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.

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(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.

chloroform it would seem that there is an initial stimulating effect which may approach the lethal value, but that if this is not actually attained the stimulating effect, which was masked, persists as a recognisable after-effect when the first danger-point has been passed. Thereafter the chloroform-content of the blood approximates to a maximal value, which is maintained until asphyxia takes place (maximum value).

If the rate of elimination were more rapid than the rate of intake, or even equal to this, it would not be easy to understand why this maximal value is so rapidly reached or maintained, and for these reasons it appeared important that we should study the rate at which chloroform was eliminated during anæsthesia.

Method.

All the experiments were performed upon cats, which were anæsthetised by ether, and the necessary operations performed after an injection of hirudin into the femoral vein in quantity sufficient to delay the coagulation of the blood during the time of the experiment. After the animal had so far recovered from ether that the reflexes had reappeared but it was still under the influence of the drug, chloroform of about 2 to 3 per cent. was administered from a Woulff's bottle of the form described in our former papers. The inhalation was stopped in some cases when the asphyxial point was reached, and in other cases at an earlier point during the period we have described as the second stage of anæsthesia. Immediately the inhalation of chloroform was stopped, samples of blood were abstracted from the central end of one carotid artery or from the cephalic end of the external jugular vein, or from the side tube of a short T-piece connecting the cephalic and thoracic end of the vein, or by the introduction of a tube several inches in length along the vein, so that a sample of blood could be taken from the right auricle at definite intervals of time. In some experiments only arterial blood was examined, in others only venous, and in other cases samples were taken *simultaneously from both the artery and vein.* The methods of collecting and analysing samples of blood were those fully described in our former papers. In some experiments, however, it was found more convenient to abstract the venous blood from the cannula by means of a syringe. During the entire course of any experiment the respirations were recorded by a tambour placed on the ensiform cartilage.

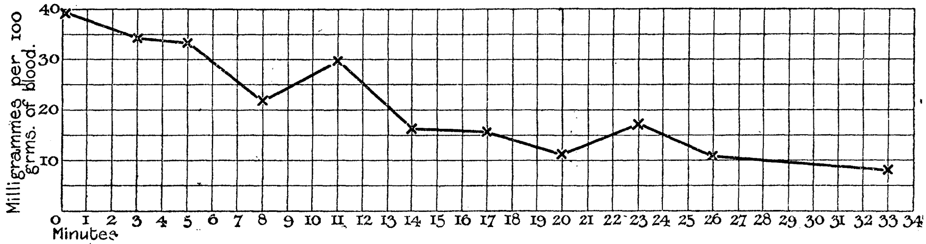
From all our experiments we have selected five typical examples, details of which are given.

Experiment I.

Cat. Weight 3·7 kilogrammes. Respiration recorded by tambour on abdomen. Samples from carotid artery.

Table I.

Time.	Anæsthetic.	Weight of blood in grammes.	Weight of AgCl in grammes.	Percentage of chlorine in grammes per 100 gr. blood.	Percentage of chloroform.	Colour of blood.	Remarks on respiration.	General remarks.
1.35	Ether on							
2.5	—	3·1586	0·0424	0·3319	—	—		Control sample
2.9	$CHCl_3$ on							
3.14	$CHCl_3$ off	—	—	—	—	—		Breathing feeble; respiration ceased half a minute later
3.14¼	—	3·0899	0·0459	0·3673	0·0397	—	No respirations	
3.15¾	—	—	—	—	—	—	Respirations began	
3.17	—	2·147	0·0315	0·3627	0·0346	Bright		
3.19	—	1·9547	0·0286	0·3617	0·0335	Very dark	Respirations had become irregular	Respirations ceased at this point
3.20	—	—	—	—	—	—	Respirations began and were regular	
3.21	—	—	—	—	—	—	Cheyne Stokes type	
3.22	—	3·2568	0·0463	0·3515	0·0222	Medium bright		
3.25	—	2·7221	0·0394	0·3578	0·029	Dark		
3.27	—	—	—	—	—	—	Respirations normal and deep	
3.28	—	2·7027	0·0379	0.3467	0·0166	Quite light ...	„ „ „	
3.31	—	3·3653	0·0471	0·346	0·0159	Very „		
3.32½	—	—	—	—	—	—		Tendon reflex just reappearing
3.33	—	—	—	—	—	—		Left eye reflex
3.34	—	2·5118	0·0348	0·3425	0·0119	Very light......	Respirations normal to end of experiment	
3.34½	—	—	—	—	—	—		Tendon reflexes were back
3.35½	—	—	—	—	—	—		Ear reflex back
3.36½	—	—	—	—	—	—		Both eye reflexes back
3.37	—	1·9495	0·0274	0·3475	0·0175	Very bright ...		Eye reflexes well marked
3.39								
3.40	—	2·9053	0·0402	0·3421	0·0115	„ „ ...		
3.40½	—	—	—	—	—	—		Tail reflexes back
3.45	—	—	—	—	—	—		Pupils normal
3.47	—	2·6158	0·0359	0·3393	0·008	Bright		

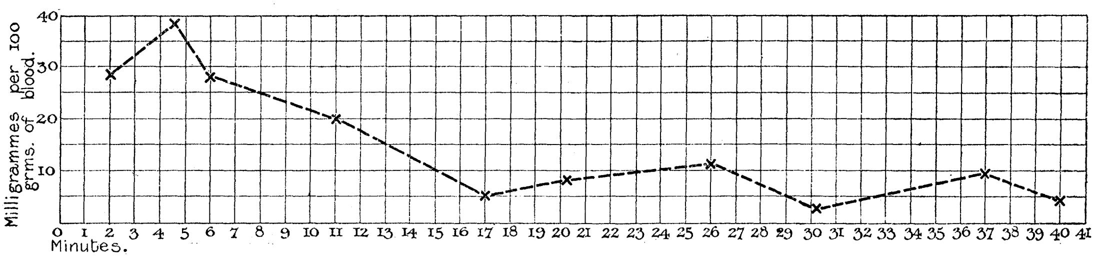


CURVE A.—Constructed from Data given in Experiment I.

Ordinates = milligrammes of chloroform in 100 grammes of blood; abscissæ = times in minutes after the cessation of chloroform inhalation; × = samples of arterial blood (eleven).

Experiment II.

Cat. Weight 3·5 kilogrammes. Respiration recorded by tambour on abdomen. Samples taken by a syringe from a long cannula introduced into the external jugular vein, so that blood was withdrawn from the circulation close to the right auricle. It was ascertained *post mortem* that this was the case. The first cubic centimetres of blood withdrawn were rejected so as to avoid taking a sample of stagnant blood in the vein.



CURVE B.—Constructed from Data given in Experiment II.

Ordinates = milligrammes of chloroform in 100 grammes of blood; abscissæ = time in minutes after the cessation of chloroform-inhalation; × = samples of venous blood withdrawn close to right auricle.

Experiment III.

Cat. Weight 3 kilogrammes. Samples taken simultaneously from the carotid artery and from the central end of the external jugular vein. The venous blood was withdrawn by a syringe from a cannula pushed down the vein so that the blood was aspirated from the superior vena cava close to the right auricle. The exact position was ascertained *post mortem.* In order to obtain the sample as close to the heart as possible, the blood stagnant in the vein was rejected. The details of this experiment are given in Table III, from which Curve C was constructed.

A number of other experiments were also performed, for example, some in

Table II.

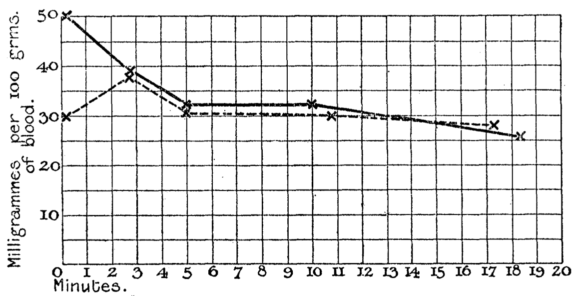
Time.	Anæsthetic.	Weight of blood in grammes.	Weight of AgCl in grammes.	Percentage of chlorine.	Percentage of chloroform.	Colour of blood.	Respiratory remarks.	General remarks.
2.15	Ether started							
2.26	—	—	—	—	—	—		Hirudin injected
2.40	—	2·2176	0·0294	0·32779	—	—		Control sample
2.43	$CHCl_3$ on	—	—	—	—	—		Reflexes well back
3.11	$CHCl_3$ off							
3.11¼	—	—	—	—	—	—	Breathing ceased	
3.12¼	—	—	—	—	—	—	Respirations commence in an irregular way	
3.13	—	2·7634	0·0395	0·3534	0·0287			
3.14	—	—	—	—	—	—	Still irregular; ceased for 25 seconds	
3.15½	—	2·1758	0·0319	0·3625	0·0389	Darkish	Irregular and shallow	
3.16	—	—	—	—	—	—	Respiration normal for this stage	
3.17	—	2·2555	0·0321	0·35187	0·027	Brighter		
3.19	—	—	—	—	—	—		Tube exploded
3.20½	—	—	—	—	—	—		Slight corneal reflex in both eyes
3.21	—	—	—	—	—	—		Tendon reflexes back
3.22	—	1·8378	0·0257	0·3457	0·02	Bright		Corneal reflexes good
3.28	—	3·1199	0·0419	0·33205	0·0048	„	Respiration normal for this stage	
3.31¼	—	2·4824	0·0336	0·33465	0·0077	Rather darker		
3.37	—	2·2745	0·0311	0·33807	0·0115	Dark	„ „	
3.41¼	—	2·3814	0·0318	0·33016	0·0026	Very dark ...	„ „	
3.48	—	2·387	0·0325	0·33663	0·0099			
3.51	—	2·3244	0·0312	0·3319	0·0046	—	„ „	

Table III.

Time.	Anæsthetic.	Artery. Weight of blood in grammes.	Artery. Weight of AgCl in 100 grammes blood.	Artery. Percentage of chlorine in 100 grammes.	Artery. Percentage of $CHCl_3$ in 100 grammes.	Artery. Colour of blood.	Vein. Weight of blood in grammes.	Vein. Weight of AgCl in 100 grammes blood.	Vein. Percentage of chlorine in 100 grammes blood.	Vein. Percentage of $CHCl_3$ in 100 grammes blood.	Vein. Colour of blood.	Remarks.
2.45	Ether											
2.56		—	—	—	—	—	—	—	—	—		Hirudin injected in femoral vein
3.14	—	—	—	—	—	—	2·9502	0·0407	0·34109	—	—	Control from vein
3.15	Ether off	—	—	—	—	—	—	—	—	—	—	Artificial respiration
3.23	$CHCl_3$ on											
4.11	$CHCl_3$ off	—	—	—	—	—	—	—	—	—	—	Resp. 53 per min.
4.11¼	—	1·9274	0·0301	0·38612	0·05	—	2·6992	0·0402	0·36823	0·03	—	„ 53 „
4.13¾	—	1·1769	0·0269	0·37597	0·039	—	2·6146	0·0397	0·37542	0·0385		
4.16	—	2·2614	0·0338	0·36954	0·032	—	3·2532	0·0485	0·3686	0·031	—	„ 50 „
4.21	—	2·9935	0·0448	0·37002	0·0324							
4.21¾	—	—	—	—	—	—	2·7019	0·0402	0·36786	0·03	—	„ 38 „
4.24	—	—	—	—	—	—	—	—	—	—	—	Eye and tendon reflexes back
4.28¼	—	—	—	—	—	—	3·6653	0·0543	0·36627	0·028		
4.29¼	—	3·4006	0·0501	0·36426	0·026	—	—	—	—	—	—	Resp. 33 per min.

NOTE.—Respiration uniform in depth throughout the experiment.

which the right external jugular vein was severed and the ends connected by means of a glass tube with a lateral branch from which the blood was withdrawn without interfering with the flow of blood, samples of blood being taken at the same time from the carotid artery. In other experiments, samples were taken simultaneously from the carotid artery and central end of the external jugular vein. In the following Tables IV and V we give the results of two types of these experiments. When the blood was taken without much disturbance to the circulation (Table IV) and was really a sample of particular venous blood coming partly from muscles and partly from the brain, obvious variations in the chloroform-content of the blood occur which may be due to variations in the rate of discharge from the tissues but of the exact significance of which we have no knowledge. Similar variations in the content of venous blood are noticed in the data given in Table V.



CURVE C.—Constructed from Data given in Experiment III.

Ordinates = milligrammes of chloroform in 100 grammes of blood; abscissæ = times in minutes after the cessation of chloroform-inhalation; ×——— = arterial blood; ×- - - - - = venous blood.

General Conclusions.

The rate of elimination appears to depend upon the physiological state of the individual animal, but when all the experiments described in this paper are considered generally and compared with those in our previous papers, the rate of output is found to be at first comparatively rapid, and then subsequently becomes slower. The initial rates of elimination are, however, much less rapid than the initial rates of the intake of chloroform, and, therefore, on the whole, elimination is a much slower process than assumption, a view which is borne out by a comparison of the times at which the various reflexes disappear and reappear.

As the results of his experiments on dogs, Nicloux* shows that the arterial blood loses about half its chloroform-content five minutes after inhalation is stopped, and at the end of one hour about one-third to one-quarter of what the blood originally held is eliminated. At the end of

* 'Comptes Rendus,' 1906, vol. 60, p. 14.

Table IV.

Time.	Anæsthetic.	Artery. Weight of blood in grammes.	Artery. Weight of AgCl in 100 grammes blood.	Artery. Percentage of chlorine in 100 grammes.	Artery. Percentage of $CHCl_3$ in 100 grammes.	Artery. Colour of blood.	Vein. Weight of blood in grammes.	Vein. Weight of AgCl in 100 grammes blood.	Vein. Percentage of chlorine in 100 grammes blood.	Vein. Percentage of $CHCl_3$ in 100 grammes blood.	Vein. Colour of blood.	Remarks.
2.15	Ether											
2.52	—	—	—	—	—	—	—	—	—	—	—	Hirudin in femoral vein
2.53	—	3·7841	0·0535	0·34955	—	—	—	—	—	—	—	Control from artery
3.0	$CHCl_3$ on											
3.20	$CHCl_3$ off											
3.20¼	—	3·5269	0·0561	0·39328	0·049							
3.21	—	—	—	—	—	—	2·2695	0·0359	0·39111	0·0466		
3.22¼	—	3·256	0·0502	0·38119	0·0355							
3.22¾	—	—	—	—	—	—	2·1454	0·0338	0·38953	0·045		
3.23¼	—	3·185	0·0487	0·37805	0·032							
3.23¾	—	—	—	—	—	—	2·447	0·0371	0·37486	0·028		
3.24¾	—	3·1778	0·0483	0·37579	0·029							
3.25¼	—	—	—	—	—	—	2·5029	0·0384	0·37933	0·033		
3.26¼	—	3·48	0·0532	0·37797	0·032							
3.26¾	—	—	—	—	—	—	2·5219	0·0392	0·38431	0·039		
3.28	—	—	—	—	—	—	—	—	—	—	—	Corneal reflexes in one eye
3.28½	—	—	—	—	—	—	—	—	—	—	—	Tendon reflex back
3.29	—	—	—	—	—	—	—	—	—	—	—	Both eye reflexes
3.30	—	—	—	—	—	—	—	—	—	—	—	Pupils dilated
3.33½	—	—	—	—	—	—	—	—	—	—	—	Tail reflexes back
3.37	—	—	—	—	—	—	—	—	—	—	—	Eyeballs move; pupils less dilated
3.44	—	—	—	—	—	—	—	—	—	—	—	Eyeballs still rolling
3.45	—	2·9613	0·0439	0·36653	0·019							
3.50	—	—	—	—	—	—	—	—	—	—	—	Not quite round

Table V.

Time.	Anæsthetic.	Artery.					Vein.					Remarks.
		Weight of blood in grammes.	Weight of AgCl in 100 grammes blood.	Percentage of chlorine in 100 grammes.	Percentage of $CHCl_3$ in 100 grammes.	Colour of blood.	Weight of blood in grammes.	Weight of AgCl in 100 grammes blood.	Percentage of chlorine in 100 grammes blood.	Percentage of $CHCl_3$ in 100 grammes blood.	Colour of blood.	
1.35	Ether											
2.40	—	—	—	—	—	—	—	—	—	—	—	Hirudin injected in femoral vein
2.45	—	2·8628	0·0376	0·32473	—	—	—	—	—	—	—	Control
2.58	$CHCl_3$ on											
3.29	$CHCl_3$ off	—	—	—	—	—	—	—	—	—	—	Resp. 36 per min.
3.29¼	—	2·0937	0·0315	0·37198	0·053	Dark	2·07872	0·0306	0·36405	0·044	—	,, 33 ,,
3.31	—	2·9353	0·0432	0·36388	0·044	—	2·0656	0·0304	0·36388	0·044	—	,, 58 ,,
3.32	—	4·1472	0·0609	0·36307	0·043							
3.32¼	—	—	—	—	—	—	1·7525	0·0253	0·35694	0·036		
3.34	—	3·8407	0·0557	0·35957	0·038							
3.35¼	—	—	—	—	—	—	1·4911	0·0217	0·35982	0·039		
3.37	—	3·2474	0·04549	0·34947	0·028	—	—	—	—	—	—	Resp. 58, but shallower
3.37½	—	—	—	—	—	—	2·5604	0·0367	0·35439	0·033	Darkish	
3.39½	—	—	—	—	—	—	—	—	—	—	—	Eye reflexes just back
3.43	—	—	—	—	—	—	—	—	—	—	—	Tendon reflexes back
3.43½	—	—	—	—	—	—	—	—	—	—	—	Tail reflexes back; pupils contracting
	—	—	—	—	—	—	—	—	—	—	—	Pupils normal
3.47	—	2·457	0·0345	0·34717	0·025	Bright	—	—	—	—	—	Respiration as last observation
3.47¼	·											

seven hours the blood still may contain 1 to 2 milligrammes per cent. of chloroform. He also observed that the palpebral reflex reappeared within $1\frac{1}{2}$ to 2 minutes after anæsthetic periods which lasted 38 and 67 minutes. In one experiment he mentions that the animal got up and walked off the table 30 minutes after the chloroform was stopped, and the animal appeared to be quite normal, though at this period there were 10 milligrammes of chloroform per cent. in the blood.

In the case of cats, the curves for arterial blood show a general similarity in form to curves which we have constructed from the data given in Nicloux's paper. The initial falls in our curves are not so rapid as in the case of the dog, and the chloroform-content of arterial blood was only reduced by 50 per cent. in about 15 to 20 minutes. In our longest experiments, about three-quarters of the chloroform was eliminated in about 30 minutes, when the animal was breathing normally. When, however, an increased ventilation of the lung is brought about by artificial respiration, a very much shorter space of time is required, as is evident from the analyses quoted in former papers.

Reflexes in our experiments reappear later than was noticed by Nicloux for dogs; but though the pinna reflex, corneal reflex, tendon reflex, and tail reflex were noted, there is no definite order in which they reappear, though as a rule the tail reflex is the last.

Not infrequently an animal goes to sleep during recovery from anæsthesia, but we have never noticed the rapid recovery of volition to which Nicloux has drawn attention.

According to Tissot's observations, it would appear that during recovery from anæsthesia the amount of chloroform in venous blood constantly exceeds the amount in arterial, as may be seen from the following table constructed from his paper. He also considers that a study of the chloroform-content of arterial blood should be made during the induction of anæsthesia and of venous blood during the disappearance of anæsthesia.

	Cessation of chloroform administration.	45 minutes later.	2 hours later.
Arterial blood ...	53·2	5·8	0·0
Venous blood ...	48·1	7·7	4·9

All these results we cannot confirm, though in Tables III, IV, and V, which are those of the chloroform-content of samples of arterial and venous blood taken simultaneously, we are in agreement with Tissot's observations that at the moment when chloroform is stopped, arterial blood contains an excess of the drug when compared with venous blood.

For the sake of argument, we will assume that during recovery from anæsthesia the blood circulates in the body, and that no exchange of chloroform takes place between the blood and tissues. Under such conditions it is clear that, given a steady elimination at the surface of the lungs, the amount of chloroform in arterial blood would be constantly less than in venous, and this difference would probably be a decreasing one. During the initial rapid elimination, this difference would conceivably be marked and easily detectable by experiment; but in the later stages, where the elimination is slow, the difference would possibly lie within the errors of experiment. But during recovery from anæsthesia there will be superimposed on this simple conception of the circulation a discharge of chloroform from the tissues into the venous blood. If this took place steadily, it would tend to increase the difference between arterial and venous blood. The problem, however, appears to be more complex. First of all, the blood comes from regions such as the muscles, viscera, etc., which are probably not charged to any great extent with chloroform, compared to what is believed to be the case for the central nervous system. The nerve centres are differently affected, and doubtless discharge at different rates, as the evidences of their activity or paralysis appear and disappear irregularly. Further, it is not inconceivable that during the elimination one region may be discharging chloroform while other cell-districts are relatively inactive in this respect, or even actually continuing to absorb chloroform. The question will be further complicated in a very marked degree by the nature of the respiration at any moment, for the depth and frequency of respirations naturally govern the elimination at any particular moment. On the whole, therefore, we should expect the chloroform-content of venous blood to be higher than that of the arterial, but this difference would be slight in the later periods of elimination. In actual experiments one would expect the result would depend markedly on the particular source whence the venous blood was taken. A comparison with Curves A and B shows a general similarity in the rate of elimination both in the case of arterial and venous blood. Both curves show irregularities in the rate. In Curve C, the chloroform-content of arterial blood is contrasted with the general venous blood of the body (sample taken close to the heart). At the moment of cessation of respiration, the arterial blood is markedly higher than the venous, but after regular respiration is established, the two curves are practically identical, the difference being within the errors of experiment.

The work has been carried out with the help of a grant which was made to us by the Government Grant Committee of the Royal Society, for which we now express our thanks.