no precautions should be thrown aside in carrying out these processes. If this is well done the observer need not seek far for stains if he wishes simply to see the parasite. A perfect differential stain to pick out the bodies alone is still to be found. The nuclear stains, such as methyl green, hæmatoxylin, are not very suitable for that purpose; like the coccidia in the rabbit's liver, the parasite seems to prefer general protoplasmic stains, and, acting on this principle, the best results of which I am aware have been obtained by Mr. Plimmer, who has used aniline blue as the special stain for the organism.

In all well-prepared specimens there is no difficulty in distinguishing the parasite from the ordinary forms of cell degeneration. It may be of interest to remark in this connection that when the coccidia in the rabbit's liver were being first investigated certain pathologists declared the appearances of this now well-known parasite as being given rise to by alterations in the surrounding liver tissue.²⁵

During this investigation I have had the opportunity of investigating over fifty cases of cancer of various organs, and in most of them, especially those more recently examined, there has been no difficulty in identifying the parasite. Taking the cases coming under my notice along with those mentioned by other observers, it has now been identified in practically all varieties of carcinoma: there are still one or two forms in which researches have not been recorded to my knowledge—for example, "rodent ulcer." At first many of my results were unsatisfactory, and still, in certain cancers, they are more difficult of discovery than in others. In my experience, they have proved most difficult of identification in colloid cancers of the alimentary tract, and in carcinomata of the skin. Taking the case of the breast once more as an example, if any difficulty is experienced in seeing them readily, in all probability the reason is that there has been some carelessness displayed during the process of hardening.

The material at my disposal has been obtained partly by the kindness of my friends at the London Hospital, and partly from cases coming under my own observation at the Great Northern Hospital.

XIV.—SARCOMA.

In reference to the question of sarcoma, it can only be said at present that parasites cannot be so easily identified by the methods I have described. Although it seems probable that parasites do exist in sarcomatous tumours, no definite opinion can yet be expressed. The subject is now under consideration.

XV.—CONCLUSION.

The further questions which arise—namely, Can the parasites be observed "undergoing reproduction," and can they be observed developing outside the body? What influence have they on epithelial cell multiplication? and, finally, have they a causative influence on cancer?—are now the points to be investigated; and it must not be considered a reproach if as yet no definite answer may be given. It will be remembered that although the very characteristic coccidium oviforme was recognised so long ago as the year 1839 by Hake in this country, it is only within the last few months that the description of the processes, apparently completing our knowledge of the anatomical changes in the life history of this organism and accounting for the enormous rapidity of its multiplication within the body of its host, have been made known by Dr. R. Pfeiffer.

Speculations on my part as to the rôle of this "cancer organism," although they are tempting, are better avoided; they will occur to all those who have studied the subject; in the meantime I am satisfied if I have placed the facts so far as they are known before you. The prospects of the research are encouraging, if it is only from the point of view of opening up the possibility of a cause of cancer, more hopeful as to curative measures than that suggested by the hypothesis which has so long held the field.

I fulfil a pleasant duty, in conclusion, by thanking the Committee of the Royal Colleges of Physicians and Surgeons for the permission they have granted me to pursue the investigations on which the remarks I have made are based in this laboratory; and another most pleasurable task remains—to record my obligations to my friends Dr. Ruffer, Mr. Plimmer, and Mr. Walker, who have been engaged in similar investigations, and especially to Dr. Sims Woodhead for much useful criticism during the course of my work here.

²⁵ Lang, *Archiv f. path. Anatom.*, etc., Bd. 41.

OPERATIVE SURGERY IN NEW YORK.—The number of deaths directly due to surgical operations in New York during 1891 is given by the *New York Medical Journal* as 133. Of this number, however, 10 per cent. are said to have followed circumcision, and as in these cases the operators were presumably rabbis, it seems hardly fair that they should be included in the surgical "butcher's bill." Among the strictly surgical cases laparotomy was responsible for the largest number of deaths (76, or 57 per cent.).

A REPORT

ON THE

PHYSIOLOGICAL ACTION OF CHLOROFORM,

WITH A

CRITICISM OF THE SECOND HYDERABAD CHLOROFORM COMMISSION.

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(Concluded from page 171.)

CRITICISM OF THE PROOFS OF THE COMMISSION THAT THE FALL OF PRESSURE IS NOT DUE TO WEAKENING OF HEART.

We have already, in the beginning of this paper, referred to the conflict of opinion upon the question whether, and in what way, chloroform affects the heart directly, and, seeing that the chief papers of late years have been collected together and published by Lawrie in the Report of the Hyderabad Commission, it is unnecessary to do more than refer to the evidence in that book as to the present state of the question. On the one hand, a large array of observers look upon it as proved that chloroform weakens the force of the contractions of the heart by its direct action upon the heart; on the other hand the Hyderabad Commission, as represented by Brunton, considers that chloroform only affects the heart in combination with an asphyxial condition of the blood, and, as represented by Lawrie, denies *in toto* any direct action of the drug upon the heart under any circumstances. To our minds it is perfectly clear that the weakening effect of chloroform on the heart is the chief, if not the only, cause of the fall of blood pressure seen upon administration of the drug, and it is difficult to understand how the Hyderabad Commission could have arrived at the conclusions they have published, for their experiments and their large number of curves confirm again and again the observations of others, and point directly to heart failure as the cause of the fall of blood pressure.

The report of the second Hyderabad Commission consists of five parts, in Part v of which all the manometer experiments are described in detail, and remarks made upon a large number of the individual experiments. This description of experiments and the remarks upon them, together with the tracings, form the most valuable part of the report, for they give the facts upon which the conclusions of the Commission are based. In their report the Hyderabad Commission do not state what is the reason of the fall of blood pressure so characteristic of chloroform poisoning; they imply, however, that such fall is not due to any direct action on the heart, but to the paralysis of the vasomotor centre through the drug. The reasons for such a belief are given on p. 137 in the discussion which follows Experiment 178.

"Experiment 178 is very like Experiment 162, in which the heart's action was temporarily arrested every time the respiratory centre was paralysed. As in 162, there was no further fall of blood pressure during the arrest, and the beats on each side of the stop were ample and strong. The most remarkable instance of this is seen at Fig. 13. For more than two minutes there were only 17 very slight pulsations recorded, and for over a minute of this tracing there was no pulsation at all. There was no fall of pressure during the arrest, and the Ludwig tracing shows how strong the beats on each side of it were. No better proof could be afforded than is to be found in these two experiments that direct weakening of the heart is not the cause of the fall of the blood pressure, which is inseparable from chloroform narcosis.

"Experiments 64, 65, 162, 178, and 186 prove three important points:—1. A general fall of blood pressure, whether sudden or gradual, is not in itself dangerous. 2. The fall of blood pressure, which occurs in chloroformisation with regular breathing, is due solely to narcosis of the vaso-

motor system, and is, if not a safeguard, absolutely harmless. 3. The fall of the blood pressure under chloroform is not due to weakening of the heart. The heart has nothing to do with producing it, unless the vagus is stimulated, or unless its nutrition fails either from imperfect oxygenation of the blood due to abnormal breathing, or from stoppage of the respiration from overdosing."

Turning to Experiment 162, we find again the same argument as in 178, and then follow the words:

"If direct weakening of the heart were the cause of the fall of blood pressure in chloroform administration, we ought to find the heart beats getting smaller and smaller up to the time when the pressure reaches its lowest; and gradually growing bigger and bigger again on the other side as the effect of the chloroform wears off."

According then to this argument the presumption is that if the beats of the heart do get smaller and smaller up to the time when the pressure reaches its lowest, and do gradually get bigger and bigger as the effect of the chloroform wears off, then at all events we must not exclude the weakening of the heart as a factor.

In the first of the conclusions of the Hyderabad Commission, *cf. Report*, p. 17,¹ the events typical of chloroform inhalation are described and illustrated by tracings from Experiments 168, 169, and 170; in every one of these curves we see that the excursions due to the heart beat as measured on the Fick manometer, do in the most typical manner get smaller and smaller as the pressure falls.

Such curves abound throughout the tracings of the Commission, and are, as they truly say, typical of the fall of pressure under chloroform. Everyone who has worked at the action of chloroform always obtains such curves, and everyone would agree with the Commission that they are of the typical kind which would be produced, if direct weakening of the heart were the cause of the fall of blood pressure in chloroform administration.

It is somewhat surprising that the Commission should have laid such stress upon Experiments 64, 65, 162, 178, and 186, as to assert that these tracings proved that the fall of blood pressure under chloroform is not due to weakening of the heart, when they make statements just before, which, applied to their typical curves, show that these are of the kind that would necessarily occur if the chloroform did cause a fall of blood pressure through weakening of the heart. It is natural to suppose that the evidence in these cases must be very strong before the Commission would allow it to have sufficient weight to overpower the evidence of what they style their typical cases. As a matter of fact these cases afford no proof whatever that the heart's action is unimpaired by the action of chloroform. In all the cases quoted, the tracings afford simple illustrations of a peculiarity of blood-pressure tracings, which is well known.

PROOF FROM SIZE OF PULSE EXCURSIONS ON THE PRESSURE TRACINGS.

The size of the excursions on the blood-pressure curve, however taken, due to the beats of the heart, depend upon the amount of blood thrown into the aorta at each beat and upon the extent of fulness of the aorta at the time when the contraction of the heart takes place. Further, the amount of blood thrown into the aorta depends upon the force of the contraction of the left ventricle and upon the amount of blood coming to that ventricle, which again depends upon the condition of the pulmonary and systemic blood vessels, and the extent of fulness of the aorta at the time depends upon the rate of heart beat, as well as its strength, and upon the amount of resistance to the flow of blood through the peripheral organs. We have then the following factors to consider:

1. Strength of contraction.
2. Rate of contractions.
3. Condition of peripheral resistance.

Both in the natural circulation and in the artificial scheme it is found that if 2 and 3 are kept constant and, 1, the strength of the contractions diminish, then the mean blood pressure falls and the excursions on it due to the heart beat are diminished in size. In fact curves are obtained precisely similar to those which the Commission recognises as typical.

If 1 and 3 are constant, and, 2, the rate of beat is diminished then it is evident that the pulse excursions on the blood-pressure curve are increased in size, even to a very great extent, with a lowered blood pressure, for clearly the throwing in of the same amount of blood into the aorta, the walls of which are less tense owing to the greater length of time between each beat, must produce a greater excursion than when the walls are more tense. This effect of slowing of rate is very clearly seen when the vagus is stimulated. The large pulse excursions seen on the blood-pressure curve so characteristic of vagus stimulation do not in the least indicate any increase in the strength of the heart contracting, for, indeed, it is very probable that the contractions during stimulation of the vagus are slightly weaker than before the stimulation.

If 1 and 2 are constant and 3 diminished, then the size of the excursions on the blood-pressure curve tend to increase slightly and show no sign of diminution, until the diminution of the peripheral resistance has reached such an extent as to diminish the amount of blood flowing into the heart.

If 3 is constant and the strength of the contractions is diminished, then with the diminished blood pressure the pulse excursions will be increased in size if the rate is slower, because more blood is able to accumulate in the heart between the contractions.

If 1 is constant and 3 is diminished to such an extent as to diminish the amount of blood flowing into the heart, then with a slower rate the pulse excursions will be increased, because there is a longer time for the blood to accumulate between the contractions, and therefore more blood is thrown out with each beat.

We see then that in trying to interpret the meaning of any alteration in the size of the pulse excursions of any curve we must always take into account any variation of rate, and especially must we bear in mind the likelihood of any increase in the height of the pulse excursions being due to a slower rate of beat.

If now we turn to Experiments 64, 65, etc., it is at once clear that their importance is greatly over-estimated by the Commission, and that the so-called proof that chloroform does not affect the heart, which is afforded by them, is in every case an instance of a slight increase of the size of the pulse excursions due to a slowing of the heart's rate.

The first instance given is Experiment 64, and the argument is given as follows in paragraph 1 of the observations on the experiment, page 55:—

"9h. 14m. 20s.—Electrical irritation of peripheral ends of both vagi, causing an immediate fall of the blood pressure almost to zero. Chloroform administration was pushed during complete inhibition of the heart's action at 9h. 14m. 30s. There was entire absence of pulse tracing for more than one and a-half minute, the blood pressure remained nearly at zero, and the breathing became slow. The irritation and the administration of chloroform were both stopped at 9h. 16m. 0s. The blood pressure rose immediately to nearly its former height. It then gradually fell, exactly as it does in chloroform administration with normal breathing, and rose again spontaneously at the end of one minute. The fall of pressure after the cessation of vagus stimulation constitutes the most interesting phenomenon in this observation. From 9h. 14m. 20s. to 9h. 16m. 0s. cardiac inhibition, with sudden and prolonged fall of blood pressure, was caused by stimulation of the vagi. The arrest of the circulation, due to stoppage of the heart, prevented the chloroform, which from 9h. 14m. 30s. was saturating the air deep down in the lungs, from getting into the blood. But when the circulation was resumed at 9h. 16m. 0s. the chloroform was forthwith taken up by the blood, and the respiration was no longer a factor in the process, except to eliminate it from the lungs. The effect of the uncontrollable absorption of chloroform into the blood was, not to give rise to any paralysis or weakening of the heart, but simply to produce the ordinary regular and gradual fall of the blood pressure, which is associated with narcosis of the nerve centres in the medulla, in normal chloroform inhalation."

It is impossible to test the assertion in the last paragraph of this quotation, because, unfortunately, no Fick tracing during the slight after-fall of pressure is given. Fick 16 is a sample taken before the stimulation of the vagi. Fick 17 shows the stoppage of the heart during the stimulation of the

¹ See also *Lancet*, June 21st, 1890, where several of the tracings referred to are reproduced.

vagi, and Fick 18 is taken six minutes after the end of the stimulation of the vagi. During the after-fall of pressure in question a pause in the Ludwig tracing occurs, as though a Fick tracing had been taken, but it is not numbered, and there is no sign of it among the Fick curves. On the other hand the series Fick 12, 13, 14, 15, and 16, afford a good instance of the typical recovery in the size of the pulse excursions after an excessive fall of pressure due to chloroform.

Experiment 65 is a fairly good instance of the effect of change of rate upon the magnitude of the pulse excursions. Thus Fick 4 in the series Fick 3, 4, 5, 6, gives larger excursions than Fick 6, owing to the much slower rate, although the mean pressure is higher in the latter curve. So also in Fick 8, 9, 10, the slowing of the heart produced by stimulation of the central end of the right vagus produces a larger pulse excursion.

Finally, the series Fick 12, 13, 14, 15, 16, 17, 18, 19 show most clearly the dependence of the size of the pulse excursions upon the rate, and also the manner in which the excursions of the pulse are diminished by chloroform. It is specially instructive to compare Fick 14, 15 with Fick 16, 17.

Experiment 162. In the observations on this experiment, p. 126, the Commission say: "If direct weakening of the heart were the cause of the fall of blood pressure in chloroform administration, we ought to find the heart beats getting smaller and smaller up to the time when the pressure reaches its lowest, and gradually growing bigger and bigger again on the other side as the effect of the chloroform wears off. Instead of this, Experiment 162 shows that there were ample pulsations on both sides of the temporary pauses. If Fick 9, with the Ludwig tracings on either side, is carefully studied, it will be seen that up to the time the heart beats ceased, the pulsations recorded in the Ludwig were ample and strong. There was then a temporary arrest of pulsation for 6 seconds (*vide* Fick 9). Immediately after Fick 9 the pulsation returned for 5 seconds (*vide* the Ludwig between 3h. 28m. 0s. and 3h. 29m. 0s.). Afterwards there was a long pause of 20 seconds without any pulsations at all. This pause was so marked that Dr. Bomford thought a clot had formed in the tube, and at 3h. 29m. 10s. he wrote on the Ludwig tracing 'clot.' Artificial respiration was just about to be commenced when the animal gave two spontaneous gasps; vigorous pulsations followed, and the pressure was raised in 5 seconds to the height it was at before chloroform was administered in Observation C."

Now the Commission, at the instance of Dr. Lauder Brunton, arranged purposely so that a mercury manometer tracing should be taken on a very slowly-running drum, for the purpose of seeing at a glance a record of a long blood pressure; in order at the same time to obtain a record of the pulsations, they arranged so as to connect up at will with a Fick manometer, which should register on a quickly-moving drum; and naturally all their conclusions as to size of heart contractions are drawn from the Fick tracings, while their conclusions as to fall of blood pressure are drawn from the Ludwig tracings. Whenever it was thought advisable during the Ludwig tracing to obtain a record of the pulse excursions, the Ludwig tracing was interrupted for a short time, and a tracing made with the Fick. This was done also in Experiment 162, with the result that the Fick tracings show in this instance, as in others, a diminution of the pulse excursions during the chloroform administration even to invisibility. These Fick tracings, 6, 9, 12, are taken in the ordinary way as samples, when the blood pressure has fallen very low, at a time when, according to the report, the Ludwig tracing showed that the heart was beating well and regularly, without any indication of any stoppage, and yet the sample taken with the Fick shows stoppage of the heart according to the Commission, in all three instances. We must say that any physiologist ought to have been very chary of drawing conclusions from an experiment in which the mere shifting of the tracing from the Ludwig to the Fick kymograph, and *vice versa*, causes the contractions of the heart to disappear and reappear again respectively. As far as the heart pulsations are concerned, the Fick manometer is the guide to which the Commission has trusted throughout (except in this instance and in Experiment 178) and in Fick 6, it is clear that the pulsations are still visible, and even in Fick 9 the line is not perfectly even; very faint indications of pulsations are visible on

it. As to the movements recorded in the Ludwig tracing on each side of Fick 9, upon which the Commission lays so much stress, even if they were due to contractions of the heart, they would not outweigh the positive evidence of the Fick tracing. There is no need, however, to suppose that they are evidence of heart contractions only; it is quite possible that they are due partly to heart beats and partly to respiratory movements so feeble as not to have been noticed by the observers who recorded cessation of respiration 55 secs. before Fick 9 was taken. If this were so, the true cessation of respiration would be signalled by the pause of 20 secs., which Dr. Bomford thought showed a possible clot in the cannula. Further, when artificial respiration was just about to be commenced the animal gave two spontaneous gasps, etc., showing that the respiratory centre was able to recover of itself, and was therefore not so very deeply affected by the chloroform. It is, however, impossible to argue about the excursions on a blood-pressure tracing, taken with a mercury manometer on a very slow-moving drum, without the simultaneous graphic record of the respiratory movements.

It is sufficient to point out that Experiment 162 gives no scientific evidence whatever that direct weakening of the heart is not the cause of the fall of blood pressure in chloroform administration, but, on the contrary, it confirms the other tracings of the Commission, that such weakening of the heart is, in all probability, the cause of the blood pressure fall.

The observations of the Commission on Experiment 178 have been already quoted. Here again we see, as in Experiment 162, that the Commission disregards the evidence of the Fick tracings, and places reliance upon the Ludwig tracings as to the strength of the heart beats, and yet the Fick tracings in this experiment throughout give the most typical curves of the steady diminution in the pulse excursions as the pressure falls: this is especially well seen in the series, Fick 14, 15, 16, 17, 18, 19, and also 20, 21, 22, 23, 24, 25, 26, 27. The series 4, 5, 6, 7, 8, 9 illustrate the effect of a slower rate on the size of the excursions; so also do the series 10, 11, 12, 13, in which the combined effect of the weakening of the strength and the slowing of the rate of the contractions is well shown. In Experiment 186 no Fick tracings are given, and the Ludwig tracing on the slow drum gives no possibility of coming to any conclusion as to the condition of the heart.

It is perfectly clear, then, that this part of the so-called proof given by the Hyderabad Commission of the absence of any direct effect upon the heart when chloroform causes a fall of pressure is no proof at all; but, on the other hand, all their curves yield evidence to the exact contrary.

PROOF FROM INJECTION INTO JUGULAR.

So also the second part of their proof, as given in paragraph 19 of their conclusions, namely: "On the other hand, it seems clear from Experiment 92 that the direct action of chloroform on the heart's substance is not the cause of the fall of pressure that occurs when it is inhaled," is equally inadequate. Experiment 92 is one of a series of experiments in which chloroform was injected into the jugular vein and so directly to the heart. In this experiment the jugular vein was tied, and then injections of chloroform were made into it as follows: 20 m at 8 h. 0 mins.; 20 m at 8 h. 2 mins. 30 secs.; 20 m at 8 h. 3 mins. 45 secs.; 20 m at 8 h. 5 mins. 45 secs. At 8 h. 5 mins. it was noticed that the cornea was not sensitive, but no observation was made before that time as to whether the cornea had been sensitive. Before the last injection no appreciable effect was produced on the blood pressure or on the respiration. Then after the last injection a rapid marked fall of blood pressure occurred. In other words, owing to the jugular being tied the injection did not really travel to the heart, but accumulated in the tied vein. In our experiments the chloroform was always injected into the vein directly by means of a hypodermic syringe, so that the circulation in the vein was bound to carry it on; in no case was it found possible by us to inject four doses of even 2 m each before producing a fall of blood pressure.

Then at 8 h. 13 mins. 20 m and at 8 h. 14 mins. 20 m were injected, followed by a still further fall of blood pressure, and then at 8 h. 33 mins. it was noticed that the cornea was slightly sensitive, the blood pressure at this time being on the

¹⁴ Report, p. 21.

rise. In other words, after the injection of 120 m of chloroform into the vascular system in addition to what had been given previously to a dog weighing 33½ lbs., the cornea was sensitive half an hour after the first injection. Then at 8 h. 40 mins. 30 secs. another 20 m injected; at 8 h. 42 mins. 30 secs. cornea still sensitive. At 8 h. 43 mins. 15 secs. another 20 m injected; at 8 h. 45 mins. cornea insensitive with a falling blood pressure. At 8 h. 46 mins. another injection of 20 m; and at 8 h. 53 mins. 30 secs. respiration stopped with blood pressure very low; at 8 h. 54 mins. thorax opened, heart perfectly still, not irritable; and at 8 h. 55 mins. 30 secs. gasping from regular rhythmical movements of the diaphragm.

It appears to us that the conclusion to be drawn from this experiment is that a large amount of the chloroform injected stayed in the jugular vein, and was only gradually brought into the circulation. It is difficult to conceive that after so large an amount the cornea could have been still sensitive if it had been all in circulation.

The experiment seems to point directly to a weakening of the heart's action, especially when we find that only thirty seconds after the cessation of respiration the heart is described as perfectly still, not irritable.

From a similar examination of Experiment 91 we conclude that as in Experiment 92 no appreciable amount of chloroform reached the circulation until the fourth injection, and then the fall of blood pressure was not incompatible with the action of chloroform on the heart.

We conclude then that the experiments of the Hyderabad Commission, as well as our own, give no support to their conclusion that the fall of blood pressure in chloroform administration is not due to any weakening of the heart's action, but on the contrary their curves if rightly interpreted agree absolutely with our own, and both confirm the commonly accepted view that the fall of blood pressure due to the action of chloroform is mainly caused by the weakening of the heart's contractions.

ACTION OF CHLOROFORM ON BLOOD VESSELS DIRECTLY.

Finally the fall of blood pressure may be due not entirely to the action of the drug upon the heart, but also to its direct action upon the blood vessels. It is clear that a fall of pressure might be caused by the action of a drug upon the blood vessels, both if the drug causes constriction and also if it causes dilatation of blood vessels. In the first case the vessels to be constricted must evidently be the pulmonary vascular system, and any long continued fall must mean so excessive a constriction of the pulmonary vessels as greatly to hinder the passage of blood from the right to the left side of the heart. The physiological result of such a hindrance must manifest itself in two ways: (1) the right side of the heart must become greatly distended with blood while the left side remains empty, and (2) the pressure in the pulmonary artery must rise as the pressure in the systemic aorta falls. Such a condition of the pulmonary vessels has been asserted lately by Johnson¹⁵ to be typical of the asphyxial condition, and he says that in all cases of death by asphyxia this condition is manifested by the enormous size of the right side of the heart and the remarkable whiteness of the lungs, due to the persistent contraction of the pulmonary vessels even after death.

Seeing the possibility that asphyxial conditions may play a decided part in death from anaesthetics such as ether and chloroform, we have made a few experiments for the purpose of testing the meaning of this extreme whiteness of the lungs when the animal is killed by occlusion of the trachea, and have found that the phenomenon depends upon the phase of respiration at the time when the tracheal tube is closed; if the lungs are distended in inspiration and the trachea closed at this moment, then upon death the symptoms described by Johnson are most manifest; if, on the other hand, the trachea is closed at the height of expiration, then upon death the lungs present the usual reddish colour and no sign of vascular constriction is to be seen. The phenomenon depends clearly enough on the emptying of the lung vessels by pressure and not by vascular constriction. There is, then, as far as we know, no evidence that the asphyxial condition brings about any special contraction of the pulmonary vessels, and so, too,

there is no evidence that chloroform causes a contraction of those vessels, but rather evidence against it. The important point is the observation of Bradford that the pressure in the pulmonary artery, as measured from a branch, does not rise when chloroform is given, but falls *pari passu* with the pressure in the systemic aorta; such an experiment is the natural result if the fall of pressure in both is due to a weakening of the central organ—the heart, but is impossible if the fall of pressure in the aorta is due to the chloroform causing an obstruction to the flow of blood through the lungs.

Further, the observations of McWilliam point to a dilatation of both sides of the heart as the effect of chloroform and not of the right side only; and although in the absence of any tracings, and with a feeling of doubt as to the validity of the methods employed by McWilliam, we are not prepared to agree to all his statements, yet we can say with confidence that in a number of cases where the heart appeared dilated after death from chloroform, both sides were dilated.¹⁶

There is no evidence, then, that the fall of blood pressure is due in any way to obstruction of the flow of blood through the lungs. There remains the question whether it is due to any extent to a direct relaxing influence of chloroform upon the muscular tissue of the systemic vascular system. Such an action is *a priori* probable because of the close relationship between the muscular tissue of the heart and blood vessels; there is, however, no evidence that direct vascular dilatation, owing to the presence of chloroform in the blood, plays any great part in the fall of blood pressure.

The original experiments of Lister showed that not only a drop of chloroform when applied, but also the vapour of chloroform, was able to produce hyperæmia in the web of the frog's foot. The evidence, however, of any direct dilatation of vessels when chloroform is inhaled does not appear to exist, and, in fact, in such a book as Dastre's, on anaesthetics, the pallor of the face so often noticed is considered to indicate vascular constriction as the effect of the drug rather than vascular dilatation; but, as far as we can gather from his book, we see no reason to suppose that the pallor cannot be explained by weakening of the heart. Roy and Sherrington¹⁷ assert that chloroform causes constriction rather than dilatation of the vessels of the brain, while, on the other hand, Hürthle¹⁸ from his experiments finds at first dilatation of the brain vessels as the direct effect of chloroform. This is followed shortly before death by constriction. We ourselves have tried to produce a fall of blood pressure by allowing chloroform vapour to pass in and out of the abdominal cavity through two openings as far removed from one another as possible, expecting that a local dilatation of the vascular area governed by the splanchnic nerves might be produced in this way, and so lead to a considerable fall of blood pressure. The experiment was, however, negative, and gave no indication that the blood pressure fall of ordinary chloroform inhalation was to any degree whatever due to direct dilatation of the abdominal vascular area. The volume of such an organ as the spleen does not increase when chloroform is given to the animal, as it would if a dilatation of its vessels or a relaxation of its muscular tissue occurred, but, on the contrary, diminishes more than can be accounted for by the fall in general pressure, showing that there is some active constriction. From these imperfect observations we are inclined to think that whatever action chloroform has directly on the blood vessels, it is insignificant compared with its much greater effects, primary and secondary, indirectly through the vaso-motor centre.

THE DANGERS OF CHLOROFORM ADMINISTRATION.

The conclusions and report of the Hyderabad Commission deal with two distinct and separate questions (1) the physiological action of chloroform, and (2) the dangers of chloroform administration. We have already discussed the first question, and have shown why in our opinion the physiology of the Commission is wrong; it is therefore with all the greater pleasure that we can now turn to the second question, and state that in our opinion the principles which have guided Lieutenant-Colonel Lawrie

¹⁶ The tracings have now been published in *Journ. of Physiol.*, xii, Dec 1892.

¹⁷ *Journ. of Physiol.*, vol. xi, p. 97.

¹⁸ *Pflüger's Archiv*, vol. xlv, p. 596.

¹⁵ *Proc. Roy. Soc.*, xlix, 144.

in the administration of chloroform are entirely in the right; that the great value of the Hyderabad Commission, for which the thanks of the medical profession will always be given to H.H. the Nizam, is the confirmation of Lawrie's views as to the safe method of administering chloroform, and also the publicity which has been given to the fact that by this method chloroform has been administered to many thousands of persons, not by experienced anaesthetists but by the students of the hospital without the occurrence of a single death.

The principle upon which Lawrie administers chloroform may be summed up in a single sentence: "Never at any moment of the administration of chloroform administer it in so concentrated a form as to cause irregularity of respiration, and cease the administration as soon as complete anaesthesia has been induced." Nature herself provides the signs and symptoms which show when the drug is being given in too concentrated a form, for when the air breathed contains too great a percentage of chloroform vapour the animal endeavours in three different ways to safeguard itself against the poisonous vapour; it struggles for the purpose of getting away, it holds its breath for the purpose of not taking more in, and its heart stops beating for the purpose of not sending on the poison to the nerve centres. Great credit is due to the Hyderabad Commission for their strong insistence upon the safeguard action of these three occurrences. Snow had previously pointed out the absence of danger from holding the breath and from stoppage of the heart, as already mentioned, but the experimental evidence of the safeguard action of the vagus nerve is due to the Hyderabad Commission. The result of the struggling is to increase the rate and depth of the respirations and to raise the blood pressure, owing, according to Zuntz and Geppert,¹⁹ to the action of the products of muscular activity in the blood.

The result of holding the breath is an after-increase of respiration and the stoppage of the heart through the vagus is followed by a reaction in the opposite direction, so that as Snow points out and as the Commission emphasises, there is now a danger of an excessive amount of chloroform being taken in, with the evil results of over-concentration.

The logical conclusion is, as Lawrie points out, to remove the chloroform further from the face until the blood pressure and respiration have recovered, and seeing that the respiration is so easily and markedly affected, he fixes his attention on that and says—Wait till the breathing is regular before the chloroform is again placed nearer the face.

What is the danger of concentration?

• Snow says the heart is only affected when the chloroform is given in too concentrated a form.

Lawrie says pushing chloroform overpowers the respiration and then the heart fails.

Cushny²⁰ says that too great concentration affects the heart.

Brunton considers the sequence of events to be as follows: first, the respiration is affected, with the result of causing an asphyxial condition of the blood, and then the combined action of chloroform and asphyxia affects the heart.

We see here another instance of an ever-recurring difficulty in physiological investigations, namely, to determine which is cause and which is effect; with an overdose, does death take place through weakening of the heart or through failure of the respiration?

What is true is this, as pointed out by the Hyderabad Commission—the respiration stops before the heart actually ceases to beat. This, however, does not necessarily imply that an overdose kills by its action on the respiration. Such a death may be brought about in two ways: 1. Weakening of respiration, causing insufficient aëration of the blood, which in its turn causes heart failure, through the combined action of asphyxia and chloroform. 2. Weakening of heart, causing an insufficient blood supply to the respiratory centre, which in its turn causes cessation of respiration through the combined action of chloroform and an insufficient blood supply.

In both cases the chloroform affects both heart and respiratory centre, in both the respiration stops before the heart ceases to beat; but (1) is a case of death from respiration failure mainly, and (2) from heart failure mainly. The rapid fall of blood pressure due to an overdose is clear evidence of a

weakening of the heart, as already proved; so that if our statements are accepted, it follows that the first explanation is less likely than the second. In our experiments we have seen very distinct evidence that the respiratory centre is much more easily affected by chloroform when its blood supply is diminished to a considerable extent.

CHLOROFORM WITH DIMINISHED BLOOD SUPPLY TO THE MEDULLA.

We have been very much struck, both in the experiments on cross circulation and on the effect of ligature of the brain arteries, to find that, after the occlusion of two or more of the brain arteries, a very slight amount of chloroform inhaled is sufficient to stop respiration; the respiratory centre is apparently working at a great disadvantage with an insufficient supply of oxygenated blood, and is therefore easily placed *hors de combat* by any paralyzing agent, such as chloroform.

In our cross-circulation experiments we attempted in a few cases to keep alive the brain of a rabbit by the blood from a dog, but found that the experiment was unsuccessful, as the rabbit always succumbed soon after the cross circulation was established. In these cases, then, we continued an experiment upon the dog, and noticed the effect of chloroform when two or three of the brain arteries were ligatured. Thus March 2nd and February 27th, 1891, were two instances, and in them we see another most striking result of chloroform under these circumstances, namely, the production of periodic respirations of the nature of Cheyne-Stokes respiration.

The amount of chloroform taken into the trachea of the dog was regulated by a slit in the cannula which could be left open or closed to a greater or less extent. When it was wide open only a small amount of chloroform was mixed with the air of inspiration, in fact under these circumstances a normal animal will continue breathing in a small amount of chloroform for a long time without any sign of danger. When the slit is completely closed the whole air of inspiration passes over the chloroform in the Wolff's bottle, with the result of causing a rapid fall of blood pressure and a speedy threatening of cessation of respiration.

In these cases, however, where two or more of the brain arteries were ligatured the connection of the tracheal cannula with the chloroform bottle, even when the slit was wide open, was sometimes sufficient to cause a marked alteration of the respirations of the nature of Cheyne-Stokes respiration. Thus on March 2nd, after both carotids were clamped, the chloroform bottle was connected with the trachea, the side slit being fully open, and the respirations, which were slow at the time, became quickly weaker and ceased in about one minute, the animal then remained for over one minute without breathing, then the respirations began again, quickly getting stronger and again dying away, till another pause of over a minute took place; the period of respiratory activity lasted about a minute, and during the whole time the trachea was in connection with the chloroform bottle, the slide slit being fully open. During the periods of respiratory activity the blood pressure rose; during the pauses it fell slightly. After the last pause the respirations again recommenced and then one carotis was unclamped, with the result that the respirations continued regularly with a regular blood pressure until by closing the side slit the chloroform was pressed and a rapid fall of blood pressure with cessation of respiration took place.

We conclude, then, that the respiratory centre is better able to resist the paralyzing action of chloroform when it is freely supplied with oxygenated blood than when it is becoming exhausted by an insufficient supply of blood insufficiently aërated, and that Lawrie's supposition that the fall of blood pressure is in itself of the nature of a safeguard, because of the diminished amount of chloroform conveyed to the medulla oblongata, is not at all likely, as the smaller amount of chloroform so conveyed is more effective on the centre already suffering from want of a sufficient blood supply. The only safeguard action throughout is at the commencement of the chloroform administration, as already mentioned, when we see struggling, stoppage of heart, and holding of breath. Afterwards, when anaesthesia is induced, the fall of blood pressure, which is due to weakening of the heart, is no safeguard, but, on the contrary, is a danger to be avoided as far as possible.

¹⁹ *Plüger's Arch.*, xxxviii, 337.

²⁰ *Lancet*, March 14th, 1891.

CHLOROFORM WITH PLenty OF AIR.

The rapidity and depth of this fall is directly dependent upon the concentration of the chloroform, so that if care is taken to give the chloroform with plenty of air it is possible to obtain anæsthesia with very little fall of pressure, for the heart is very little affected by blood containing only a small amount of chloroform. On the other hand, administration of chloroform with plenty of air, continued after complete anæsthesia has been produced, does ultimately overpower the respiration, although the heart is beating sufficiently well to maintain the blood pressure at a fairly good level.

These statements are well illustrated by an experiment on December 11th, 1890 (Fig. 11),²¹ where chloroform was administered to a rabbit continuously for a long period of time by dropping it on to a cloth placed round the head of the animal in a conical shape, so as to leave a free opening for air about two inches in diameter. Every now and then the part of the cloth upon which the chloroform was poured was brought closer to the nose and mouth of the animal, and the moment of bringing the chloroform nearer and of removing it again was noted on the kymograph paper. In the tracings *a*, *b*, *c*, *d*, *e*, *f*, Fig. 11, samples of the respiration and blood-pressure curves are given at various times throughout the experiment; as stated already, chloroform was steadily administered during the whole time.

In Tracing *a*, taken before the administration of chloroform at 3.34 we see: mean blood pressure, 64; pulse rate per minute, 222; respiration rate per minute, 30. The chloroform was then placed on the cloth, and the effect of bringing the chloroform nearer and removing it further tried for a number of times. An example of the effect produced is given in Tracing *b*, showing the inhibition of the respiratory movements, the slowing of the pulse, and the rise of blood pressure owing to the stimulation of the trigeminal and pharyngolaryngeal nerves, when the chloroform is more concentrated; immediately the cloth is removed further from the nose the blood pressure returns to its normal condition, and the slowed respiration gradually quickens up to its previous rate. This experiment was repeated again and again with similar results.

The effect of the continuous administration of chloroform in this way for 14 minutes is given in Tracing *c*, taken at 4.48, where we see: mean blood pressure, 67; pulse rate per minute, 218; respiration rate per minute, 31. Further continuation of the same experiment shows that the inhibition of the respirations and the slowing of the pulse when the chloroform is brought nearer to the nose become less marked; and, finally, after 3.56—that is, 22 minutes after the beginning of the experiment—the blood pressure and the respirations remained absolutely unaffected when the chloroform was brought close to the nose. At the same time, it was noticed that the corneal reflex was entirely abolished.

Tracing *d*, at 3.57, shows the absence of any effect upon temporary concentration of the chloroform, and we see: mean blood pressure, 69 mm.; pulse rate per minute, 204; respiration rate per minute, 42. It is noticeable that at this period, when all reflexes were abolished and the animal was in a condition of complete anæsthesia, the blood pressure was not lower than before the commencement of the experiment, and the only sign of the action of the anæsthetic is to be found in the quicker respiration.

At 3.58 the respiration rate per minute had increased to 46, the pulse tracing and respiration both remaining absolutely regular. At 3.59 the respiration was 45 per minute, at which it remained till 4.1, the mean blood pressure being then 62 mm. Both respiration rate and blood pressure continued steadily to diminish, and at 4.3, when Tracing *e* was taken, we see: mean blood pressure, 50 mm.; pulse rate per minute, 218; respiration rate per minute, 37. At 4.5 the respiration rate was 35; at 4.7, 31; at 4.8, 29; and at 4.9 the respiration had ceased. The termination of the experiment is shown in Tracing *f*, in which is seen the diminishing force of the diaphragm contractions, with the final rate, and we see: mean blood pressure, 48 mm.; pulse rate per minute, 126; respiration rate per minute, 24.

It is noticeable in this case, as in others (Figs. 1, 2, and 3),²²

how markedly the muscle strip of the diaphragm elongates when the respiration is failing. This points strongly to the conclusion that the respiratory centre possesses a distinct tonic influence on the diaphragm muscle, so that the failure of its action causes a loss of tone in the muscle as well as a diminution in the strength of each contraction. The pressure of 48 mm. at the time when the respiration ceased is not very low for a rabbit, and, indeed, the heart continued beating well for a considerable time, and then, by means of artificial respiration, the animal was easily recovered, and both blood pressure and respiration became normal, as is seen in Fig. 1, Tracings *a* and *b*, which represent the final ending of the experiment.

The danger, then, of chloroform administration consists (1) of causing a serious fall of pressure owing to weakening of heart from too great a percentage of chloroform in the air, which, combined with the action of the chloroform on the respiratory centre, in its turn causes failure of respiration; and (2) cessation of respiration after long administration owing to keeping on the chloroform, although given with plenty of air, too long a time after complete anæsthesia has been established.

ON HAFKINE'S METHOD OF VACCINATION
AGAINST ASIATIC CHOLERA.

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THE subject of M. Haffkine's anticholeraic vaccinations has already been treated of in the BRITISH MEDICAL JOURNAL, notably in an able paper by Mr. Hankin. In response, however, to a kind suggestion from the Editor, and in view of the great importance of the matter, we propose to give further details of M. Haffkine's method of vaccination as demonstrated by him at Netley during the past week. We gladly avail ourselves of this opportunity to express our sense of gratitude to him for his kindness in coming to Netley for this purpose.

It may perhaps conduce to clearness of exposition if we present the facts of cholera vaccinations in their relation to certain broad generalisations which have been made in connection with the subject of microbial infective processes.

Microbial infections are conveniently subdivided into "septicæmias" and "intoxications." In the case of the former the bacteria multiply freely in the blood and produce their poisons there. In the case of the latter the micro-organisms do not proliferate in the blood, but bacterial poisons become absorbed into the system from some point—generally a point on the inner or the outer surface of the body—at which the bacteria have effected a lodgment. Asiatic cholera belongs to the latter class of infective diseases, for the specific organisms which set up the disease are strictly confined to the alimentary canal. They are never found in the tissues, and they are very rapidly killed off when they are artificially introduced either into the blood or into the hypodermic tissue. For these reasons we may characterise the system as "bacteria proof" with respect to the specific organisms of Asiatic cholera. On the other hand, both experiment and clinical observation establish that the system is acutely susceptible to the poisons which are generated by the comma bacilli in the intestine. In view of the above facts, it will readily be understood that immunity against cholera can only be brought about by rendering the system "poison-proof" (*gift-fest*) with respect to the poisons of the cholera bacillus.

M. Haffkine's method of anticholeraic vaccination consists in such a process of chemical vaccination. The protection against cholera is brought about by acclimatising the system first to a weak cholera poison (first vaccine), and afterwards to a strong cholera poison (second vaccine). For adequate protection it is essential that this second vaccine should consist of the strongest obtainable cholera poisons.

²¹ BRITISH MEDICAL JOURNAL, January 28th, 1893, p. 169.

²² BRITISH MEDICAL JOURNAL, January 21st, 1893, p. 108.