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REPORT XCIV.

ANAESTHETICS AND RENAL ACTIVITY :

AN EXPERIMENTAL INVESTIGATION INTO THE EFFECTS OF
PROLONGED CHLOROFORM AND ETHER NARCOSIS.*

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PART I.—CHLOROFORM NARCOSIS.

SOME years ago, when seeking for the cause of certain effects of intravenous injections of sodium chloride solutions upon renal activity, it became necessary to ascertain the corresponding influence of the anaesthetic employed—namely, a mixture of two parts of ether and one of chloroform.

The inquiry subsequently extended itself into the present research, but its prosecution has suffered interruption from various causes.

METHODS.

The experiments were made upon dogs and comprise observations on the effects of (a) chloroform, (b) ether, and of two mixtures containing these, namely, one (c) known as the A.C.E. mixture, the other (d) a combination frequently employed in physiological laboratories, composed of chloroform one part, ether two parts.

As a rule the animals received no food for twenty-four hours before the observations began, the exceptions are indicated. A moderate allowance of water was given on the day previous, but none on the day of the experiment till after the observations were completed. The animals then in most cases drank freely.

Two classes of experiments were carried out with each anaesthetic.

(a) Ureter Experiments.

The urine was collected from cannulae placed in the ureters for definite periods before, during, and after the administration of the anaesthetic. To avoid opening the peritoneal cavity the cannulae were inserted as a rule from behind. Records of carotid blood pressure were also taken in most of these experiments, not continuously but at intervals varying from ten minutes to a quarter of an hour. To induce anaesthesia preparatory to the operative procedures, small doses of morphine were given, and during the operations the morphine was supplemented, when necessary, by inhalation of the ether-chloroform mixture referred to above. Events showed that neither the morphine nor the ether-chloroform mixture was wholly without influence upon renal secretion, but of the two the former had the less effect in moderate doses. Accordingly, in the later ureter experiments the dose of morphine was somewhat increased and the volatile anaesthetic used as little as possible. When the ether-chloroform mixture was given during the preparatory operations an interval of half to three-quarters of an hour was allowed to elapse before collecting the normal sample of urine.

(b) Catheter Experiments.

These were made to observe the influence of the anaesthetic upon renal secretion without previous operation of any kind and without the administration of morphine. The urine was drawn off from the bladder of the female animal by sterilized glass catheter, pressure on the abdominal wall being employed to ensure complete emptying. Collections in this way were made for periods varying in number from three to five, and, as a rule, of two hours' duration each. During the first a normal sample of urine was taken; during the second the anaesthetic was administered; during the third, fourth, and fifth periods the after-effects were observed. Except during Period II the animals were kept in a metabolism cage. To avoid struggling in giving the anaesthetic the animal was at

* Preliminary communications giving the earlier and some of the interim results were published in the *Journal of Physiology*, vol. xxv, p. 491; in the *BRITISH MEDICAL JOURNAL*, 1900, vol. ii, p. 833; also in the former journal, vol. xxxii, under *Proceedings of the Physiological Society*, p. xxi.

first placed in a box till sufficiently insensible to be transferred to a table. Here the anaesthesia was afterwards maintained in the ordinary way by enveloping the head in a towel and pouring the anaesthetic on a piece of cotton-wool. The table was provided with a warm-water pan, the dog being also covered with a light cloth. When afterwards brought into the metabolism cage the animal was also covered.

In most of the cage experiments full anaesthesia was maintained, such as would be necessary for the performance of an operation. In a few it might be described as light. This applies particularly to the ureter experiments where morphine had previously been given. No attempt was made in the present series of experiments to graduate the percentage of the anaesthetic given. Nevertheless, the results obtained are, I think, of sufficient interest to justify publication. An extension of the research is in progress, in which the effects of graduation, together with other questions, are under investigation.

Examination of the Urine.

The quantity secreted was observed stage by stage. The different samples were analysed for total nitrogen in most cases (Kjeldahl's method), for urea in a few, (Mörner's method), for chlorides in a large number (Volhard's method). Examinations were also made in several of the experiments for reducing osazone-yielding substances, as well as for albumen. The procedures employed in these latter observations will be given later. In the tables throughout this paper the quantities of urine are given in cubic centimetres per period, the quantities of nitrogen and chlorides in grams per period or per cent. as the case may be.

A.—CHLOROFORM.

I.—Effects on the Quantity of Urine.

Kemp¹ found that under chloroform the quantity of urine remained copious till the general circulation became considerably affected, when the flow diminished. Buxton and Levy,² without giving details, state that their results agree in the main with those of Kemp. The urine in both researches was collected from the ureters.

In the following investigation two opposite effects were noted during the period of administration, both in the "ureter" and "catheter" experiments. In a majority the secretion of urine was diminished. An example of this effect is shown in the following figures, which represent in cubic centimetres the quantities of urine secreted in a catheter experiment during five successive periods of two hours' duration each. The quantities for the anaesthetic periods are throughout given in thick type; the Roman letters refer to the periods.

I.	II.	III.	IV.	V.
38	6	3.5	42	9

At one stage two chloroform periods were adopted in succession in order to ascertain if a continued retention of water in the system would ultimately induce an increased urinary secretion. The reverse happened.

In a minority of the experiments an increased flow of urine was observed, of which the following is an example, taken from a "ureter" experiment:

I.	II.	III.	IV.
12.6	25	32.75	24

The after-effect in both classes of experiment, almost without exception, was a marked increase in the rate of secretion, which as a rule reached its maximum in the period succeeding the removal of the anaesthetic. The following table gives further illustrations of the two varieties of effect:

TABLE I.—CHLOROFORM: EFFECTS ON THE QUANTITY OF URINE.

Experiment.	I.	II.	III.	IV.	V.
<i>Ureter Series.</i>					
1	12.6	25.0	32.75	24.0	—
2	57.3	7.0	11.8	5.2	—
3	11.0	7.8	11.15	9.4	9.4
<i>Catheter Series.</i>					
1	23.2	19.0	20.0	—	—
2	23.5	3.6	40.0	114.0	62.0
3	64.0	26.0	67.0	21.0	—
4	4.5	1.0	10.5	31.0	—
5	28.0	3.5	204.5	201.5	—
6	7.0	10.0	4.5	26.0	—
7	9.5	74.5	55.0	58.0	30.0
8	84.0	127.0	126.0	105.0	80.0

Of the foregoing "ureter" experiments, two showed a decrease and one an increase in the rate of secretion. Of the "catheter" experiments, five showed a decrease, three an increase. These latter are placed together at the end of the table, but they did not occur in this order in the series of experiments. The after-effect in all (with one possible exception, where the observations did not extend beyond Period III) was a striking increase in the volume of urine. In most cases this reached its maximum during Period III.

Expressing the above results in averages, those of the "decrease" experiments for the five periods are as follows:

I.	II.	III.	IV.	V.
28.64	10.02	68.4	116.85	62

That is to say the secretion of urine dropped in the anaesthetic period to 35 per cent. of the normal and rose during the period of maximum after-effect to 415 per cent. of that amount.

The "increase" experiments gave the following averages per period expressed as before:

I.	II.	III.	IV.	V.
33.5	70.5	61.8	63	55

Here the maximum flow of urine occurred during the administration of the chloroform, and reached to 210.4 per cent. of the normal. During the two subsequent periods the rate of flow was hardly less.

It seemed that these two divergent forms of effect were due to different degrees of the chloroform influence, the increase in all probability being caused by an earlier or lighter action, the decrease by a deeper effect. This was suggested by the increase in some of the "ureter" experiments, where morphine had previously been administered and consequently less chloroform was required. The point was also tested in two additional "ureter" experiments not included in the foregoing table, but given in subsequent tables as Ureter Experiments 4 and 5. In the first of these the chloroform period is divided into three stages, the lengths of which are: (a) Three-quarters of an hour, (b) one hour, (c) one hour. The rates of secretion are as follows:

I.	II.	III.
7.2	(a) 4.2 (b) 12.8 (c) 4.6	12.8

In the second experiment the half-hourly rates of secretion for each period were as follows:

I.	II.	III.
8.5 11.95	6.1 6.0 4.9 2.2	14.8 17.65

Thus in one of these two additional experiments the increased effect produced by light anaesthesia is obvious. It did not occur in the second, notwithstanding very gradual administration at the outset. It would appear, therefore, not to be an invariable result, and this agrees with the table as a whole where both effects are seen. The depressing influence, however, occurs with much greater frequency than the opposite. Further, when the increase during administration does take place, it is probably preceded by a short period of depression, as seen in one of these experiments. It should be added that no ether-chloroform mixture was required during the preparatory stages of either of the experiments now considered.

II. Effects on the Excretion of Nitrogen.

Eulenburg-Strübing³ found nitrogenous metabolism diminished as a whole by chloroform narcosis with a relative increase in the excretion of phosphorus. This latter was attributed to a decomposition of lecithin. Kappeler⁴ states that in the human subject the excretion of urea varies. In twenty observations, a diminution was noted in thirteen instances, an increase in five, while in two the urea remained unchanged. Salkowski⁵ found an increase of nitrogen in the urine, as did also Strassmann⁶ to the extent of 20 per cent. Kast and Mester⁷ noted an increased excretion of nitrogen along with decline of body-weight, after prolonged chloroform narcosis. Kobert⁸ states that Ken Taniguti found metabolism to be increased after internal administration of chloroform, even when the dose was insufficient to produce narcosis.

The results obtained in the present research are given in the following table. It will be seen that with one exception the excretion of nitrogenous solids per period was diminished. This applies even to experi-

ments where the quantity of urine was considerably increased.

TABLE II.—CHLOROFORM: EFFECTS ON THE EXCRETION OF NITROGEN PER PERIOD.

Experiment.	I.	II.	III.	IV.	V.
		<i>Ureter Series.</i>			
1	0.3916	0.3647	0.2969	0.2990	—
2	0.2085	0.0225	0.0618	0.0592	—
4	0.2096	(a) 0.0828 (b) 0.2522 (c) 0.0445	0.1861	—	—
5	0.1425	(a) 0.382 (b) 0.0376 (c) 0.0348 (d) 0.0076	0.0870	0.1547	—
		<i>Catheter Series.</i>			
2	0.5593	0.0492	0.3819	0.5658	—
3	0.3351	0.1136	0.9281	0.2975	—
4	0.1285	0.0224	0.1676	0.3046	—
6	0.1384	0.270	0.0833	0.4856	—
7	0.2851	0.2743	0.3665	0.5651	0.5157
8	0.2117	0.1920	0.5574	0.6233	0.4301

N.B.—In Ureter Experiment 4, the quantities given for the anaesthetic period represent the excretion of nitrogen in successive stages (a) of 45 minutes, (b) of one hour, (c) of one hour. In Ureter Experiment 5, the corresponding quantities represent the half-hourly rates of excretion during the period.

The averages per period for one hour duration for the "ureter" series, making the necessary deductions in Period II of Experiments 4 and 5, are as follows—the quantities being given in grams:

0.2380	0.1462	0.1584	0.1709.
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During the anaesthesia the output of nitrogen diminished to 61.43 per cent. of the normal. It will be seen, moreover, especially in Ureter Experiment 5 that there was a continuous decline in the output of nitrogen during this period, and that in its later stages the excretion fell to a rate much below that represented by the average of the period.

In considering the "catheter" series the experiments are divided into two groups—those in which the quantity of urine was diminished, which are named "decrease" experiments; and those in which the opposite effect was observed, which are named "increase" experiments. From the former group, two of those included in the first table are omitted, the urine being employed for other analyses than that of total nitrogen. Of the three "decrease" experiments remaining, the averages per period of two hours are:

I.	II.	III.	IV.	V.
0.3409	0.0617	0.4925	0.3893	—

Those of the three "increase" experiments are:

0.2117	0.2277	0.3357	0.558	0.4729
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In the former group the output of nitrogen fell during anaesthesia to 18 per cent. of the normal—a much greater fall in proportion than occurred in the volume of urine for the same group. The quantity of urine for the three experiments in question only fell to 35 per cent. The difference is of importance in showing that the depressing effects of the anaesthetic are greater on the output of nitrogenous solids than on the escape of water.

In the "increase" group the same influence is revealed, though somewhat masked. The output of nitrogen during Period II rose only to 7.56 per cent. above the normal, although the quantity of urine exceeded that amount by over 110 per cent. Further, in one of the "increase" experiments the influence of the anaesthetic on the two factors—urine volume and output of nitrogen—was in opposite directions. In Catheter Experiment 8, notwithstanding a large increase in the water constituent of the urine, the output of nitrogen fell considerably. The same is seen to a less degree in Catheter Experiment 7.

The conclusion to be drawn from these results seems clearly to be that the influence of the anaesthetic on renal activity cannot be wholly due to its effect on the blood flow through the organ. If this were so, one would expect to find the influence on the excretion of nitrogen proportionate to, or at all events not greater than, that upon the secretion of water.

Additional light is thrown upon the matter by an examination of the concentration of the urine secreted in the different periods. It will be seen that the rule which

holds good under normal conditions—namely, that a diminution in the volume of urine goes hand in hand with increased concentration—does not apply in chloroform anaesthesia.

Effects on the Concentration of the Urine.

The table below shows that in every instance, with one exception—namely, Experiment 6, Catheter Series—the urine of the anaesthetic period is more dilute than normal. This holds good both in the “ureter” and “catheter” series of experiments. One would naturally have expected the opposite relationship, particularly in the decrease “catheter” experiments, and yet all of these conform to the rule. It is also remarkable that in the later stages of the narcosis, where the volume of the urine is most reduced, the percentage content of nitrogen is also most diminished. This is illustrated in column II of the table, by the figures opposite Ureter Experiments 4 and 5, which represent the concentration of the urine secreted at different stages of the anaesthetic effect.

TABLE III.—CHLOROFORM: EFFECT ON THE PERCENTAGE OUTPUT OF NITROGEN.

Experiment.	I.	II.	III.	IV.	V.
		<i>Ureter Series.</i>			
1 ...	3.1080	1.4580	0.9128	1.2460	—
2 ...	0.3640	0.3220	0.5236	1.1396	—
4 ...	2.9106	(a) 1.9746 (b) 1.0360 (c) 0.6274 (d) 0.3472	1.4540	—	—
5 ...	0.7056	(a) 0.6274 (b) 0.5272 (c) 0.7098 (d) 0.3472	0.2940	0.4382	0.5082
		<i>Catheter Series.</i>			
2 ...	2.3800	1.8664	0.9548	{ 0.5376 0.3416 }	—
3 ...	0.5236	0.4368	1.2320	1.7024	1.4168
4 ...	2.8560	2.4400	1.5960	0.9828	—
6 ...	1.9768	2.1700	1.8508	1.8676	—
7 ...	3.0016	0.3982	0.6664	0.9744	1.7192
8 ...	0.2520	0.1512	0.4424	0.5936	0.5376

N.B.—(a), (b), (c), (d) represent different stages of same period as explained under Table II.

The above results appear to have an important bearing on the mechanism of urinary secretion. They are difficult to account for, except on the hypothesis that the escape of watery constituents at the glomerulus is supplemented by a secretion of nitrogenous solids into the tubules. Chloroform affects both these processes, but the latter to a greater degree than the former. The exception referred to, where the urine secreted during anaesthesia was more concentrated, belongs strangely to the group where the flow of urine was at the same time increased. It is therefore doubly anomalous, and in a sense the counterpart of the decrease experiments, both as regards concentration and urine volume. It shows also that chloroform may stimulate nitrogenous metabolism in certain cases as claimed by Kappeler.⁹ In Stage (c) of Ureter Experiment 5 the concentration of the urine is also slightly increased.

Effect on the Chlorides of Urine.

An increased excretion of urinary chlorides after chloroform narcosis has long been known. The form in which the chlorine occurs has, however, been a matter of dispute. Zweifel¹⁰ found unaltered chloroform. Steinauer¹¹ somewhat later discovered the existence of chlorine in organic combination in normal human urine, and Kast¹² showed that part of the excess of chlorine which occurs after chloroform narcosis is also in the form of organic chlorides. Zeller¹³ found that of chloroform administered per os 20 to 25 per cent. escaped by the lungs; the remainder left the body as alkaline chlorides in the urine. Pohl¹⁴ confirmed the occurrence of traces of unaltered chloroform in the urine, as did also Wagener,¹⁵ but the latter found it in only two instances out of fifteen, and the subjects in these cases had frequently been chloroformed. Dioscoride Vitali¹⁶ denies that the urine contains more organic chlorides after chloroform narcosis than normal, but Kast and Mester¹⁷ confirm the earlier observations of the former, especially after prolonged administration.

The following table gives the excretion of chlorides per period in six of the catheter experiments taken from the foregoing series:

TABLE IV.—CHLOROFORM: EFFECT ON THE CHLORIDES OF URINE.

Experiment.	I.	II.	III.	IV.	V.
		<i>Catheter Series.</i>			
1 ...	0.0046	0.0550	0.0460	—	—
2 ...	0.2300	n d.	0.1100	0.6600	0.9300
3 ...	0.0500	0.4400	0.8200	0.6200	—
5 ...	0.0728	0.0168	{ 0.8083 0.1822 }	0.9873	—
7 ...	0.0237	0.0611	0.2255	0.0812	—
8 ...	Nil	0.7239	0.1386	0.1260	0.3280

In every case an increase occurred, sooner or later, after the chloroform, generally during the period of administration. The averages in grams per period for the six experiments are as follows:

0.0635 0.2593 0.3718 0.4949 0.6240

A steady increase in the output is thus seen, reaching in the third period, after removal of the chloroform, to ten times the normal amount. The observations did not extend beyond this period, which ended six hours after removal of the chloroform. In two cases an examination for organic chlorides was made by the method of Kast.¹⁸ The results were negative. It is to be remarked, however, that the examination was not made immediately after collection of the urine, and that possibly chloroform in the interim may have escaped, also that the content of chlorides in the normal urine of the dog is very small.

Control Experiments: No Anaesthetic Administered.

In considering the foregoing results it has been assumed throughout that renal activity remained constant during the periods of observation. It seemed, however, desirable to make certain that this was so by actual observation. A series of five “catheter” experiments was therefore carried through, the dogs being treated in the same way as in the corresponding anaesthetic experiments, except that no anaesthetic was given. The urine was then analysed for total nitrogen and chlorides. The following table gives the rates of secretion observed in the different normal periods:

TABLE V.—THE NORMAL RATE OF URINE SECRETION.

Experiment.	I.	II.	III.	IV.	V.
		<i>Catheter Series.</i>			
1 ...	25.5	22.0	21.00	19.0	21.5
2 ...	23.0	14.5	13.00	12.5	13.5
3 ...	9.0	8.5	8.75	9.0	8.0
4 ...	9.0	11.0	7.50	6.5	6.0
5 ...	31.0	29.5	25.50	20.5	20.5

The averages from the above series give the periodic rates as follows:

19.5 1.71 15.15 13.5 13.9

showing a slight tendency to decline from beginning to end. The fluctuations are unimportant, and except in Period II are in the opposite direction to those seen after anaesthetics.

Table VI gives the output of nitrogen per period in the foregoing series.

TABLE VI.—NORMAL OUTPUT OF NITROGEN.

Experiment.	I.	II.	III.	IV.	V.
		<i>Catheter Series.</i>			
1 ...	0.3320	—	—	0.3805	0.3883
2 ...	0.2737	0.2842	0.2912	0.2933	0.3251
3 ...	0.2699	0.2256	0.1933	0.1466	0.1062
4 ...	0.1867	0.1608	0.1474	0.1318	0.1445
5 ...	0.1979	0.2015	0.2156	0.2095	0.2141

The average excretion of nitrogen per period is as follows:

0.2520 0.2180 0.2119 0.2323 0.2356

The fall in nitrogen during Periods II and III is somewhat more in proportion than the corresponding fall in the quantity of urine, but not such as to vitiate the conclusions drawn from the effects of the different anaesthetics.

The following shows the excretion of chlorides in the control experiments:

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Fig. 1.—Chloroform effects on blood pressure and urinary secretion. Ureter Experiment 2.

TABLE VII.—EXCRETION OF CHLORIDES WITHOUT ANAESTHETICS.

Experiment.	I.	II.	III.	IV.	V.
1 ...	0.0280	<i>Catheter Series.</i> 0.0484	0.0210	0.0152	0.0430
2 ...	0.0069	0.0029	0.0026	0.0012	0.0027
3 ...	0.0540	0.0586	0.0866	0.0675	0.0432
4 ...	0.0027	0.0033	0.0090	0.0026	0.0018
5 ...	0.0031	0.0177	0.0076	0.0041	0.0081

The averages from the above are :

0.0189 0.0262 0.0251 0.0181 0.0197

A slight increase in the output is thus seen during Periods II and III, but this is insignificant when compared with the results shown in the chloroform series.

VASCULAR EFFECTS.

It was considered necessary, as the starting point of an inquiry into the causation of the foregoing effects, to ascertain the relationships between urine secretion, blood pressure, and kidney volume throughout the different periods.

(a) Relationship between Blood Pressure and Urine Secretion.

The results obtained by Kemp, as well as those of Buxton and Levy, have already been referred to. In the present investigation a comparison of blood pressure, with rate of urine secretion, was made in most of the "ureter" experiments. Figs. 1 and 2 give records from two of these. In Fig. 1 (taken from Ureter Experiment 2) the urine curve has been superposed on the actual blood pressure tracing.

On examining the two curves it will be seen that urine secretion rose considerably just before the chloroform was given, and then fell continuously, till actual cessation took place after forty minutes' administration. When the chloroform was removed, the secretion returned, but did not again reach the normal rate seen at the beginning of the experiment. This end-result is typical of several of the "ureter" series, and differs from that seen in the "catheter" experiments, where a striking after-increase was the rule. The deviation in the ureter experiments is probably caused by the morphine injected before the operations were begun. In the experiment from which the tracing was taken morphine had thus been given, and the morphine narcosis was further supplemented by a short inhalation of the ether-chloroform mixture. To the after-effects of the latter I attribute the increase in urine secretion seen immediately before the chloroform was begun.

Reviewing the relationship between the curves as a whole, it will be seen that the correspondence is at most relative, not by any means complete. Points of deviation are obvious at more than one situation, and the arrest of urine secretion occurred with a comparatively high blood pressure. This latter is fully 95 mm. in the carotid artery, more than double that which is sufficient under other conditions to maintain a flow of urine through the kidney.

Fig. 2 gives curves constructed from the blood pressure and urine outflow in Ureter Experiment 4.

Three phases are shown in the chloroform effect upon the urine secretion. During the early period of light anaesthesia the flow, with some fluctuation, declined on the whole. This is followed by a marked increase, which in its turn is succeeded by a second fall, not proceeding, however, to actual suppression. After removal of the anaesthetic a great rebound of secretion took place.

The blood pressure corresponds in the main to the outflow of urine except at two stages, namely, during the intermediate phase of increase, and also during

CHLOROFORM.

Fig. 2.—Chloroform effects on blood pressure and urinary secretion. Chart from Ureter Experiment 4.

the fall before conclusion of the experiment. The deviation between the two curves in the intermediate stage is no doubt to be accounted for by the dilating effects which Embley and Martin¹⁹ also Schäfer and Scharlieb²⁰ have shown to be exerted upon blood vessels by chloroform. The fall in urine secretion during the later stages of the experiment is not explained by the condition of blood pressure, which was higher than at any another period.

(b) Kidney Volume and Urine Secretion.

The effects of chloroform on kidney volume have been observed by Kemp, by Embley, and also by Embley and Martin, but in no case for long periods at a time. Both Kemp and Embley, during the administration, found an early increase of volume, followed later by a decrease. The after-effect in Embley's experiments was a great increase.

Kemp simultaneously collected urine from the opposite ureter and found the flow to correspond on the whole with kidney volume.

In the present investigation four chloroform experiments were performed in which records of kidney volume, of general blood pressure, and of urine secretion were made. One, however, failed, and one was but a partial success. The left kidney was in each instance chosen and Roy's oncometer was used in all, but the recording instrument was varied. In one experiment the piston recorder (Hurtle's pattern) was employed, in another the oncograph of Roy, in a third a sensitive Marey's drum, in two others the bellows recorder of Brodie. In each case the recorder was previously tested for leakage. A warm water-jacket kept at constant temperature such as I used in previous kidney experiments²¹ was placed over the oncometer to prevent cooling.

The conditions to be fulfilled in prolonged oncometer experiments with the kidney, made it difficult to successfully carry out the observations. Curare could not be used owing to its effect on the secretion of urine. The preliminary morphine anaesthesia had to be carefully graduated for the same reason. The dose given in these experiments was from 5 to 6 mg. per kilo of body-weight. Nor could the morphine narcosis be supplemented by the use of a volatile anaesthetic without an exceedingly long wait afterwards—at least four hours—during which time the kidney tissue suffered, and in the end ceased to be normal. The periods had also to be reduced in length to avoid the same possibility.

The following table gives the secretion per period from both kidneys for the four experiments. It was accepted, that if any marked divergence was shown in the rate of secretion on the two sides, the results could not be considered reliable. Applying this test to the group of experiments below, one (Experiment 4) must be discarded. The remaining three, however, fulfil the conditions while showing varying degrees of chloroform influence.

TABLE VIII.—EFFECTS OF CHLOROFORM UPON URINE SECRETION AND OUTPUT OF NITROGEN IN ONCOMETER EXPERIMENTS.

Experiment.	I.		II.		III.	
	L.	R.	L.	R.	L.	R.
1 ...	2.28	3.28	0.24	1.00	3.86	8.45
2 ...	1.72	1.95	(a) 0.80 (b) 0.00	{ 1.70 0.53 }	1.70	2.65
3 ...	3.75	2.80	(a) 2.30 (b) 2.10	{ 2.10 2.30 }	2.90	3.00
4 ...	14.60	17.40	3.40	16.00	2.80	10.50
Excretion of Nitrogen per Period.						
3 ...	0.0689		{ (a) 0.0576 (b) 0.053 }		0.0628	
4 ...	0.1958	0.1681	0.0639	0.1631	0.0889	0.1325

Duration of Periods.—Experiment I, 40 minutes.

" " 2, 20 "

" " 3, 60 "

" " 4, 60 "

N.B.—(a) and (b) in this table under Period II represent duplication of the anaesthetic period, not subdivision into stages.

The average rates of flow per period taken from the first three experiments in the above table are for

Kidney in oncometer	2.58	1.09	2.82
Kidney <i>in situ</i> ...	2.68	1.53	4.70

These correspond with that obtained as a rule in ureter experiments and show a medium degree of chloroform influence. A tracing from Experiment 2, upon which the curve of urine secretion is superposed is given in Fig. 3 (p. 613).

The somewhat different results of Experiment 3 expressed in curve form are given in Fig. 4. The curves from above downwards are those of kidney volume, carotid blood pressure, and urine outflow. The height of the first above the abscissa line is arbitrarily chosen.

If Figs. 3 and 4 be carefully examined it will be seen that while there is a general correspondence in the curves in both, there are at the same time considerable deviations. The short dilatation of the kidney seen in both tracings at the early stage of the chloroform influence is not reflected in Experiment 2 by an increased outflow of urine. It is, however, succeeded in Fig. 4 by such an increase, but in the same figure divergences are elsewhere

seen in the curves, notably in the third half-hour of the administration. The tracings also emphasize the fact that the arrest of secretion which occurs in Experiment 2 (Fig. 3) and the extreme slowing amounting almost to arrest in Experiment 4 are not satisfactorily explained by

CHLOROFORM.

Fig. 4.—Chloroform effects on kidney volume, blood pressure, and urine secretion. Oncometer Experiment 3.

the vascular conditions of the organ as revealed by either blood pressure or renal volume. The concentration of the urine in the oncometer experiments during the chloroform period was greater than that of the normal sample, so that these experiments do not assist in explaining the converse effect which was noted in nearly all the previous chloroform experiments.

Other Effects.

Observations on the solids of the blood were made in some of the experiments. The results, however, are incomplete and are reserved for future publication. The same applies to measurements of the rate of blood flow through the organ.

Meanwhile it may be permissible to state that the facts which appear most to require explanation are: (1) The arrest of urinary secretion, often with a comparatively high blood pressure; (2) the diminished concentration of the urine accompanying a lessened flow; (3) the enormous increase in the volume of urine seen as an after-effect in the experiments where morphine was not used.

It may also be of interest to relate a fact which may throw light upon the above question. On many occasions, perhaps the majority of the experiments—though of the number no complete record has been kept—floculi of variable sizes were observed in considerable numbers in the urine secreted, after the anaesthetic was removed. These were examined microscopically in a few of the recent experiments, and found to consist of aggregations of leucocytes recently exuded from the blood capillaries. Nachod²² also found leucocytes, often in large numbers, in the urine of patients after chloroform narcosis. With these, casts, mostly hyaline, were also present. Their numbers in my own experiments point to a great accumulation of leucocytes, probably in glomerular capillaries. Such a condition would account for the diminution of the secretion under the vascular conditions, as regards blood pressure and renal volume, that were actually observed. It would also entail a certain amount of damage to the capillary walls, and thus probably lead to an increased permeability of the filtering mechanism, which, taken with the other factors, would explain the after-increase of urine flow, and likewise the occurrence of albuminuria in some of the cases. A similar but more pronounced effect is also produced by ether, as will be seen later.

The diminished concentration which accompanied the diminished volume of the urine, secreted during the full effects of the anaesthetic, must be taken to imply either a lessened production and absorption of nitrogenous solids, or a lessened reabsorption of water from the urinary tubules. The former, I think, seems the more likely, and would have to be accepted unless it can be shown that the fluid presented to the glomerulus for segregation is greatly diluted by the effects of the anaesthetic.

ALBUMINURIA AFTER CHLOROFORM NARCOSIS.

The quantity of urine obtainable for each period placed a limit upon the possible number of analyses. In consequence attention was not specially given to the occurrence of post-anaesthetic albuminuria. The subject, moreover, has received abundant attention from other investigators.

Observations were, however, made in five of the experiments given in Table I—namely, "Ureter" Series 2, "Catheter" Series 4, 5, 7, and 8. The reagent chiefly used was that of Spiegler. A positive reaction was given by one of the normal samples

Fig. 3.—Chloroform effects on kidney volume, blood pressure, and urine outflow. Taken from Oncometer Experiment 2.

(Catheter Experiment 7), and the effect of chloroform in this instance was to reduce the amount of albumen during Periods II and III. Afterwards the quantity increased, but at the end of the experiment it appeared to be less than in the normal urine.

Of the remaining experiments, in only one was a distinct albumen reaction obtained at any period after chloroform, and in one other an evanescent, doubtful result. The literature of the subject is vast, but most investigators agree that chloroform narcosis is followed only in a minority of cases by albuminuria, which corresponds with the results just given.

REDUCING SUBSTANCES IN THE URINE AFTER CHLOROFORM.

The occurrence of reducing substances in the urine after chloroform narcosis has

long been known. Hegar and Kaltenbach²³ appear to have first shown that the reduction was not due to sugar. Zweifel,²⁴ who found traces of chloroform in the urine, confirmed the existence of a reducing substance, not chloroform, and not uric acid or sugar. The occurrence of traces of chloroform was confirmed by Pohl.²⁵ V. Mering discovered that an alcoholic extract of the solids of human urine after chloroform administration was laevorotary. Zeller²⁶ observed the same in experiments with dogs. Kitz²⁷ attributed the optical activity to the use of phenol during the operations and in the dressings, which became absorbed, and was subsequently excreted as conjugated acid. Steinauer²⁸ discovered that traces of the chlorine of normal urine occurred in organic combination, and Kast²⁹ found similar organic chlorides in greater quantity after the use of chloroform and chloral hydrate. This was confirmed

by Kast³⁰ in a later investigation, in which he found that the reducing property of chloroform urine was destroyed by removal of the organic chloride compound. The carbohydrates were not increased, and the copper-reducing substance was in all probability a body analogous to urochloralic acid—trichlor. ethyl glycuronic acid—derived by oxidation from the chloroform and subsequent combination with the glycuronic acid. On the other hand, Vitali,³¹ as already stated, found no more organic chlorides in urine after chloroform than before, while Nachod³² attributes the reduction to an increase of kreatinin.

In this investigation the urine after chloroform narcosis was examined in seven of the experiments for substances giving osazone crystals, namely, Ureter Experiment 1 and Catheter Experiments 3, 4, 5, 7, 8, also in that quoted on p. 609, but not included in the table.

No osazone crystals were obtained from any of the normal samples. Crystals were present after chloroform in five of the experiments, and were wholly absent in two. In the majority of cases the crystals were unlike those of glucosazone in appearance, and gave melting points in impure condition, ranging about 130° C. In two there were undoubtedly glucosazone crystals present as well; the appearance was typical, and after fermentation with yeast they were no longer obtainable. Fermentation was also tried in other cases, where the first type of osazone crystal only was found. In one or two cases CO₂ gas was obtained, but only after a prolonged stay in the thermostat, during which time decomposition changes probably had occurred.

In one of the experiments examination with the polarimeter gave slight laevorotation. To obtain sufficient urine for the purpose the samples secreted during the anaesthetic and post-anaesthetic periods were added together and clarified by basic lead acetate. The mean of four readings in a 40 cm. tube gave -0.16. The examination was not quantitative.

The melting points and laevorotation indicate a glycuronic compound, similar to that suggested by Kast. It should be added that the reactions with orcin, phlorglucin, and hydrochloric acid, and also the reaction with P. bromphenyl hydrazine gave negative results both before and after boiling with dilute sulphuric acid. The quantity of urine available for the examinations was, however, very small, and much stress cannot be laid on the failure to obtain positive results in the latter tests. The investigation on these points is not yet completed.

SUMMARY OF RESULTS.

Chloroform.

1. The volume of urine secreted by the kidney is, as a rule, affected during chloroform narcosis in two ways. In the early stages, when the anaesthesia is light, the quantity is frequently increased. During full anaesthesia the secretion is always diminished, and may be suppressed.

2. The after-effect is invariably a great increase, which in certain periods may reach to four times the normal volume for the same period of time. The maximum outflow occurs about three hours after removal of the anaesthetic.

3. The total excretion of nitrogen is, as a rule, greatly reduced—more so than the quantity of urine. The averages taken from experiments with diminished urine volume show that during the anaesthetic period the excretion of nitrogen fell to 18 per cent. of the normal, whereas the quantity of urine in the same series fell only to 35 per cent. of that amount. In a minority of the experiments with increased urine volume the total nitrogen per period was also increased, but to a much less extent than the volume of urine in the same experiments.

4. The urine secreted during chloroform anaesthesia is almost invariably more dilute (contains less nitrogen per cent.) than the normal urine. This holds good even when the volume of urine is diminished, hence it is inferred that chloroform affects not only the blood flow through the glomerulus, but also the secretion of nitrogenous solids into the tubules and the latter even more than the former. The result, therefore, favours the theory of urinary secretion advanced by Bowman.

5. There is a general but not accurate correspondence between urine outflow, kidney volume, and blood pressure. The relationship between the first and second is closer than between the first and third. A state of almost com-

plete suppression may coexist with a comparatively high blood pressure.

6. In prolonged narcosis, with marked diminution of urine volume, there is a considerable exudation into the renal tubules of leucocytes, which subsequently escape with the urine. The condition is probably produced by more or less vascular stasis in the glomerular vessels.

7. The excretion of chlorides is much increased both during and after chloroform narcosis. In the fourth period after removal of the anaesthetic the amount may be ten times the normal quantity in the urine of the dog.

8. Albumen appears in a small proportion of experiments after chloroform inhalation.

9. Reducing substances other than glucose are almost invariably increased. The nature of the reducing substance has not been definitely determined.

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(To be continued.)

SOME EXPERIMENTS IN DENSIMETRY

WITH A VIEW TO ASCERTAINING THE PERCENTAGES OF CHLOROFORM SUPPLIED BY JUNKER'S INHALER.

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THE great convenience afforded by Junker's inhaler in midwifery cases makes it desirable to ascertain, as far as possible, whether its use is safe within certain limits.

The bottle, which is graduated up to 8 drachms, can be suspended to the bed. If, in the later stages of labour, some intermittent anaesthesia is considered to be desirable, the patient can be entrusted with the mask, which is of no use without the propulsion bulb. To work the latter requires voluntary muscular movement. The patient may be allowed to seize the mask and to grope for the propulsion bulb at the onset of a pain; this takes some time, and since muscular movement ceases when the senses are dulled, the supply of chloroform ceases with the cessation of muscular movement. Such consolatory anaesthesia is safe enough as far as it goes, and a doctor alone in the country, needing both his hands and all his attention, may find it of great help to him, notwithstanding much upbraiding on the part of the patient. He may even, if no other assistance is available, for the purpose of turning or the like, be tempted to entrust the bulb and mask to a nurse. For these and other uses to which Junker's inhaler may be put its convenience should not be the sole justification; we should also have some knowledge of the percentage of chloroform which is being supplied to the patient.

Two forms of mask or facepiece are supplied with this inhaler. Happily the simplest and safest is also the cheapest and most durable, and can be more easily cleaned after use. This is the rigid vulcanite facepiece without a cushion at the rim. There are certain difficulties to be met with in experimenting with any form of Junker's apparatus. An endeavour has been made in these experiments to obtain for examination as far as possible a portion of the vapour which is actually presented to the patient by simulating the conditions when the mask, in this instance of vulcanite, is closely but not absolutely adapted to the irregularities of the face.

If the mask is in complete adaptation to the face, or the whole face aperture is closed by a diaphragm, the mask