A REPORT ON THE PHYSIOLOGICAL ACTION OF CHLOROFORM, WITH A CRITICISM OF THE SECOND HYDERABAD CHLOROFORM COMMISSION.

By W. H. GASKELL, M.D., F.R.S.,
Lecturer on Physiology in the University of Cambridge,
AND

L. E. SHORE, M.D.,
Demonstrator in Physiology in the University of Cambridge.

INTRODUCTORY OBSERVATIONS.

IN the summer of 1890, when Surgeon-Lieutenant-Colonel Lawrie was in England, he asked one of us (Gaskell) to look over the curves of the Second Hyderabad Chloroform Commission, and make a report on them, supplementing that report with experimental investigation, if necessary.

At the very outset it was evident that the Commission did not supply any answer to the most important question connected with the action of chloroform—namely, What is the reason of the fall of blood pressure which always occurs when a large dose of chloroform is administered? Before, therefore, it was possible to report on the curves of the Commission, it was necessary to make up our minds upon the meaning of this fall of blood pressure. For that purpose, we have carried out a number of experiments, and propose in this paper to give the results of those experiments, as well as a criticism of some of the conclusions of the Hyderabad Commission. The funds for this research were most generously provided by H.H. the Nizam, upon the application of Surgeon-Lieutenant-Colonel Lawrie; and we beg here to thank them for their aid in carrying out this investigation.

As far as the physiological action of chloroform is concerned, the controversy which has raged so long about the safety of its administration resolves itself into the question of its relative action upon the central nervous system and the peripheral organs. On the one side, we find the evidence given by Lawrie and the Hyderabad Commission, that chloroform acts essentially, if not entirely, as a paralyser of the central nervous system, but does not act directly upon any of the peripheral organs; while, on the other hand, the evidence of Snow, and in recent years of the Glasgow Commission, of Wood, and of McWilliam, is to the effect that chloroform acts directly as a paralyser of the heart, as well as on the nervous system.

So much has been written and spoken about chloroform of late years, that it is hardly necessary to write out the history of its experimental investigation; but it is perhaps advisable to mention some of the original observations and conclusions of Snow in 1858, seeing that at the present time the older observations are apt to be overlooked.

Snow's experiments on animals were performed without the graphic methods of modern days, and were largely directed towards the investigation of the relative effects upon the heart and respiration of air containing chloroform to a varying amount. His experiments show that if the air breathed contains 3 to 6 per cent. of chloroform vapour then respirations cease while the heart sounds are very distinct; but if the air contains 8 to 10 per cent. of chloroform vapour then the action of the heart is always extremely feeble, even if it does not actually cease before the arrest of the respiration; and on page 89 he observes with respect to the danger of concentration of the chloroform vapour, "If the air the patient breathes never contains more than 5 per cent. of chloroform vapour the pulse can never be seriously affected by the direct action of chloroform, and the state of the breathing affords the best warning against continuing the inhalation too long a time."

He further says that the pulse sometimes becomes inter-

mittent or irregular during the administration of chloroform, but adds that he has never seen any danger in this condition. Also, page 90, "the patient sometimes holds the breath after he is unconscious and before he is insensible; in other cases, in the third stage of narcosis, where there is rigidity of muscles. In neither case is there danger in this condition *per se*." He points out that after the cessation of inhalation the symptoms of poisoning may increase owing to the absorption of chloroform still in the lungs. Also struggling and rigidity with holding of breath, which usually occurs when the patient has nearly absorbed the necessary amount, requires careful looking after, owing to the excessive inspirations which follow and may lead to the intake of a large amount of chloroform unless precautions are taken.

After the advent of graphic methods of registration we have the evidence of the Glasgow Commission in which special prominence was given to sudden stoppage of the heart and to capricious effects of chloroform. Such effects are seen mainly at the beginning of chloroform administration, and are clearly free from danger, as asserted by Snow, being simply Nature's safeguard against an irritant vapour, as pointed out by the Hyderabad Commission. Such effects are: (1) stoppage of respiration reflexly through the trigeminal and other nerves; (2) slowing or stoppage of the heart through the vagus nerve—both reflex actions for the purpose of preventing access of the vapour to the blood and so to the nervous system. In this of itself there is no danger; the only danger is in the after-effect, as maintained by the Hyderabad Commission; namely, in the likelihood of too large a dose being taken in owing to the excessive inspirations.

It is agreed on all sides that the effect of a large dose of chloroform is to cause insensibility, diminution of reflexes, a marked lowering of blood pressure, and finally slowing and cessation of respiration.

The Hyderabad Commission does not attempt to explain the reason of the fall of blood pressure, though it is evident, from the following remarks of Lawrie, that he at all events is inclined to attribute it to the action of the drug upon the vasomotor centre. He says: "The Commission has given no opinion as to the cause of the fall produced by diluted chloroform alone. It is obvious from all their experiments that the effects of chloroform are first exerted upon the nervous tissues, the vasomotor centre is very soon involved, the respiratory centre becomes paralysed, then the muscular tissues become affected, and last of all the heart."

So also the Glasgow Commission and Wood regard the paralysis of the vasomotor centre as a possible factor in producing the fall of blood pressure, but do not attempt to distinguish between its share and that of the heart.

Even McWilliam,² who makes so much of the dilatation of the heart by chloroform, says: (Par. 17) "The fall of blood pressure is in its earlier stages due mainly to the depressing effect of the anæsthetic on the vasomotor centre, preceded often by a slight stimulation; the later stages are associated with failure of the heart as well as of the vasomotor centre." In fact, the fall of blood pressure is looked upon by most observers as largely due to paralysis of the vasomotor centre, and yet, as far as we can find out, this conclusion is not based upon any direct experimental evidence. Further, seeing that the initial part of the blood pressure fall is that part which is especially attributed to the paralysis of the vasomotor centre, and also that the fall of blood pressure is an early symptom in chloroform administration, it follows that experimental evidence ought not only to show a paralysis of the vasomotor centre by the action of chloroform, but also that centre ought to be more susceptible to the paralyzing action of the drug than the neighbouring respiratory and cardio-inhibitory centres, seeing that the fall of blood pressure begins before the respiration shows any signs of paralysis and vagus effects upon the heart can still be produced after the blood pressure has commenced to fall.

PLAN OF OUR EXPERIMENTS.

In considering the relative share played by the heart and the vasomotor centre in the production of this blood pressure fall there are two possibilities: 1. The fall of blood pressure

¹ *Hyd. Com. Report*, p. 244.

² *BRITISH MEDICAL JOURNAL*, October 18th, October 2th, and November 1st, 1890.

may be due in the first instance to failure of the vasomotor centre, the heart not being affected until a very excessive dose has been given. 2. The fall of blood pressure may be due from the very first to a weakening of the heart's action, the vasomotor centre not being affected until a very excessive dose has been given.

The object of our investigation then was to determine (1) the primary effect of chloroform, and (2) the ultimate effect of a large dose on the vasomotor centre and on the heart respectively. Our object was to separate, as far as possible, the application of the drug to the medulla oblongata and to the heart, and for this purpose we made, in the first instance, the following experiments:

1. Direct application of chloroform to the exposed fourth ventricle.

2. Injection of chloroform into the jugular vein.

3. Injection of chloroform into the internal carotid artery.

4. Injection of chloroform into the vertebral artery.

In this set of experiments we found, as will appear below, a decided difference of effect according as the chloroform was injected heartwards or brainwards. We felt, however, that a legitimate objection might be taken to drawing any conclusions from these experiments as to the behaviour of chloroform when administered by inhalation, because it did not necessarily follow that the injection of chloroform into a blood vessel was strictly comparable in its effects with chloroform vapour in the blood. We therefore determined to supplement these experiments by another set, the object of which was to administer chloroform by inhalation, and, at the same time, to isolate the brain in such a way that it alone might be subject to the action of the chloroform, or, on the other hand, so that it alone might be exempt from that action. In order to do this we have used in each experiment two animals so arranged that the brain of the one (called the *fed*) was supplied by the blood of the other (called the *feeder*), and was therefore isolated from its own heart; chloroform could be administered to either animal after the cross circulation was established, with the result naturally, as far as the fed animal was concerned, of conveying chloroformed blood to the brain only, or to the heart and all other organs with the exception of the brain. The necessary procedure for the successful carrying out of these experiments was, as can be imagined, long and laborious, but the results amply repaid the trouble, as will, we hope, be evident from the detailed description of these experiments.

Both sets of experiments point to the same conclusion, namely, the fall of blood pressure caused by administration of chloroform is due primarily to a weakening of the heart's action, and not to a paralysis of the vasomotor centre. On the contrary, the primary effect of blood containing chloroform vapour on the vasomotor centre is an excitation, causing thereby a marked rise of blood pressure, and it is only after an excessive dose has been given that there is any evidence of any paralysis of this centre.

In our investigations we have used rabbits and dogs. Most of the experiments were made on rabbits, because we desired to register the movements of respiration as well as the condition of the blood pressure, and, in our opinion, no better method exists for the registration of the movements of respiration, both as regards rate and nature of muscular contraction, than that introduced by Head,³ a method which is only applicable to the rabbit, and consists of the direct registration of the contractions of an isolated strip of the diaphragm muscle itself. In all cases a dose of chloral hydrate was given to the rabbit before the experiment commenced, and, in the case of dogs, they were always under the influence of acetate of morphine before the chloroform was administered.

The blood pressure, taken either from the carotid or femoral artery, was measured by a mercury manometer, recording in the ordinary way on Ludwig's kymograph.

For artificial respiration we used the very efficient apparatus designed by the Cambridge Scientific Instrument Company. By this apparatus an active withdrawal of air from the lungs, as well as an active supply of air, is secured. The rate, depth, and character of the respiration, that is, the relative duration of the inspiratory and expiratory phases, could be regulated with great nicety and maintained with accuracy.

COMPARISON OF THE INJECTION OF CHLOROFORM INTO THE JUGULAR VEIN AND INTO THE BRAIN ARTERIES: INJECTION INTO JUGULAR.

The Hyderabad Commission assert that in Experiment 92 repeated injections of 20 minims of chloroform were made into the jugular vein, and its effect was not to paralyse the heart, but to produce anaesthesia and a gradual fall of blood pressure exactly as if the chloroform had been inhaled. The amount of chloroform injected into the circulation in this experiment was 180 minims, given in 20-minim doses at varying intervals of time during 46 minutes. In other words, this large amount of liquid chloroform was said to have been sent into the circulation, and it was clear from its anaesthetic action on the brain and its effect on respiration that it circulated over the whole vascular system, and yet it produced exactly the same effects as if the chloroform had been inhaled.

Our experiments agree with those of the Hyderabad Commission as to the nature of the effect produced when chloroform is injected into the jugular vein; we do not, however, interpret these effects in the same way.

When a small amount of chloroform is injected into the jugular of a rabbit it always causes a fall of blood pressure, during which (1) the excursions due to the heart beats are diminished in size, and (2) the respiratory curves on the blood-pressure tracing are very much smaller, and may, indeed, almost vanish. During this fall of blood pressure the respiration is not necessarily altered either in rate or force; the blood pressure then recovers either entirely or partially, the pulse and respiratory excursions of the blood-pressure curve become again more conspicuous, and with the rising pressure the respiration may be affected, and the anaesthesia become more profound. Repeated small injections depress the blood pressure more and more, the pulse excursions become less and less visible until, when the pressure is very low, they vanish altogether; the respirations, after having continued vigorously for a long time, gradually slow off with diminishing force of contraction, and finally cease at a time when the heart beats have long ceased to be visible on the blood-pressure tracing.

Such a sequence of events is clearly to be explained by the gradual weakening of the heart's contractions in consequence of the injection, with the final result of a gradual cessation of respiration; and it is noteworthy how the heart is capable of recovering itself after each injection, for some considerable time at all events.

In such a case as this it may be said, without fear of contradiction, that death is due to failure of the heart's action, even although it may be found, on opening the chest, that the heart is very feebly beating after the respiration has stopped. The type of this effect of the injection of chloroform into the jugular vein is given in the following table taken from an experiment on December 11th, 1890, and is illustrated by the tracings in Fig. 1.

It is impossible to reproduce the whole length of the tracing from which this table was compiled, so we have endeavoured, in this case and in others, to give the general effect of the experiment by the publication of portions of the original tracing taken at the times indicated in the corresponding table.

In all the figures, with the exception of Figs. 6, 7, 8, 9, 10, the upper tracing records the contractions of the slip of diaphragm, the upstroke corresponding to the contraction of the muscle, and therefore to a movement of inspiration. The lower tracing is that of the blood pressure, and is recorded from the carotid artery, except in Figs. 6, 7, 8, 9, 10. The points in these two tracings which correspond as regard time may be seen by the two short vertical lines drawn on each figure. The base line, or line of zero pressure, was carefully determined at the end of each experiment, and its position is shown in each figure. In all cases a record of time in seconds was taken, an example of which is reproduced in Fig. 2 upon the base line. An electric signal marker was also attached to the kymograph by means of which the moment of application of chloroform or other important event was registered. The tracings all read from right to left.

Injection of chloroform into the jugular vein frequently causes a fatal result in quite a different manner, death occurring through failure of the respiration, and not through

³ *Journ. of Physiol.*, vol. x, p. 1.

FIG. 1.—December 11th, 1890. Rabbit. Injection of Chloroform into Jugular Vein.

Time.	Blood Pressure in mm.	Respiration Rate per min.	Amount of Chloroform Injected.	Remarks.
H. M. S.				
1 33 0	70	23	—	a in Fig. 1 represents a portion of tracing at this time.
1 34 8	70	23	1 m	
1 34 38	45	—	—	b in Fig. 1 shows disappearance of respiratory curves.
1 36 0	62	32	—	c in Fig. 1 shows recovery of blood pressure.
1 36 27	62	32	1 m	
1 37 0	40	—	—	Respiratory curves nearly disappeared, and did not return throughout experiment.
1 38 0	56	—	—	d in Fig. 1.
1 38 22	56	—	1 m	
1 38 46	40	32	—	Pressure did not recover before next injection.
1 40 21	39	32	1 m	
1 41 0	38	32	—	e in Fig. 1.
1 42 0	38	—	—	
1 43 0	38	—	—	
1 44 0	38	—	—	
1 45 0	38	—	—	
1 45 32	38	—	1 m	
1 47 0	36	—	—	
1 48 12	36	—	2 m	
1 49 30	36	—	—	
1 51 23	34	—	2 m	
1 52 30	32	34	—	f in Fig. 1; pulsations barely visible.
1 53 30	30	—	—	
1 55 0	29	33	—	g in Fig. 1.
1 57 0	23	—	—	Pulsations still visible.
1 58 0	24	—	—	Pulsations not visible.
1 58 0	23	22	—	
1 58 22	23	—	2 m	
1 59 52	—	—	—	Last respiration, h in Fig. 1.
2 15 0	—	—	—	Artificial respiration was put on and continued until 2.52, when it was stopped, as animal was quite dead. Heart examined at 3.3 and was found to be cold, still, and dilated.

FIG. 2.—December 10th, 1890. Rabbit. Injection of Chloroform into Jugular Vein.

Time.	Blood Pressure in mm.	Respiration Rate per min.	Amount of Chloroform Injected.	Remarks.
H. M. S.				
4 20 30	86	42	—	Respiratory [curves of blood pressure well marked.
4 21 50	88	42	1 m	
4 22 2	50	51	—	Temporary quickening of respiration. Respiratory curves diminished during the fall of blood pressure.
4 22 30	60	44	—	
4 23 30	78	42	—	
4 25 0	88	42	—	The blood pressure had entirely recovered from the effects of the previous injection.
4 25 30	88	43	1 m	The effect of this injection is shown in Tracing a.
4 25 45	42	49	—	Temporary quickening of respiration.
4 27 0	86	41	—	
4 28 30	80	41	1 m	
4 28 45	29	—	—	Active expirations alternating with inspirations. Marked diminution of size of respiratory curves of blood pressure and of pulse excursion.
4 30 0	52	35	—	Respiratory curves of blood pressure and pulse excursions recovered.
4 31 0	51	27	—	Respiration markedly slowing. Strip of diaphragm muscle elongating.
4 32 0	50	12	—	Pulse excursions and respiratory curves of blood pressure very prominent, as seen in the beginning of Tracing b.
4 33 0	12	—	—	
4 34 0	4	—	—	Immediately afterwards a few gasping respirations, and then absolute cessation of respiration as shown in end of Tracing b. Heart at the time beating well. After cessation of respiration blood pressure fell quickly, and at 4.39, on examining heart, auricles and ventricles were still and inexcitable, the right ventricle being much dilated, and the left slightly.

failure of the heart. In these cases the blood pressure recovers after every injection, and finally the respiration ceases at a time when the blood pressure is fairly high, and the heart is beating well. An example of this effect is given in the preceding table, taken from an experiment on December 10th, 1890, and is illustrated by the tracings in Fig. 2.

In other cases the respiration fails with perhaps the very first injection, simultaneously with the fall of blood pressure. Such an experiment as that of December 10th shows that the heart has managed to rid itself of the chloroform after each successive injection, and consequently the blood pressure recovers either entirely or partially; the chloroform thus got rid of by the heart has then passed to the medulla oblongata in amount sufficient to hinder, and finally to paralyse, the action of the respiratory centre. Further it suggests that this chloroform in the medulla oblongata does not paralyse the vasomotor centre simultaneously with the respiratory; for at the time of cessation of respiration the blood pressure was rising rather than falling.

When the respiration ceases with the very first injection, simultaneously with the fall of blood pressure, this means that in these cases some of the chloroform has managed to pass into the medulla oblongata with the very first beats of the heart.

INJECTION INTO BRAIN ARTERIES.

Upon the assumption that the injection of chloroform into the vascular system acts in the same way as inhalation, it follows that injection of chloroform into the brain arteries and so directly to the vasomotor centre ought most markedly to produce a fall of blood pressure due to the paralysis of the vasomotor centre, if the inhalation of chloroform causes a fall of blood pressure mainly because it paralyses the vasomotor centre. On the contrary, if in reality the injection of chloroform into the jugular vein causes a fall of blood pressure by the weakening of the heart's beat, then naturally such a fall would not occur upon injection into the carotid or vertebral arteries until an amount of chloroform sufficient to affect the heart had passed through the brain region.

We have injected chloroform in small amounts into one of the carotid arteries (in all cases the external carotid was first ligatured) or into one of the vertebrals, and have found that in both cases the effect of the injection is to cause a rise of blood pressure, and not a fall; in both cases the respiration ceases when the blood pressure is still high; in both cases the conjunctival reflex is abolished, although naturally more quickly when the injection is made into the carotis. The contrast between the injection into one of the brain arteries and into the jugular vein is most marked; in both cases the production of anaesthesia and the cessation of respiration is brought about by the action of the drug very much in the same way as in ordinary inhalation; in both cases the injection is not necessarily associated with signs of strong irritant action upon the nervous system. Occasionally upon the first injection into the carotis a certain amount of contraction of various muscles takes place; but not only is there no such sign upon subsequent injections, but also the injections of normal saline solution may produce the same effects.

Chloroform injected into the vertebral artery does not produce quite the same effects as when injected into the carotis; such differences are of considerable interest from a physiological point of view, although they do not affect the main argument as to the action of chloroform. These effects may all be summed up by the statement that chloroform first excites, then paralyses, the different centres in the medulla oblongata.

Contraction of various muscles and excessive rapid respiratory movements usually take place when chloroform is first injected into the carotis; subsequent injections, however, show less and less sign of any primary excitation of muscles, and at the same time the conjunctival reflex is abolished, so that the primary excitation effects upon the muscular system of the body appear to be connected rather with the injection of the chloroform into the higher parts of the brain than into the medulla oblongata. In confirmation of this supposition it is found that muscular movements are much less likely to be produced when the chloroform is injected into the vertebral than when it is injected into the carotis.

Injections into the carotis or into the vertebral both kill the animal invariably by causing cessation of the respiration.

FIG 1 (Half Original Size)

FIG 2 (Half Original Size)

FIG 3 (Half Original Size)

In both cases the respiration becomes markedly slower before it ceases, and, as a rule, the final stoppage takes place with great suddenness. We see, however, a very marked difference between the carotis and vertebral injections as far as each individual contraction of the diaphragm is concerned. Carotis injections not only slow, but produce also a remarkable lengthening of each individual contraction, as is seen in Fig. 3, *d*, so as to produce a type of respiration called by Fig. 3.—December 11th, 1890. Rabbit. Injection of Chloroform into Internal Carotis.

Time.	Blood Pressure in mm.	Respiration Rate per min.	Amount of Chloroform Injected.	Remarks.
H. M. S.				
4 57 0	76	48	—	Tracing a.
4 57 17	—	—	—	Left vagus cut.
4 57 25	—	—	—	Right vagus cut, leading to rise of blood pressure.
4 58 0	102	32	—	—
4 58 30	100	34	—	—
4 59 30	102	38	1 m	1 m injected into external carotid, and so to internal carotid. Tracing b.
5 0 0	144	35	—	Sudden slowing of ventricular beat to half previous rate; this lasted 1 min. 20 sec.
5 0 30	144	36	—	Tracing c.
5 1 20	—	—	—	Contractions of abdominal and limb muscles.
5 6 30	142	18	—	Tracing d.
5 7 50	128	—	—	Inspiratory movements suddenly ceased 8 min. 20 sec. after injection. Tracing e.
5 9 0	24	—	—	—
5 10 0	12	—	—	After this heart beats no longer visible on tracing.
5 40 0	—	—	—	Chest opened, heart still, not dilated.

FIG. 4.—July 7th, 1891. Rabbit. Injection of Chloroform in Distal End of Subclavian, and so to Vertebral Artery.

Time.	Blood Pressure in mm.	Respiration Rate per min.	Amount of Chloroform Injected.	Remarks.
H. M. S.				
11 47 0	78	49	—	Tracing a. Vagus nerves not cut.
11 47 7	—	—	1 m	Contractions of abdominal and limb muscles, in consequence of which the respiration lever became shifted in position and required readjustment, so that levels of respiratory tracing before and after injection do not correspond.
11 48 30	90	42	—	Tracing b.
11 49 30	73	42	—	—
11 50 36	67	42	1 m	The last respiration occurred at 11 h. 50 m. 41 s., as shown in Tracing c.
11 51 30	102	—	—	Pressure falling; Tracing d.
11 52 0	—	—	—	—
11 53 30	50	—	—	—
11 54 30	47	—	—	Tracing e.
11 55 30	38	—	—	—
11 56 30	25	—	—	Heart beats very regular and conspicuous; Tracing f.

Marckwald⁴ inspiratory spasms; this type of respiration is frequently associated with a steady shortening of the muscle strip, as though the tonic contraction of the diaphragm was increased by the injection of chloroform into the carotis. On the other hand, chloroform, when injected into the vertebral, causes a slowing, with a diminishing strength of contraction, and a relaxation of the diaphragm strip; there is here no sign of any lengthening of each contraction, but, on the contrary, the contractions diminish steadily in extent (see Figs. 4 and 5, *a, b, c*). At a later stage of the injection into the vertebral, it frequently happens that the relaxed condition of the diaphragm muscle gives way to a condition of tonic contraction, just as though the chloroform had, upon the first injection, reached and affected some part of the nervous centre

concerned with inhibition of the respiratory contractions, and, later on, had reached some higher part, so as to affect respiration in the same way as injection into the carotis.

A very similar difference in action is seen on the blood pressure tracings when chloroform is injected into the vertebral and carotid arteries respectively; in both cases the main result is a marked rise of blood pressure, but, in the case of vertebral injections, that rise is often preceded by a preliminary fall of slight extent, a good deal resembling the fall of pressure which can be obtained by stimulation of the depressor nerve (see Fig. 5, *a, b, c*).

Another difference in the blood-pressure curve consists in the frequency of occurrence of well-marked periodic undulations, resembling Traube-Hering curves, after injection into the vertebral, in comparison with their rarity after carotis injections. The effects produced by injection into the carotis and vertebral arteries respectively are illustrated by the tables and tracings of December 11th, 1890 (Fig. 3), July 7th, 1891 (Fig. 4), and July 9th, 1891 (Fig. 5).

FIG. 5.—July 9th, 1891. Rabbit. Injection of Chloroform into the Vertebral Artery by means of a Cannula placed in the Subclavian distal to the Vertebral; Vagi Intact.

Time.	Blood Pressure in mm.	Respiration Rate per min.	Amount of Chloroform Injected.	Remarks.
H. M. S.				
1 38 0	70	82	—	Tracing a.
1 38 30	70	82	0.25 m	No movement whatever.
1 39 30	57	62	—	Tracing b.
1 40 0	54	62	—	Marked diminution in strength of contractions of the diaphragm slip, coincident with the slowing.
1 40 30	52	62	—	Tracing c. From this point the blood pressure began to rise, and was accompanied by a steady increase of the size of the diaphragm contractions.
1 41 0	53.5	62	—	—
1 41 30	59	52	—	Tracing d.
1 42 0	70	52	—	Tracing e. The contractions of diaphragm had now reached the maximum.
1 42 30	74	36	—	—
1 43 30	68	25	—	—
1 43 43	64	—	—	Tracing f, showing the last respiration. The mean blood pressure continued at 64 for half a minute after the last respiration, and then began to fall.

In one case of injection into the carotis, the first injection caused a marked primary fall of blood pressure, the respiratory contractions were not lengthened, and the Traube-Hering curves were well marked; in fact, in this instance the chloroform seems to have reached mainly that part of the central nervous system which is supplied by the vertebral artery.

In whichever artery the chloroform is injected, the rise of blood pressure is ultimately followed by a fall; this fall takes place in both cases after the respiration has ceased, the difference between them being that, when the injection is made into the carotis, the fall of blood pressure usually occurs suddenly, and is absolutely coincident with the cessation of respiration, as in Fig. 3, while, in the case of injections into the vertebral, the pressure may continue high for some little time after the cessation of respiration, and then gradually sink, as in Figs. 4 and 5.

This fall of pressure in carotis injections coincident with a sudden cessation of respiration appears to be due to the chloroform paralysing the vasomotor centre at the same time as the respiratory centre ceases to act, for, in the first place, there is never an asphyxial rise of blood pressure after the respiration has stopped such as is always observed if the vasomotor centre is intact, and, in the second place, stimulation of a sensory nerve is unable to cause the pressure to rise. On the other hand, the characteristic of injections into the vertebral is an asphyxial rise of pressure after respiration has ceased (see Fig. 4 *c*), and the vasomotor centre is found to be susceptible to the action of such a nerve as the depressor. Again, cessation of respiration is caused by a very much smaller amount of chloroform when injected into the vertebral artery than when injected into the carotis;

⁴ *Movements of Respiration*, trans. by McKendrick.

thus, a single injection of as small an amount as $\frac{1}{4}$ m. has sometimes proved sufficient in the former case (for example, Fig. 5), while in the latter from 1 to 2 m. are necessary to produce any effect, and usually three or four injections of 1 m. each must be given before the animal ceases to breathe. It is worthy of notice that the primary fall of blood pressure which occurs in many cases upon injection into the vertebral is seen only when the amount injected is small, such as $\frac{1}{4}$ m.; with larger doses, such as 2 m., the blood pressure rises immediately after the injection.

In many cases when the injection is made into the carotis, a well-marked slowing of the heart occurs soon after the injection, and it is striking to see how these slow beats of the heart are unable to lower the blood pressure, owing to the simultaneous stimulation of the vasomotor centre, as is well shown in Fig. 3c. In this case the slowing of the heart observed cannot be attributed to stimulation of the vagus nerves, for both vagi were cut before the chloroform was injected into the carotis. In other instances where well-marked slowing was obtained in consequence of chloroform administration, such slowing was undoubtedly due to vagus stimulation, for the effect was dependent on the integrity of the vagi. We have, however, observed in the course of our experiments many instances similar to the one quoted, where undoubtedly, owing to the fact of previous section of the vagi, some other explanation must be found; and careful measurement has shown us that in the majority of such cases of slowing, the rate of beat was diminished to exactly half the immediately preceding rate, as in the instance quoted. This suggests very strongly that the slowing in question is an indication of a partial block between auricle and ventricle, in consequence of which the ventricle responds only to every second auricular contraction, a phenomenon which is well known to occur in the hearts of both cold- and warm-blooded animals. We have observed this peculiar form of slowing under many different circumstances, but have not yet been able to make up our minds as to the paramount condition for its occurrence; in some cases it has appeared to be associated with an asphyxial condition of the blood; it certainly is not necessarily dependent on the presence of chloroform in the blood, for we have never observed it after the injection of chloroform into the jugular. It is not advisable to discuss the question further in this place, but we hope to be able to throw further light upon the causation of such a dropping of beats upon a subsequent occasion.

CHLOROFORM APPLIED TO FOURTH VENTRICLE.

Finally, to finish up with the effects produced by the direct action of chloroform on the nervous centres, we have found that the respiration can be easily stopped by the direct application of one or more drops of chloroform to the fourth ventricle of the brain. We have not as yet made a sufficient number of such experiments to enable us to discuss the differences observed in connection with the differences of effect of the carotis and vertebral injections.

It is remarkable how small an effect is produced on the anæsthetised animal by the opening of the atlo-occipital membrane; a large amount of cerebro-spinal fluid runs out as a rule, yet neither the respiration or the blood pressure is appreciably affected; when the chloroform is first applied muscular movements often occur and the respirations are increased in depth and frequency. Upon the application of a second drop no movements of the animal take place as a rule, but the respiration is temporarily quickened and increased. The cessation of respiration takes place gradually, not suddenly; the diaphragm contractions become weaker and weaker, and finally cease. At the commencement of this weakening each contraction for some time is apt to be lengthened as in the case of carotis injections. The paralyzing effect on the respiration of the chloroform, when applied to the fourth ventricle, is its most striking effect, and is in marked contrast to the action of such a stimulant as nitrate of silver, which, according to Gad,⁵ does not stop respirations when applied to the fourth ventricle.

The effect on the blood pressure is not well pronounced, as far as can be judged from the few experiments we have made; in some cases there is a slight primary fall followed by a slight rise; in others a rise only, without any preliminary

fall. The respiratory blood pressure curves are apt to be very well pronounced, and the gradual fall which takes place with the gradual cessation of respiration is not broken by an asphyxial rise. Periodic undulations resembling Traube-Hering curves were not observed as the result of the application of chloroform to the fourth ventricle.

From these experiments we may draw the conclusion that chloroform, whether injected into the cerebral arteries, or applied directly to the medulla oblongata, first stimulates, then paralyses the parts of the brain with which it comes in contact: thus the stimulation of the respiratory centre is shown by increased frequency and force of the contractions of the diaphragm strip; these last but a very short time and then the respiratory movements become slower and weaker or slower and longer up to complete cessation, or cease somewhat suddenly. The stimulation of the cardio-inhibitory centre may be shown by the occurrence of heart slowing dependent upon the integrity of the vagus nerves; this effect also is seen only for a short time after injection. The stimulation of the vasomotor centre is shown by the marked rise of blood pressure, which continues for a long time and gives way ultimately to a paralysis, as shown by the absence of any asphyxial rise of pressure after respiration has ceased, and also by the absence of any reflex rise of pressure upon stimulation of a sensory nerve. Perhaps also the presence of the periodic undulations resembling Traube-Hering curves indicates the action of a strong stimulus upon a less excitable centre, as seems to be the case in many instances of periodic rhythmical activity of the central nervous system.

(To be continued.)

REPORTS TO THE SCIENTIFIC GRANTS COMMITTEE OF THE BRITISH MEDICAL ASSOCIATION.

A PRELIMINARY REPORT ON CEDEMA.

By VICTOR HORSLEY, B.S., F.R.C.S., F.R.S.,

Surgeon to the National Hospital for the Paralysed and Epileptic;
Professor of Pathology in University College, London; Assistant-
Surgeon to University College Hospital.

AND

R. W. BOYCE, M.B.,

Assistant Professor of Pathology in University College, London.

SINCE the process of transudation is essentially a vital one, it will long remain a fertile source of inquiry to the physiologist; it is still more important to the pathologist. The passage of fluid from the circulating blood through the wall of the blood vessel into the cell spaces and then into the capillary lymphatics was supposed by Lower in 1669 to be due to mechanical pressure in the blood vessels produced by venous stagnation. This idea has survived to the present day. As a matter of fact, of course, the complex processes of living tissues are not to be so easily explained by the simple statement of Lower. Two hundred years after Lower (namely, in 1869) Ranvier proved that another factor must be considered, namely, the action of the nervous system. We will subsequently return to the discussion of his facts, which have received scant attention in this country.

Enumeration of Various Factors in the Production of Edema.
—Twenty years after Ranvier we have the remarkable researches of Heidenhain, in which the concurrence of the various factors is first stated comprehensively, in a thorough and accurate analysis. Being responsible in lecturing on general pathology for giving a reasonable exposition of this commonly supposed simple subject, we have always felt the necessity of setting on foot further investigation of the questions it involves. Having with this object entered on a research of this kind, we intend on this occasion to refer only to certain points that may be readily illustrated, and to for-

⁵ *Verhandl. der physiol. Gesellsch.*, 27th June, 1890.