THE GLOMERULAR CONTROL OF THE KIDNEY BLOOD FLOW.

By J. M. O'CONNOR.

(*From the Physiology Department, University College, Dublin.*)

THE pronounced influence of the blood-pressure on the activity of the kidney is a characteristic feature of that organ. Ludwig, believing this influence to be direct, held it a strong argument in favour of the formation of urine by filtration. Heidenhain, on the other hand, thought that the pressure acted indirectly by influencing the quantity of blood flowing through the kidney. Richards and Plant(1) have recently given an interesting account of these opposing views, and with an ingenious technique, by which a constant quantity of blood could be forced through the kidney, have supplied evidence that the pressure, and not the resulting flow, is the essential element in this circulatory influence. Keeping the flow constant, the blood-pressure varied with the quantity of urine. They thus confirm Ludwig's original view and appear to disprove Heidenhain's explanation.

A consideration of the anatomy of the kidney shows, however, that the dependence on blood-pressure may be given a different significance reconciling it with a purely secretory theory. The flow of urine along a uriniferous tubule requires a head of pressure. This pressure must be a maximum at the top of the tubule in the capsule of Bowman. The capsule almost completely surrounds the glomerulus. If consequently as a result of an increased secretion pressure or a fall of blood-pressure the pressure of the urine in the capsule becomes higher than the pressure of the blood in the glomerular capillaries these will be completely closed. This will result in the blood supply through the efferent vessel of the glomeruli being cut off and any formation of urine not only from the glomerulus but also in the tubule will cease until the pressure of the urine within them has fallen sufficiently to permit the re-opening of the glomerular vessels. The driving head of pressure and consequently the flow of the urine would be limited by the glomerular pressure even if filtration plays no part in the process.

The laws governing the flow of fluids in elastic tubes have not been examined. Professor A. W. Conway, whom I must thank for the trouble he has taken, informs me that the expression governing the relation between pressure and flow in elastic tubes will be approximately of the following form:

$$F = F_0 (1 + KP),$$

where F is the quantity flowing in unit time, F_0 the flow according to Poiseuille's law, P the pressure head and K a constant depending in part on the elasticity of tube. Values permitting the application of this law are not available, but there is no objection to applying Poiseuille's law directly to determining the pressure prevailing under steady conditions, as has been done by Brodie(2), provided that reliable values can be got. In the case of the rabbit approximate calculations on probable values from previous observations(3), making the arbitrary assumption that the urine comes altogether from the glomerulus and that there is no absorption, give a pressure of the urine in the capsule as 10 mm. Hg above that in the collecting tubules. In this calculation the bore of the tubule was taken as 10μ if it were really 8μ—and it is not possible to be confident in such measurements—the pressure difference would be 25 mm. Hg. No significance can be attached to such calculations, but they show that there is nothing improbable in thinking that the pressure of the urine in the capsule of Bowman may approximate to the capillary blood-pressure in the glomerular loops, which itself has not been definitely determined. If the pressure of the urine goes above the pressure of the blood in the glomeruli these soft structures would, so far as one can judge, offer no resistance to the compressing force.

The suggestion put forward is, then, that this theoretically possible play of urine pressure on blood flow through the kidney is of functional significance; that urine is formed by a process of secretion, and that one function at least of the glomerulus is to modulate the blood flow and consequently the quantity of urine formed from it in accordance with the momentarily prevailing distension of the tubules and ducts. In the absence of some such mechanism a sudden increase in the flow of urine as the result of a diuretic stimulus might cause an injurious distension of the higher portion of the tubules. At this point attention may be called to the fact that according to the reconstruction of Huber(4) not only the proximal but also the distal convoluted tubule coil is in the immediate neighbourhood of the glomeruli from which it originates, and consequently that the blood supply of each tubule, except for the loop portion, passes to a very large extent through the corresponding glomerulus.

According to this theory, there would be in many cases no great difference between the pressures on opposite sides of the glomerular membrane, and consequently a fall of arterial pressure would cause a disturbance of this balance which would show itself in the blood flow through the kidney. Experiments have been done on this, and in considering them the assumption will be made for simplicity of expression that urine is formed purely by secretion. After the evidence has been presented the justification for this assumption in the light of the results obtained will be examined.

The following was the experimental procedure. The animals (rabbits) were anæsthetised with urethane. The intestines from the pylorus down were removed; a cannula introduced into the left ureter; a loop passed round the vena cava just above the left renal vein and the abdominal aorta ligatured low down. All side branches into the cava, from the renal vein down, were tied and a cannula sealed on to a large glass tube introduced upwards into the cava. This "bleeding tube" was previously well coated with paraffin wax. From a stopper in the upper end of the "bleeding tube" a connection was made through a T-tube with a bellows recorder. The third limb of this T-tube was attached to a glass tube the opening of which was held suspended by a weight over a trough of mercury. By pressing a lever the tube was dipped into the mercury, thus sealing off the connection between the bellows and the bleeding tube from the atmosphere, while at the same time a stop-watch was started to show the time during which the side tube was closed. Thus by keeping the lever pressed down for the time indicated by the watch, the quantity of blood entering the bleeding tube during this period was recorded on a moving drum. To take an observation the clip on the cava below the renal vein was opened and the loop above tightened. The blood from the left kidney then flowed into the tube and the blood-pressure fell. The bleeding tube was placed as horizontally as possible so that the increase in venous pressure when the tube was filled was not more than 2mm. Hg. While the bleeding tube was filling the side tube of the bellows recorder was closed for a number of successive periods of 10 secs., the interval between each observation during which the side tube was open being usually no longer than sufficient to permit the recorder to return to its base line. Simultaneously records of the arterial pressure and the falling drops of urine were recorded. The heights of the outflow records were subsequently accurately measured and compared with the corresponding mean blood-pressures. At the end of an observation on a suitable readjustment of clips the blood was blown back into the circulation. In many cases as a matter of convenience the renal flow included also that from the left suprarenal and accompanying lumbar vein. Preparatory injections of saline and 5 p.c. glucose were given when necessary to increase the blood-pressure or produce a flow of urine.

Before passing on to the results with the secreting kidney it is first necessary to consider how the flow of blood commonly varies with the blood-pressure. This was tested by an obvious rearrangment of the procedure described above, in which the blood flow from the hind limbs and lumbar region was directed out into a bleeding tube introduced into the left renal vein. As may be seen from Fig. 1 the curve is for a great

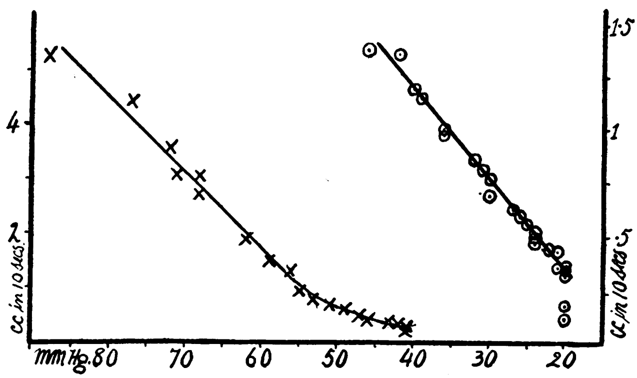

Fig. 1. On left, blood flow through hind limbs, etc. Ordinates on left. On right, blood flow through kidney not secreting (renal nerves cut). Ordinates on right.

part of its course indistinguishable from a straight line. It may be incidentally noticed that the blood flow becomes relatively negligible at quite high arterial pressures.

It is to be noted that as the terminal pressure rose, though but slightly, owing to the filling of the bleeding tube, while the arterial pressure fell, the pressures, marked out on this and subsequent graphs, do not give the true change in the head of pressure. If allowance were made for this, the straight portion would become slightly more convex towards the abscissa, as an application of Professor Conway's formula (for it is true uniform pressure) to the circulation would require. In some cases the convexity is distinct without any such allowance having been made (Fig. 3).

We may now turn to consider how we might expect the graph of pressure and flow through the kidney to be modified if the expectations put forward be realised. There are three possibilities.

If there be no formation of urine, an interference due to pressure of the urine on the glomeruli would not be expected. This seems to be realised as in Fig. 1. Attention may here be called to the contrast between the graph of kidney flow and hind limb flow. The straight line portion of the graph tends to cut the abscissa at much lower pressures. In other experiments, however, in which without a mechanical obstruction no urine emerged from the cannula, a different result was obtained. There was during a portion of the graph a relative increase in blood flow with falling pressure. This might be explained in the following way. The kidney is being stimulated to secrete, but in the steady state the pressure in glomeruli is so low that the blood supply becomes cut off before the head of pressure rises sufficiently high to force out the urine at an appreciable rate.

The second case to be considered is one in which the ureter is obstructed. Here one would expect the pressure of the urine to have risen to such a height that the glomeruli would all be closed. In fact one finds during a portion of the range of the graph that the blood flow rises, at least relatively, with falling blood-pressure. In this, as in the previous case, the explanation offered is that with the fall in tension in the arteries the kidney tubules are able to expand more freely, and in spite of the falling capillary blood-pressure, permit the glomeruli to open, giving free paths to the previously restricted flow.

The third case is where there is no obstruction to the flow of urine. One would under steady conditions expect all the glomeruli to be open and the only possible change would be a sudden diminution of the capillary blood-pressure below the urine pressure, with a consequent sudden diminution of blood flow. This is the common result and is shown in Fig. 2 in which the blood-pressure fell steadily and the outflow for the

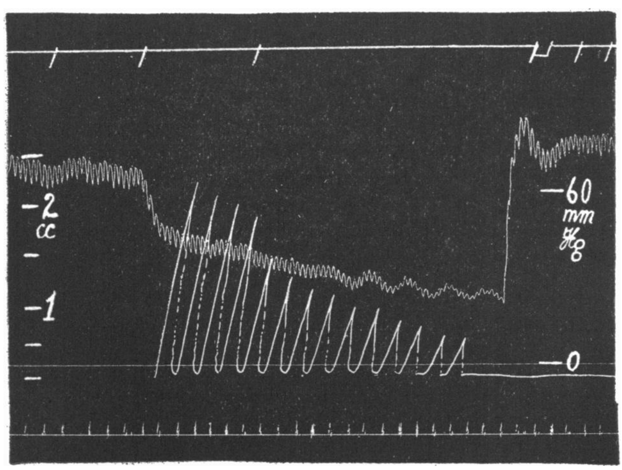

Fig. 2. Record of blood flow in 10-second periods in an active kidney. There are recorded from above downwards: drops of urine; blood-pressure; quantity of blood flowing in successive periods of 10 seconds; and the time in 10 seconds.

first four 10-second periods fell uniformly, the 5th however drops suddenly, and only from the 7th onwards does the fall in flow accompanying the fall in pressure again become uniform. Occasionally, experiments are met with in which the kink, instead of being negative, as in this case, is of a positive kind. Some of these are no doubt due to partial obstruction at the cannula. The experiment given in Fig. 3 illustrates this. During the first observation the urine was flowing through the cannula but the ureter was visibly distended—a "positive" kink is recorded. Before the subsequent observation the ureter was cut open—a marked "negative" kink is visible. All the experiments do not seem to be met by this

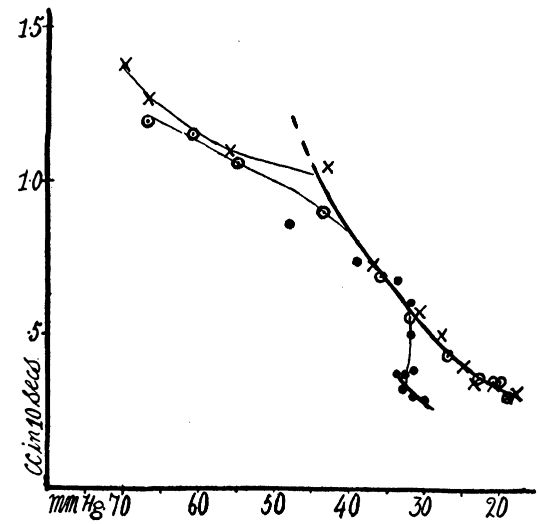

Fig. 3. Renal nerves cut. Crosses and white circles, observations with obstructed ureter. Initial B.P., 90 and 78 mm. Hg respectively. Black circles, ureter cut open, B.P. 56 mm.

explanation. However, according to the theory advanced, it is possible that the balance between opening and closing of the glomeruli is a delicate one and the fall of blood-pressure so alters the state of mechanical tension within the fibrous capsule of the kidney that in one case uriniferous tubules are allowed freer expansion, the pressure within them falls and some previously closed glomeruli open, whereas, in the other cases glomeruli merely close as the result of the fall in blood-pressure being more pronounced than the fall in urine pressure.

Occasionally both varieties of kink are met with during the one outflow observation. The experiment illustrated in Fig. 4 is an example. In this the blood-pressure which had been 91 mm. Hg had fallen to 76 before the first 10-second period was recorded. There was then a slight rise of pressure but the blood flow was smaller and the third and fourth

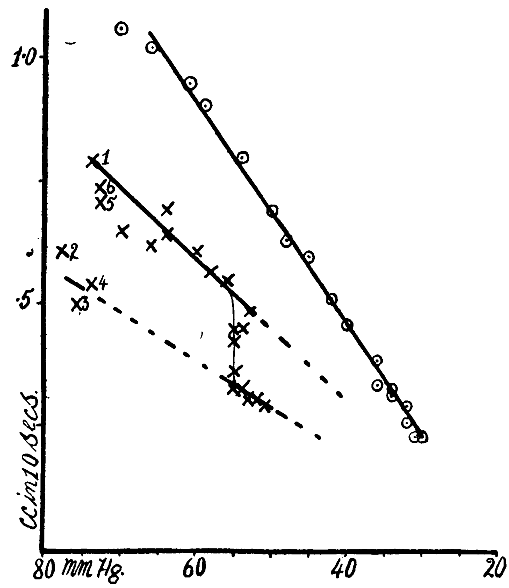

Fig. 4. See text. First observation, crosses; second observation, circles.

10-second periods corresponded with this. It is suggested that the glomerular blood-pressure had just at this point fallen below the urinary pressure. In most experiments the blood flow would now follow the lower line but here the flow rose again to the old level. It is suggested that the tubules had in the meantime expanded and the pressure of the urine fallen below the pressure of the blood with the result that the glomeruli re-opened. The flow graph now proceeds to follow along a straight line until a pressure of about 55 mm. Hg is reached, when there is again a vertical drop in the graph due, it is suggested, to a renewed collapse of the glomeruli. Further points now lie along another straight line at a lower level but similar to the previous one. This line, if produced back, cuts the group formed by the second, third and fourth points. Whether the explanation is correct or not, it seems that a resistance to the blood flow, which was thrown in for the second, third and fourth points and then disappears, is again thrown in towards the end of the observation. This particular experiment has a further interest. The blood was forced back into the circulation but the urine which had been flowing at a drop (*circa* 30 c.mm.) in 30 secs. practically ceased

(1 drop in 200 secs.). Another blood flow observation taken within 3½ minutes of the first gave a straight line graph which can be correlated with the absence of urine formation.

It can be objected that the first six points on the first of these two graphs occur with but very minute changes in pressure and that it is difficult to imagine the changes described in such a narrow range. Against this, however, it must be remembered that the initial blood-pressure was higher than the first recorded on the graph and that six observations occupied slightly over a minute during which the changes described going at different rates might well occur. A further objection against not only this but all similar experiments is that the kinks described might well be due to vasomotor reactions, particularly vasomotor reactions against hæmorrhage. Although it is possible to argue against this, it is obviously better to rely on experiments in which the kidney has been denervated (Figs. 1, 3, 5).

Vasomotor reactions against hæmorrhage are commonly believed to occur, but the evidence for them does not seem to be extensive (5, 6).

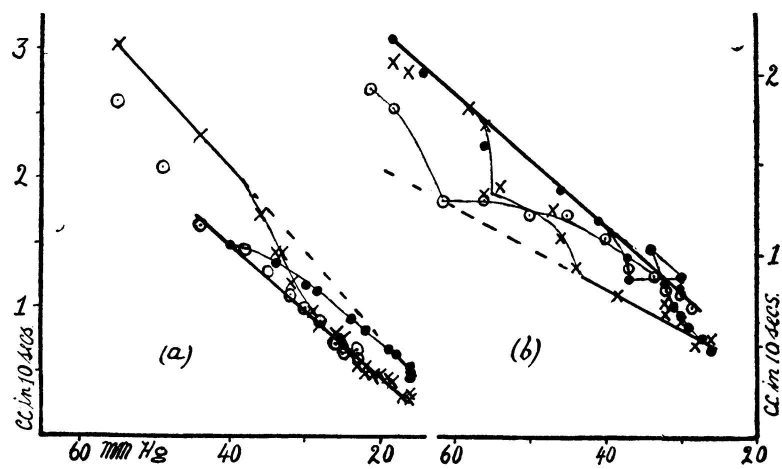

Fig. 5. (*a*) Observations on kidney with renal nerves cut. Ordinates on left.

Black circles...	no urine	Initial blood-pressure,	58 mm. Hg.
White „ ...	1 drop in 90 secs.	„ „	104 „
Crosses ...	1 „ 60 „	„ „	87 „

Observations taken during ¾ hour. 80 c.c. saline between 1 and 2.

(*b*) Observations on kidney with renal nerves cut and suprarenals removed. Ordinates on right.

Crosses ...	1 drop in 20 secs.	Initial blood-pressure,	92 mm. Hg.
White circles...	„ 10 „	„ „	80 „
Black „ ...	„ 20 „	„ „	78 „

Observations taken in 20 minutes.

Fig. 5 shows the results obtained (*a*) with a kidney in which the nerves running in the pedicle have been cut; (*b*) in an animal in which in addition to nerve section both suprarenals had been ligatured off. Taking experiment (*a*), it will be noticed that the points of each observation sway between two straight lines. In the first observation urine was not flowing, and on fall of pressure the flow passed from the line of low flow to the line of larger flow. This has been already explained as being due to the pressure of the urine being sufficiently high to keep the glomeruli closed but not sufficiently high to force out urine at an appreciable rate. In the other observations in both of which urine was being secreted, we find the pressure-flow graph swaying from the high line on to the low. That is the same resistance which in the previous case was shown being removed is now shown being put in. In the third case the flow record has apparently reached the low line before points could be recorded. We have then this graph explicable by the throwing in or out of the same resistance in three observations, a resistance not due to any stimuli passing through the kidney nerves.

In the second set of observations on Fig. 5 not only were the nerves cut but the suprarenals ligatured off. Here any individual set of observations tends to sway somewhat irregularly, but taken all together they can be seen to be explicable by the same resistance being introduced or removed at various blood-pressures, so that the beginnings of the graphs in two cases, and the ends in all, lie along two straight lines.

In these experiments, and others of a similar kind, the kink is not to be explained by any interference through the renal nerves or by a secretion of adrenaline from the suprarenals. The fact that the different observations in one experiment overlap to the extent described—an overlapping which, as can be seen from Fig. 4, is not to be got where the nerves are not cut—seems to confirm the natural expectation that extrarenal influences in the intervals between the observations have not affected the kidney circulation, and the sudden changes in the blood flow during the observations are scarcely attributable to such external influences. It can none the less be legitimately suggested that cutting the kidney nerves and ligaturing the suprarenals is not sufficient to completely isolate the kidney. Nerve impulses might pass through the vessel walls or some less obvious hormonal mechanism be excited to activity by the fall of blood-pressure.

To meet this objection the following experiment was done (Fig 6). A maximal vaso-constriction was produced by a continuous infusion of 3 c.c. adrenalin 1 : 50,000 per minute, immediately before and during the observation of the blood flow. The blood-pressure rose from 96 mm. to 186 mm. on starting the injection. The record of flow then taken shows a positive kink. That is, there is a sudden diminution of resistance to blood flow although the vessels were maintained in a state of maximal constriction.

In the experiments considered so far an effort has been made to disturb the presumed balance of pressure between urine and blood at

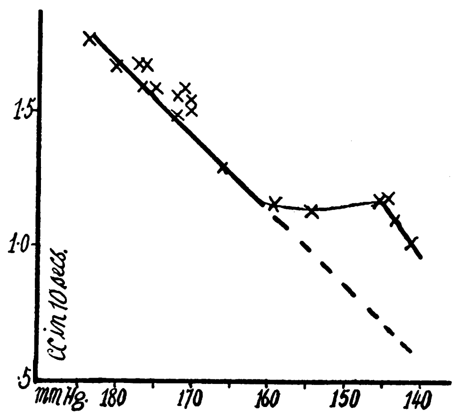

Fig 6. Original B.P. 96 mm. Hg. 1 drop urine in 10 secs. Continuous infusion of 1:50,000 adrenalin 3 c.c. per min.; rate of urine falls. 80 secs. later B.P. 186 mm. Hg. record of flow started.

the glomerulus by lowering the blood-pressure. Observations were also made in which it was attempted to disturb the balance by increasing the pressure of the urine by forcing fluid under pressure into the ureter. In fact decided falls of flow disappearing on removal of the pressure were produced, confirming results obtained by others, such as Burton-Opitz and Lucas(7). Apart from the difficulty or impossibility of forcing fluid back into tubules from the ureter, these observations are vitiated by the rise in pressure in ureter presumably pressing on the veins. In fact, the diminutions of flow produced are usually very much greater than those produced in experiments previously alluded to; and are in part, if not altogether, to be explained as venous obstructions. These experiments need not be considered in detail.

On the secretion theory of urine formation there is another method by which these pressure interactions in the kidney might conceivably be disturbed. If, as the result of some diuretic stimulus, a sudden increase in the secretion of urine occurs, a brief time will elapse before the tubules and ducts have sufficiently expanded to allow a free outflow of the increase, and consequently a brief closure of the glomeruli and diminution of blood flow might be detectable. Experiments with a slightly different technique into which it is unnecessary to enter, did not give this result, but, as owing to difficulties, few were successful, and the diuretic used (30 c.c. 5 p.c. glucose) caused a rise in blood-pressure and a fall in blood viscosity, this negative result is of no significance.

The observations made in the flow of blood with falling pressure are then reconcilable with the suggested mechanism. It remains to be considered in the first place what criticism may be obviously made against this interpretation of the results, and finally, what influence, if any, the results might be considered to have on the theory of the formation of urine.

With regard to the first consideration the following points may be mentioned. If it be taken that extra-renal influences are excluded it would be none the less rash to assume that the blood vessels are inert. Vasomotor changes, the result of accumulation of waste products, or perhaps the lack of oxygen, might conceivably produce vaso-constrictor or vaso-dilator changes which would account for the records obtained. The fact that such changes have not been found in the hind limb observations is against this, but under the conditions of the experiment these are not very active organs. Owing to technical difficulties, experiments on the same lines with the intestine and other organs were not successful.

Further, if it be taken that the results are to be explained by mechanical obstruction, there is no direct evidence pointing to the glomeruli as the seat of the obstruction. Experiments in which pressure in the ureter was used have been rejected owing to a presumption of compression of the kidney veins, but it may be held that those experiments in which the ureter pressure has not been directly attacked are really due to a similar interference. It might be imagined, for example, in the case of the "negative" kink, that the venous pressure in the small veins falls so much with falling blood-pressure that the pressure of the urine in the uriniferous tubules and collecting tubules is sufficient to cause collapse of some of the veins and produce the diminution of blood flow observed. Against this criticism attention may again be directed to the experiments recorded in Fig. 5. Here we find that the amount of obstruction measured by the angle between the two lines on which the points of each observation lie, or between which they swing, is identical in all observations. The obstruction appears or disappears at different arterial pressures, but its amount is in all identical. This would consequently seem to be no accidental obstruction, such as would be caused by the pressure of tubules on veins lying between them, but rather to be due to some essential feature of the vascular arangement such as the glomeruli.

If, however, this argument be held sound another point arises. According to the observations of Huber(8), practically all the blood of the kidney, cortex and medulla, passes through the glomeruli. But in none of the experiments has the obstruction to blood flow found been even approximately complete. This, however, would be explained by the commonly held view that only a fraction of the tubules are active at one time and a quantity of blood flows without hindrance through the glomeruli of quiescent tubules.

If the experiments are to be explained on the lines suggested it is not yet in any sense proved that this mechanism is of significance. That there is a positive pressure in the glomerular capillaries and a positive pressure of the urine in the capsule is certain. Further, it seems certain from the anatomical arrangement that if the pressure of the urine goes above the glomerular blood-pressure the blood flow must be cut off. The experiments demonstrating a negative kink show, subject to criticism, that this does occur when the blood-pressure falls. This is broadly reconcilable with the view that the pressure in the tubules was due merely to filtered blood plasma. Although the experiments showing a "positive" kink are not to be explained so easily, the attribution of a functional significance to the anatomical relation is still surmise. The results at least suggest further experiments, and the theory on which they are based may be the true explanation of the dependence of the activity of the kidney on the pressure of the blood.

In conclusion my thanks are due to the Editor for criticism.

SUMMARY.

1. Owing to the anatomical structure of the kidney a secretion pressure of the urine at the head of the uriniferous tubule could not go above the pressure of the blood in the capillaries of the Malpighian tuft without cutting off the blood supply from the kidney tubules. This would explain on a purely secretory theory the dependence of the formation of urine on the blood-pressure.

2. A similar cutting off of the blood flow through the kidney might be expected to occur when the blood-pressure falls. An arrangement for determining the flow of blood for brief periods during a fall of blood-pressure is described.

3. Observations on the hind limbs show that the graph of blood-pressure and blood flow is for a great part of its course practically a straight line.

4. Observations on the kidney show that in these a similar graph is broken by decreases or increases in the blood flow. Such kinks can be seen when the renal nerves are cut and the suprarenals ligatured off, and are explicable on the postulated obstruction to the blood flow at the glomerulus.

5. The bearing of these results on the theory of urine formation is discussed.

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