcely noticeable in respiration tracing. No stepping movements
			2	,,	—	13	—	—	—	—	0·028	—	Sample 100 minutes after asphyxiation showed traces of $CHCl_3$. Next experiment 22 minutes afterwards. Respirations very deep and rapid and ceased before second stage had fairly begun
						4	—	—	—	—	not done	—	Experiment re-done after 20 minutes. Cessation of respiration at first stage. Animal recovered artificially and we decided to proceed with third portion of experiment. Pupils not dilated in the least in the last two experiments
									41				
			2	,,	—	—	41	—	—	—	—	0·035	Interval of 1 hour elapses. Transition from stage 1 to 2 scarcely noticeable
XXIV	3·4	N_2O	3	Bottle	64	—	—	—	—	0·0442	—	—	No complications observed. First stage passed naturally. Transition well seen on tracing
								30					
			2·5—3	,,	—	76	—	—	—	—	0·0598	—	Interval 75 minutes. Blood found free of chloroform. First stage passed naturally. Transition well shown on tracing
									40				
			3	,,	—	—	49	—	—	—	—	0·0508	After replacement of blood, transition passed naturally, well shown in tracing
XXV†	4·6	N_2O	3	Bottle	119	—	—	—	—	0·061	—	—	
								38					Transition stage not well marked. No complications
			3	,,	—	31	—	—	—	—	0·0597	—	Interval 76 minutes for recovery. Sample showed that blood still contained a little $CHCl_3$. Tracing showed second stage was reached
									50				
			4	,,	—	—	34	—	—	—	—	0·0489	Interval of 80 minutes, during which animal slept for almost entire time. No N_2O required. Transition stage not well marked in this experiment

† In this experiment both animals were injected with hirudin before chloroform anæsthesia. Each animal received 0·03 gramme of hirudin dissolved in 2·5 c.c. of isotonic sodium sulphate. This amount removed any tendency to clotting in the cannula and greatly facilitated the removal of samples of blood.

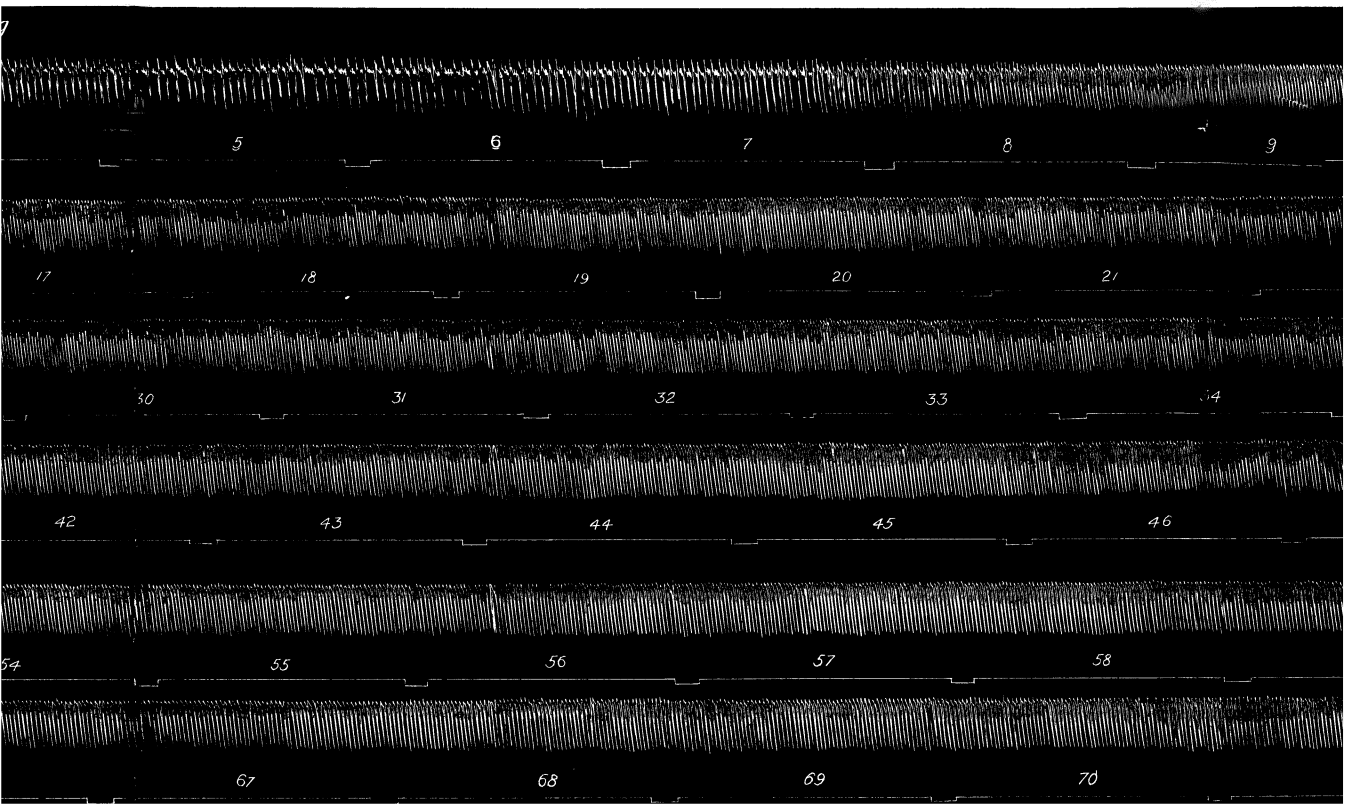


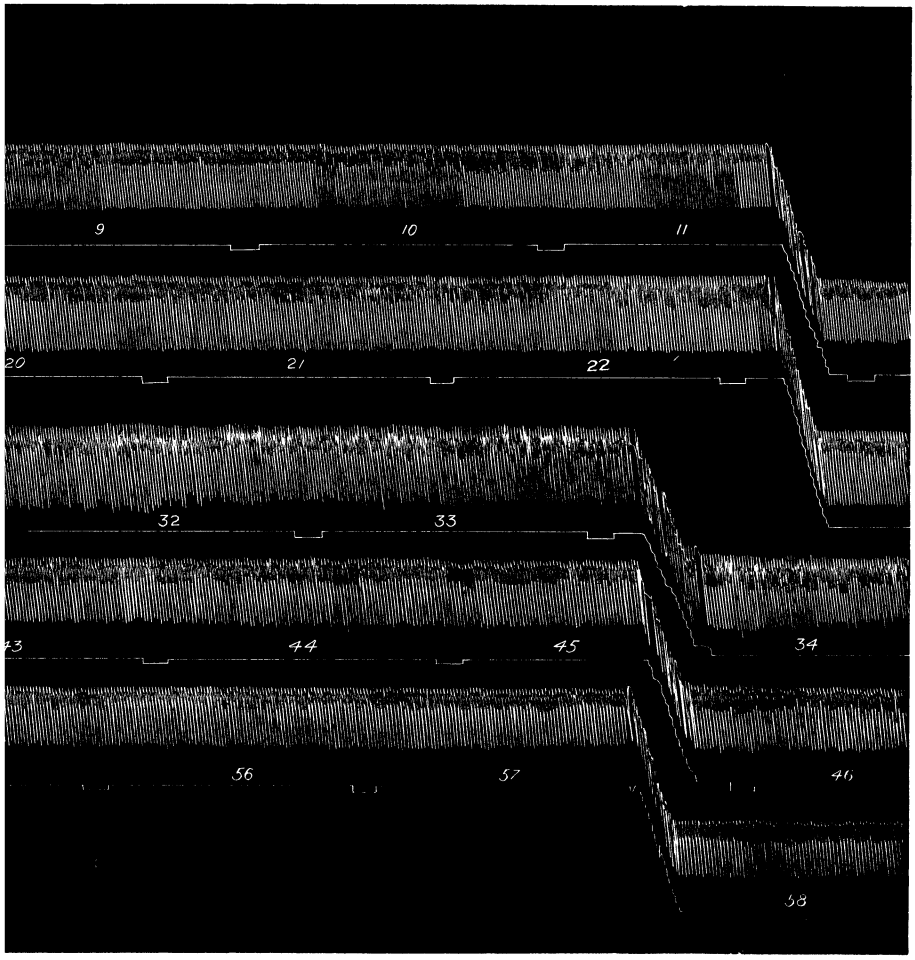
1. EXPERIMENT XXIV.—Respir





.—Respiratory tracing before hæmorrhage. Figures indicate minutes after the commencement of chloroform inhalation.

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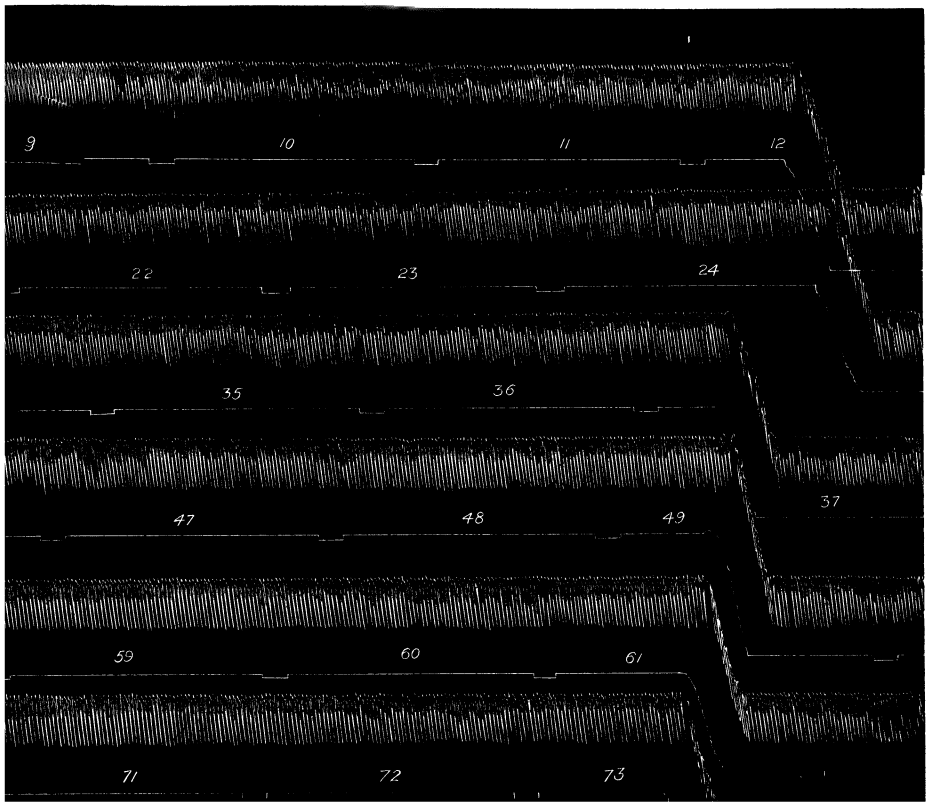
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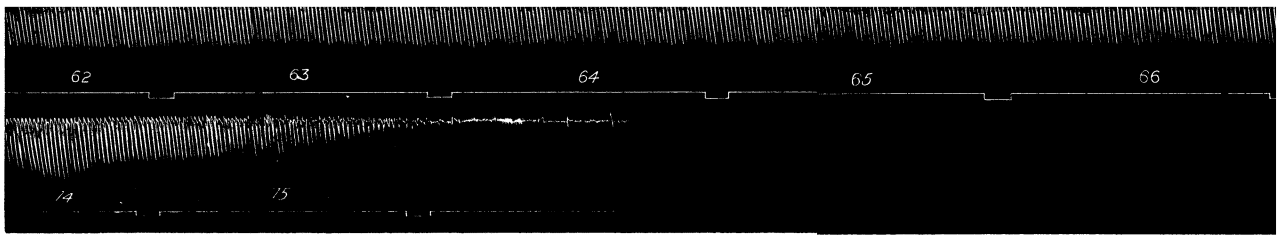
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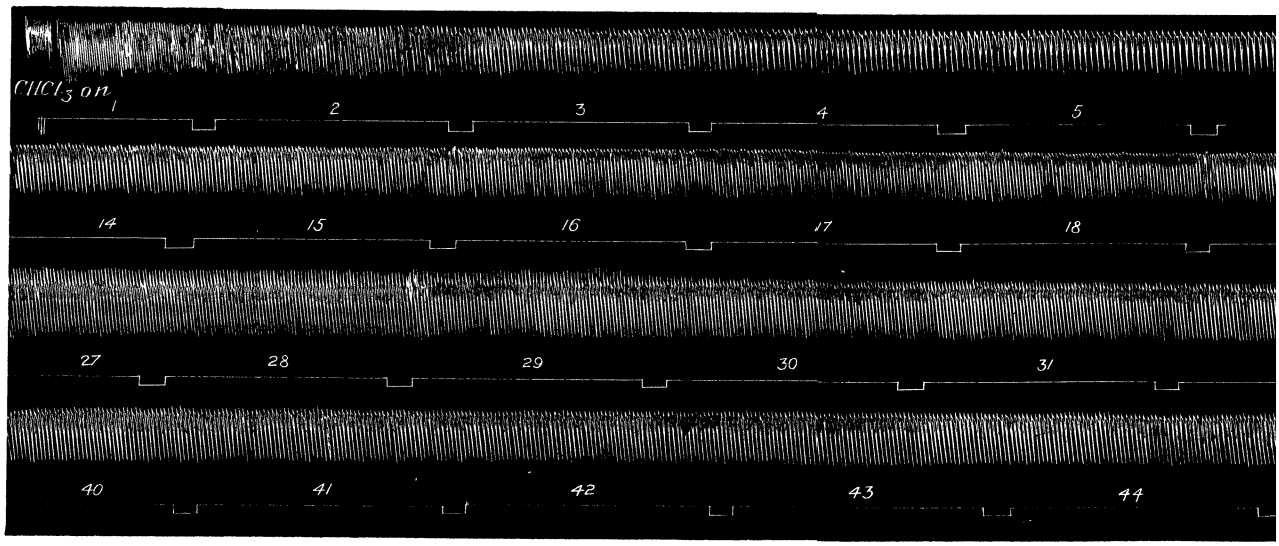
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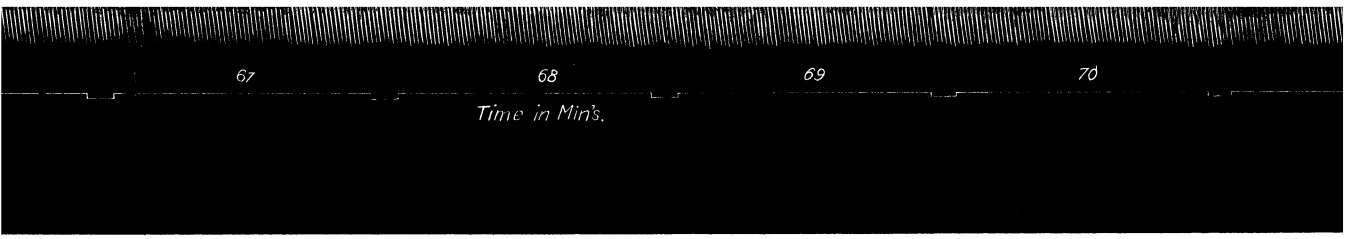
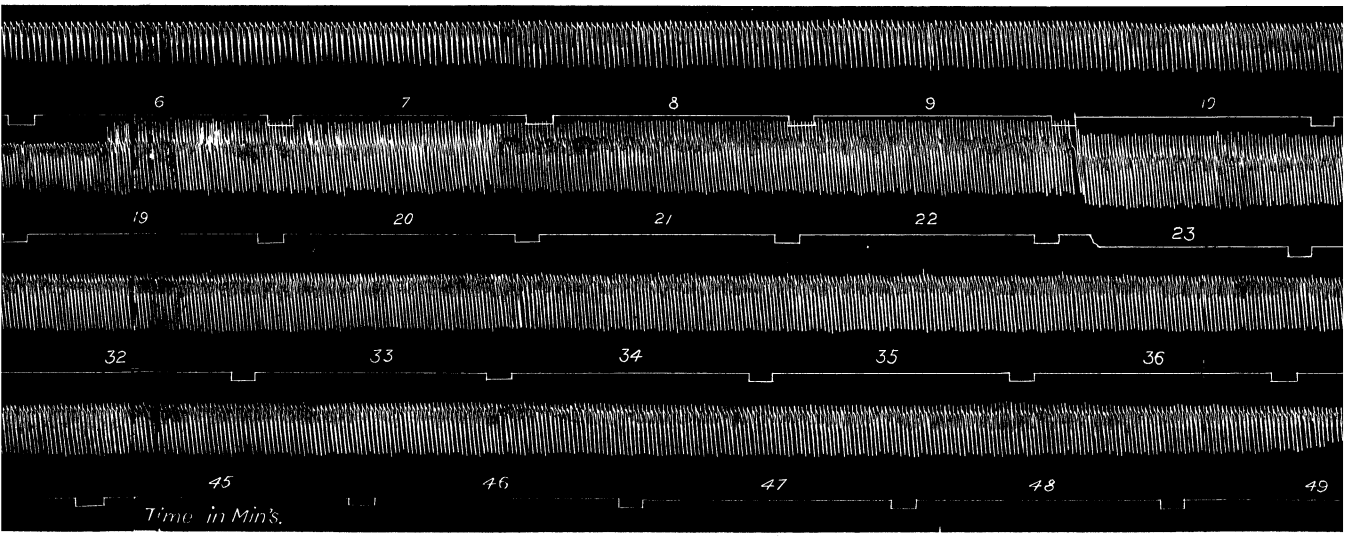
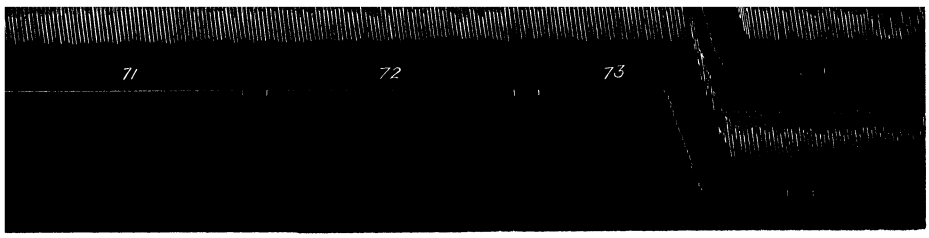


2. EXPERIMENT XXIV.—Respiratory tracing taken after hæmorrhage.



3. EXPERIMENT XXIV.—Respiratory tracing taken after replacement of blood.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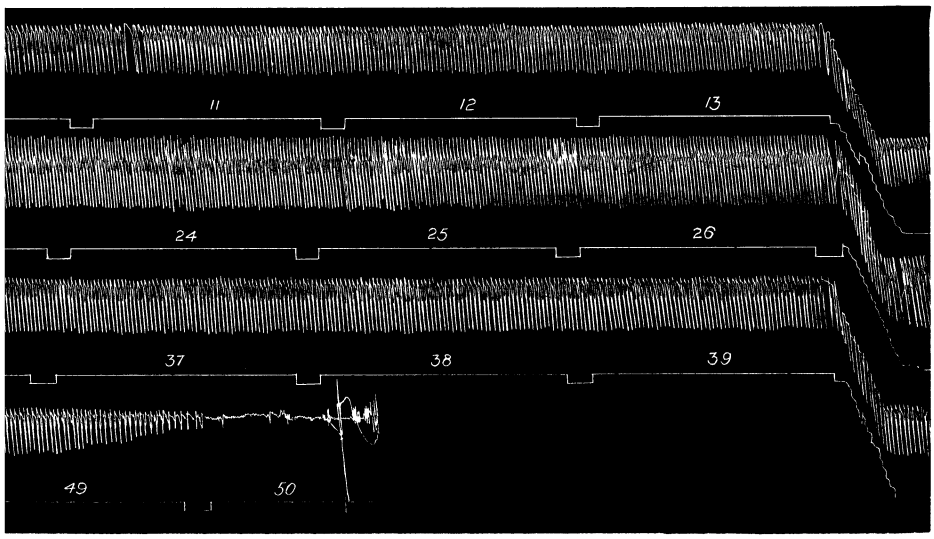
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of blood is practically the same. In the third experiment a small increase is noticed after restoration of blood. In the case of the two incomplete experiments the percentages of chloroform in the blood after replacement are of the same order of magnitude as is found in normal animals at the stage when respiration ceases.

Experiments in which comparisons were made of the percentage of chloroform in the blood at the asphyxial state in the normal animal, after a hæmorrhage, and after the replacement of the blood which had been withdrawn by the blood of another animal of the same species.

The mode of experiment was the same as that already described; the results are given in table (No. V).

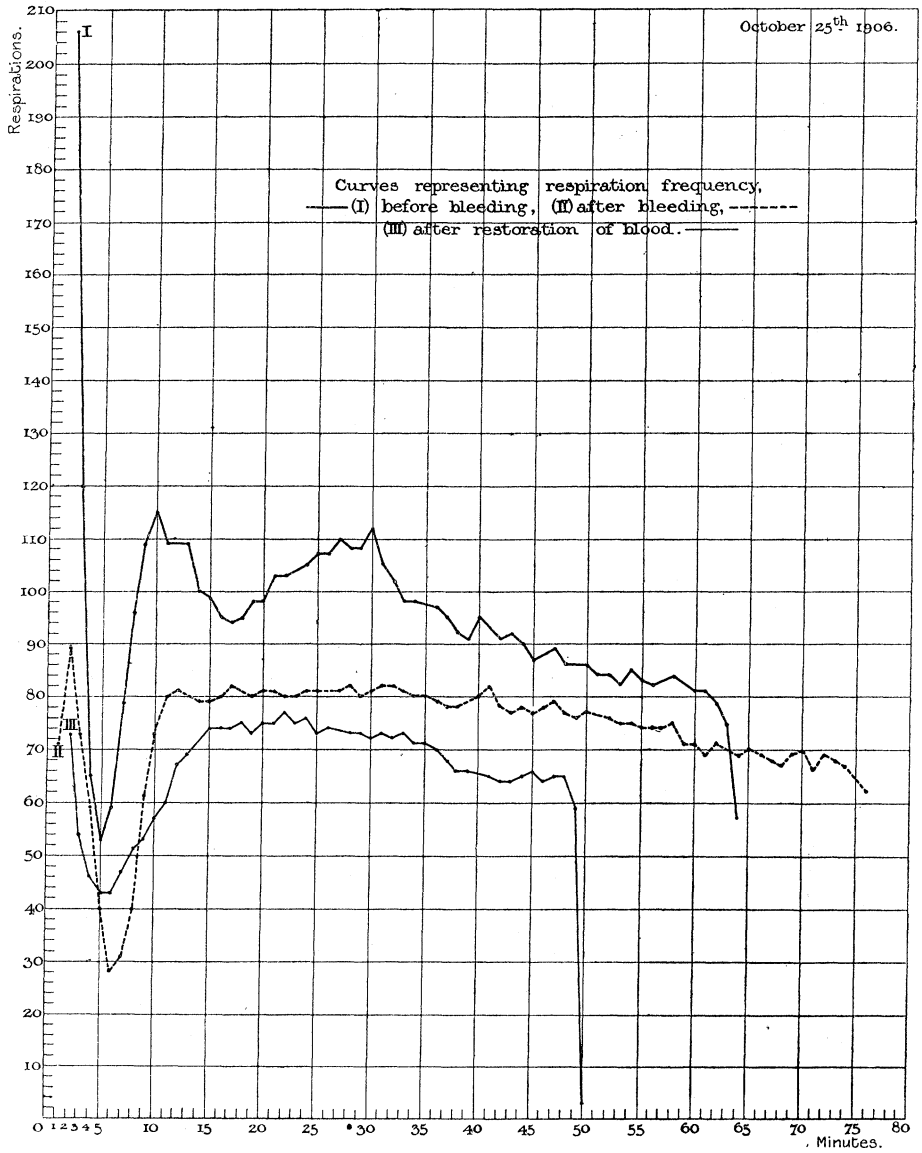
The results given in Table V confirm generally the results of the experiments quoted in the previous tables. Closer results cannot be expected when the prolonged and complex nature of the experiment is taken into consideration. In connection with Experiment XXIV we have thought it advisable to give the tracings of the respiratory movements which were obtained before bleeding the animal, after withdrawal and after replacement of blood, together with curves indicating the rate of the respirations during these three conditions. These tracings and curves are broadly typical of a large number of experiments. In the case of all the experiments in which Woulff's bottle was used, the figures given for the percentage of chloroform administered were obtained by a densimetric estimation at the end of the experiment, and, therefore, only represent the strength of the chloroform-air mixture for the particular time they were taken. They probably indicate, however, within narrow limits, the average value during the experiment.

Conclusions.

The experiments we think show that the percentage of chloroform in the blood does not suffer any variation corresponding to differences in the volume of circulating blood, and the results are therefore in accord with what we should have expected would be the case if the red corpuscles were the essential agents for the transport of chloroform.

As to the duration of time which elapses between the commencement of the inhalation of chloroform and cessation of respiration, it will be noticed that the length of time does not vary according to the volume of blood in circulation; sometimes this was shorter, sometimes longer after than before a hæmorrhage. A somewhat greater equality in time is apparent in those experiments where the respiration ceased at an early period of anæsthesia.

These results are in accordance with the views expressed in a former paper.* We may mention here that a large number of experiments besides those described were made with a view to ascertain this particular point,



EXPERIMENT XXIV.

whether a loss of blood had a direct influence on the duration of anæsthesia, taking as the end-point the cessation of respiration. The results are in

* 'Roy. Soc. Proc.,' *ibid.*

agreement with those we have described above, and therefore do not think it necessary to publish them in detail.

We take this opportunity of expressing our thanks to the Government Grant Committee of the Royal Society for assistance in carrying out this work. We also desire to express our indebtedness to our assistant, Mr. G. W. Ellis, for the care he has taken in carrying out many of the analyses.

On the Rate of Elimination of Chloroform from the Blood after Anæsthesia.

By GEORGE A. BUCKMASTER, Assistant Professor of Physiology, University College, University of London, and J. A. GARDNER, Lecturer on Physiological Chemistry, University of London.

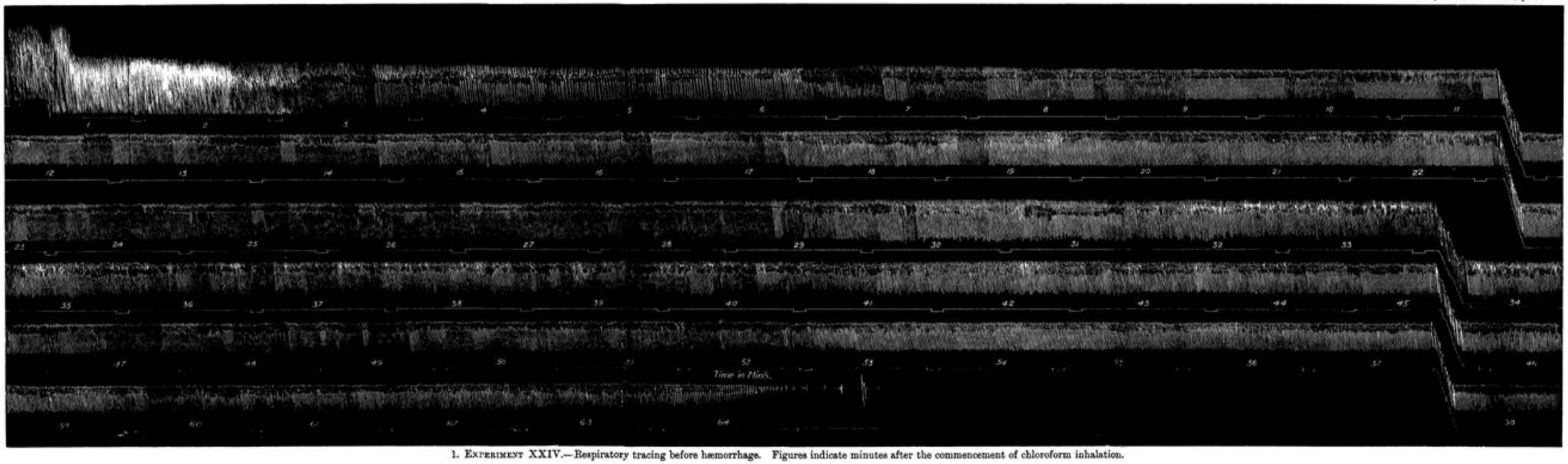
(Communicated by Dr. A. D. Waller, F.R.S. Received July 19, 1907.)

(From the Physiological Laboratory of the University of London.)

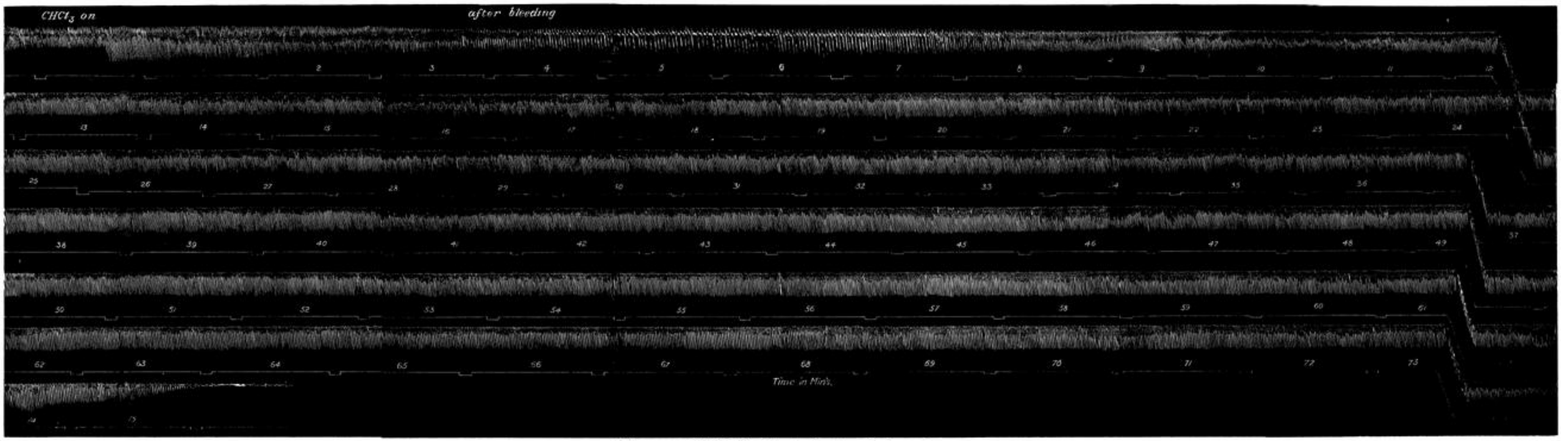
In a paper* on the rate of assumption of chloroform by the blood, we showed that the percentage of chloroform rises very rapidly to a maximal value. This is the cause of an early danger-point in anæsthesia. Subsequently a rapid fall takes place, followed by a more or less rapid rise towards a maximal value, which is maintained during the rest of anæsthesia.

The following remarks will illustrate our conception of the anæsthetic process. The blood at first rapidly becomes charged with chloroform, which is held almost entirely by the red corpuscles. The respiratory centre or centres in the cat become affected quite early, and discharge impulses less frequently than the normal. As a result of this the intake of chloroform is lowered, and consequently the percentage of chloroform in blood falls, either owing to the tissues rapidly storing up the drug at the expense of the blood, or because the elimination of chloroform is as rapid or more rapid than the assumption, or to both these causes. If the first danger-point is safely passed, the respirations improve in frequency and become rapid. It is known that many chemical substances, for instance, the group of alcohols, ether or chloroform, which are lethal, primarily act as exciting agents on living cells. Thus those bodies which in a given concentration are lethal for protoplasm, in lower amounts check its activities, but in still less amount, so long as this is above the indifferent point, inversely will act as a stimulus and augment the energy-discharges of protoplasm. In the case of

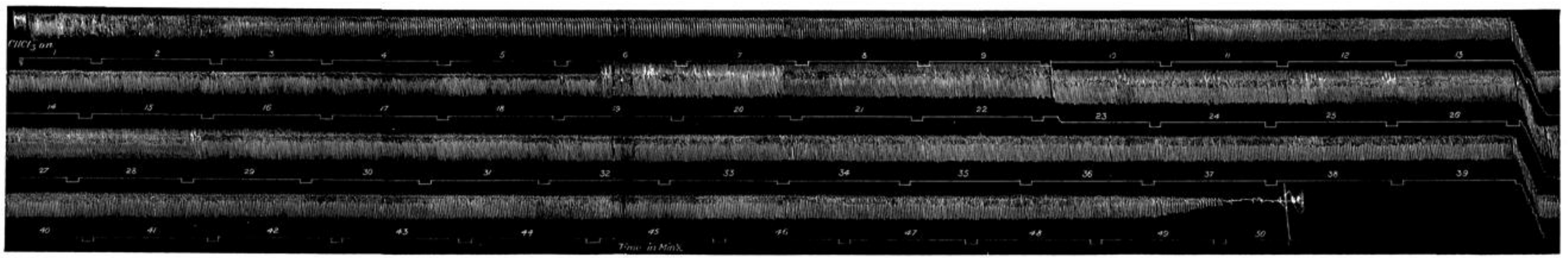
* 'Roy. Soc. Proc.,' this volume, p. 555.



1. Experiment XXIV.—Respiratory tracing before hæmorrhage. Figures indicate minutes after the commencement of chloroform inhalation.



2. Experiment XXIV.—Respiratory tracing taken after hæmorrhage.



3. Experiment XXIV.—Respiratory tracing taken after replacement of blood.