SUPPRESSION OF URINE AND DEFICIENCY OF RENAL SECRETION.*

By HENRY WADE, C.M.G., D.S.O., M.D., F.R.C.S. Ed., and IAN LAWSON DICK, M.D., F.R.C.S. Ed.

I. Mr Wade.

FOR the secretion of urine, three factors are necessary: (1) an adequate blood pressure, (2) a kidney that will function, and (3) an open outflow channel. When the first is at fault and suppression of urine occurs, it is spoken of as pre-renal anuria. Failure of the second gives rise to renal anuria. When the outflow channel is occluded, post-renal anuria results. Whatever the underlying cause may be, the result is extremely serious, and if unrelieved inevitably proves fatal. At the same time, the majority of patients with anuria, when first seen, appear so well and have so few complaints, apart from the stoppage of the flow of water, that it seems hard to believe that they are critically ill.

I will cite an illustrative case as it was met with in a doctor's practice.

CASE I.—The patient, E. G., originally came under my care in March 1929. She was then 52 years of age. She was a cripple with an ankylosed hip-joint, the site of healed tuberculous disease. For this she was operated on, and ultimately a satisfactory result was obtained, after a stay in the Royal Infirmary and the Astley Ainslie Institution amounting to many months. To be perfectly frank, she was somewhat spoilt, owing to the length of her residence with us, and the fact that she came from my own native county. In January 1930 she was discharged. On 14th February of that year, less than a month after leaving hospital, I received the following letter from Dr L.

"DEAR MR WADE,

"You remember Miss G., on whose femur you did an operation lately. A most curious thing has just happened with regard to her. Her sister, Miss M. G., had an attack of renal colic and had to be seen by me. The attack subsided in the normal way and she is up now and about. When I was seeing her, I mentioned that you were also an expert in kidney conditions.

"About a week later I was called to see Miss G., upon whom you operated, and found her with pain exactly like her sister's, but this time

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affecting apparently the right kidney and ureter. I asked for a sample of urine and gave much the same directions as I did for her sister, but I wondered whether this was not merely a hysterical 'copy' of her sister's attack. Somewhat to my surprise I found that she passed no more urine after I had asked for that sample, and her sister, who was to bring another sample of her own urine, told me no sample was forthcoming of Miss G.'s.

"I went over and examined her abdomen, but could find nothing amiss. The bladder was apparently empty and this was confirmed by passing a catheter, but she did not look uræmic or much out of condition.

"Since Monday till to-day (Monday, 10th February 1930 to Friday, 14th February 1930) she has passed no urine apparently and secreted none.

"Now I can easily imagine that a stone, for instance, might stop all flow from one ureter, but why should it stop the flow from both? She doesn't seem collapsed, nor does she so far show much sign of being specially ill. I put her on urea and large quantities of water, but she is now really œdematous and yet no urine is forthcoming.

"I have considered the question of 'shock' and can find no evidence. I have no means of telling whether she has been passing urine without confessing it. There is the chance that some mental effect has really stopped the flow.

"The thing that makes me a little suspicious is that I had mentioned you as an expert in kidney conditions and to-day her sister mentioned that she thought of taking her through to see you on Sunday as that was your receiving day.

"The cessation of pain and suppression of urine occurred apparently at once after I had asked for a sample of urine and there was no pain or suggestion of such a thing till I mentioned you *apropos* of her sister's case. The lack of anything but the weakness due to living on water rather puzzles me.

"I could send her through if you can take her for investigation. You could observe much more closely in hospital than I can here—if she is really ill, hospital would be the best place for her. I should have arranged for her transport sooner but for the doubt regarding her illness.

"She would have been 'housekeeper in charge' had her sister remained ill and she certainly enjoyed her sojourn in your wards—possibly a day or two would 'cure' her even if the case were hysterical."

On the following day she was admitted to my wards. She looked remarkably well but still suffered from anuria which had existed for six days. It had commenced with an attack of severe renal colic on the right side. Never previously had she suffered from any similar attack—in fact, never in her life down to that date had she shown by sign or symptom that the kidneys were otherwise than in perfect health, and during the months she had been previously with us no abnormality in this respect had been detected. We thought it advisable, first of all, to have a preliminary X-ray examination of the urinary tract carried out. This, fortunately, at once explained the cause of the anuria and indicated its appropriate treatment. The left kidney had been entirely destroyed as a functioning organ by antecedent disease.

The right kidney, on the other hand, contained several calculi, one of which appeared to be blocking the outlet of the pelvis.

She was accordingly operated on forthwith, twilight sleep and gas and oxygen being employed as an anæsthetic. When the kidney was exposed, it was found lying within the perinephric box in a pool of blood-stained exudate. It was extremely tense and very much enlarged. The positions of the calculi were made out by means of careful palpation. The upper one, which occupied the upper major calyx, was first removed, after the kidney had been mobilised. The second large calculus, which was in the second major calyx, was next dealt with. The smallest and lowest calculus was sought for and found to be plugging the pelvi-ureteral junction. It was removed and the obstruction freed. The kidney was drained. From the moment the obstruction was relieved, slightly blood-tinged urine escaped and this continued actively, 50 oz. being excreted that day and 90 oz. during the following day, with the result that the blood urea, which on admission had stood at 200 mgm. per cent., rapidly returned to normal. She had an excellent convalescence and has since enjoyed excellent health.

I have cited this case at length, as it appears to illustrate in so excellent a manner the circumstances under which a case of this nature may arise. It was a case of post-renal anuria, due to total obstruction of the outflow channel from a single functioning kidney. It does seem strange that during all the months she had been a patient with us, we never once suspected that she was suffering also from renal calculus. The routine examination of the urine revealed no abnormality. The X-ray photographs of the hip-joint just fell short of the kidney level. Should we have made a complete urological examination when she first came under our care and thus recognised the disease? There was no apparent indication for this and we do not make a routine practice of it in all cases, a course we purpose continuing to follow despite this experience.

The second interesting point is the question raised with reference to hysterical anuria. Personally, I have never known of a case of this, and if it has ever occurred I should like to know the physiology of its inception.

A third most interesting point is neatly put by the doctor in his letter, wherein he asks for an explanation of the onset of the anuria and blockage of the outflow channel by means of a ureteral calculus and how both ureters come to be synchronously occluded, for it raises at once what I consider the most important question in all urological surgery—the incidence

of the single functioning kidney of congenital origin. If you will consult any standard text-book of urology you will note there the figures given as regards the incidence of this malformation. In most cases the work of Morris is referred to, and the statement is made that the single functioning kidney is met with once in 2400 autopsies. Other figures are given which claim to demonstrate that it is of even greater rarity. Our experience here in Edinburgh is that it is a malformation met with in 1 per cent. of all cases and therefore clinically not uncommon. It is thus essential that as a routine part of all investigations there must be demonstrated whether or not the patient possesses two kidneys as independent organs and normally situated. A single functioning kidney may suffer from any form of renal disease. In such circumstances the treatment is much more difficult and the prognosis much more serious.

Case II.—J. C. was a case of this nature. The history he gave us was that of pain in the left renal region accompanied by severe hæmaturia which had reduced him to a very weak, exsanguine condition and a state of critical ill-health. Cystoscopic examination revealed the absence of the right ureteral orifice, and deeply blood-stained urine came from the left side. Multiple calculi were revealed in the left kidney, which was also heavily infected with coliform bacilli. Most reluctantly we were compelled to operate. A blood transfusion was first given and the kidney was exposed. It was found to be practically devoid of healthy renal parenchyma. The pelvis and calyces were grossly dilated and contained five large calculi. The patient succumbed later, and at the post-mortem examination the left kidney was found to be composed of a large number of hydronephrotic sacs which were infected; scattered here and there between the sacs normal kidney substance was found, but this was small in amount. No kidney or ureter was present on the right side.

Post-renal anuria due to bilateral obstruction is occasionally met with and cases of it may be readily overlooked, as in the following case:—

Case III.—J. H. He was 40 years of age and had been ill for about a year. From the first he was obsessed with the idea that he was suffering from malignant disease, and in consequence his alimentary canal was most carefully investigated in another surgeon's charge, and neither clinically nor by X-ray findings were any signs of new growth revealed. A physician and neurologist found nothing definite, and an "anxiety state" was considered to be the cause of his symptoms. Four

days before admission, anuria suddenly developed. He vomited two to three times a day and suffered from persistent headache. On examination he appeared pale and puffy, and had marked œdema under his eyes. The left kidney was just palpable. The right could not be felt. Our provisional diagnosis was anuria of renal origin due to a form of acute Bright's disease.

A cystoscopic examination was carried out. The bladder was found to be empty. Its walls were œdematous but otherwise healthy. Ureteral catheters were passed into both ureters, but progress was arrested at 5 cm. and they could not be advanced further. No secretion was collected from either side. A mistake in technique led to their withdrawal before a pyelogram was taken. It was thus difficult to be certain whether they were arrested from organic obstruction with occlusion of the ureter, or from other cause. Valuable time was thus lost, and a failure to appreciate that we were here dealing with post-renal anuria led to the adoption of other lines of treatment unsuitable for such a case. Repeated transfusions were carried out and he died ten days after the onset of the anuria.

At the post-mortem examination a carcinoma of the pelvic colon blocking both ureters was revealed, with associated hydronephrosis of both kidneys. At the pelvi-rectal junction of the colon there was a small carcinomatous growth infiltrating the tissue and binding the rectum firmly to the sacrum. The right kidney showed only slight hydronephrosis and its ureter was only slightly dilated. Below the promontory of the sacrum it was fixed to and infiltrated by the tumour which constricted its lumen but did not completely occlude it. The left kidney showed pronounced hydronephrosis. Its ureter was considerably dilated, and below the pelvic brim it was involved in the tumour mass which completely occluded its lumen.

The operation of nephrectomy is now carried out so frequently and the patient in consequence left with a single kidney, that it is not surprising that anuria from the blockage of the outflow channel from a single kidney, the other having been removed at operation, is not of infrequent occurrence. I have had three such cases of this nature to deal with. In two of them it was possible to displace the stone which was obstructing the outflow from the pelvis and give temporary relief, but, ultimately, they all required operative treatment for the removal of the stones and relief of the obstruction. In all of them the degree of destruction of the renal parenchyma made me doubt very much whether restoration of renal function would ever be possible, but each had a normal convalescence and normal renal function was recovered.

This illustrates the power of repair of a secreting organ when there is an active call on its functional activity. This power of repair is also observed, and to a much greater degree, when the liver is damaged. It differs here, however, in that new liver cells are actively formed.

With regard to reflex anuria, two opposing lines of thought have always held the field and receive about equal support. On the one hand there are those who believe that when a kidney is damaged, as from obstruction producing severe renal colic, a reflex stimulus from the damaged painful kidney may lead to entire suppression of secretion in the other healthy organ by direct nerve impulse to the opposite side. There are others who hold, and I share their opinion, that such anuria is really pre-renal in origin and due to the marked lowering of blood pressure that the shock of the pain produces. It is important, however, to remember that a case may be considered in error as one of reflex anuria which is really due to organic obstruction to the outflow channel, congestive in origin, as was illustrated in Mr Leslie Stewart's case of R. S.

Case IV.—This patient was referred to our Ward by Dr S. In sending him in as an emergency case the doctor wrote as follows:—

> "Bearer, R. S., aged 58, history of passing no urine since Sunday. Acute pain over left side in kidney region. Abdomen distended and tympanitic. No urine in bladder. No. 10 soft Coud passed easily. Some acute surgical condition of left kidney. Hydronephrosis or abscess. Pulse full and bounding. Patient seems fairly ill."

When admitted he had had complete anuria for forty-eight hours, and had acute pain and tenderness in the left renal region. Preliminary X-ray examination showed no calculus obstructing the ureter. Immediate operation was carried out under twilight sleep and gas and oxygen anæsthesia. A swollen and congested kidney was revealed, the pelvis being intra-renal did not appear markedly distended. A drainage tube was inserted, and after a few minutes slightly blood-stained urine began to come away in drops and before the parietal incision was closed about 1½ oz. had been collected. An abundant secretion of clear urine took place through the tube during the following week, but except on one occasion no urine was voided from the bladder. As the patient's condition had markedly improved, a cystoscopic examination was now carried out and both ureters were catheterised, and when the right renal pelvis was entered a limpid secretion came away in copious amount. This catheter was left in for two hours and then removed. The

immediate effect was to bring about an active secretion of urine from the right kidney, but this gradually diminished in amount until escape of urine from the bladder again finally ceased. A further cystoscopic examination was made and again both ureters were found to be markedly congested, and although the catheters could be introduced they could not be passed up to the renal pelves. A right-sided pyelotomy was now carried out and active secretion thus obtained from the right kidney. When the urine came to be voided again by the natural channel, this was followed by a rise of temperature which soon subsided, and he had a normal convalescence thereafter. The case was one of bilateral obstruction from congestion and œdema of the ureters which did not respond to relief by ureteral catheterisation, but was rapidly recovered from after drainage of both pelves.

It is quite possible that an explanation somewhat similar in nature may account for certain of those cases where anuria appears as a distressing complication after certain pelvic operations. We recently had to deal with such a case where complete anuria followed a uterine operation. Three days after its onset a bilateral pyelotomy was done. The pelves were found to be greatly distended and the kidneys congested, and rapid relief followed bilateral lumbar drainage.

A form of renal anuria with which the surgeon has had to deal has been that arising from acute bilateral cortical necrosis. In recent years this subject has been fully and ably dealt with by Davidson and Turner, and Kellar and Melville Arnott, in papers communicated to the Edinburgh Obstetrical Society. I was asked to co-operate in the treatment of two of the cases.

Case V.—The first was that of a woman, 33 years of age, who was admitted to the Royal Maternity Hospital in January 1930, under the care of Dr Young. I saw her there. Anuria had developed the day prior to delivery and had persisted since then, there having been no urine secreted for five days. Her face was pale and the lips were somewhat cyanosed, but what impressed me was that her mental condition was perfectly normal. She had entirely failed to respond to any form of treatment to induce the flow of urine. Cystoscopic examination revealed a normal bladder, and both ureters were catheterised without difficulty but no secretion obtained. The blood urea estimation was 200 mgm. per 100 c.c. blood. The following day the operation of bilateral decapsulation was carried out by myself. The feature of the operation that impressed me most was the appearance of both kidneys. To me they resembled closely the appearance I had previously seen in a case of phosphorus poisoning. They were large, tense and firm,

mottled in appearance, of a dark plum colour where petechial hæmorrhages were present, with lighter areas where fatty change was present, in the intermediate tissue. The pelvis was lax and empty. The left kidney presented a similar appearance, and again the capsule was found to be tense when decapsulation was carried out. No benefit followed this treatment, and at post-mortem examination—the findings of which have been fully described by Dr Davidson—the characteristic appearances of bilateral cortical necrosis were seen, with ante-mortem thrombosis in the ovarian veins.

My recollection of the case was my feeling of utter hopelessness from the surgical standpoint as I viewed a kidney such as I had never seen before except in the Pathological Department, and I felt that decapsulation or any form of treatment could never help in so grave a condition; but I am now convinced I was wrong. The destructive process in acute cortical necrosis may be extensive, but, at the same time, I doubt if ever it is complete. The power of repair of a damaged parenchymatous tissue, if even a fragment alone remains, is great, and this fact is borne out especially clearly in a case recorded by Kellar and Melville Arnott wherein the patient died on the twenty-third day after the onset of the anuria, eighteen days after entering hospital. At first the anuria was complete, but later a scanty secretion took place, and on the day before death an output of 16 oz. was recorded. In all probability if her strength could have been supported a little longer, or the return of renal function expedited, natural recovery might possibly have taken place.

This fact may possibly explain the case that was referred to us more recently by Dr Johnstone. Mr Dick will describe it more fully; and if we are correct in our assumption that in all probability it was a case of cortical necrosis less severe in degree, the recovery that followed the treatment that he instituted was dramatic in its rapidity and its efficiency.

Pre-renal anuria: Anuria due to a diminished blood pressure must necessarily only be of a transient nature. We have put it forward as an explanation of a case of alleged reflex anuria. Its importance to the operating surgeon is great, as it is particularly advisable where an operation on the kidney, bladder, or prostate is being carried out, to maintain the blood pressure and keep renal secretion active. So important do some consider it that Swift Joly discourages the use of a spinal anæsthetic in prostatic surgery on account of the lowered blood

pressure with which he has found it associated. Recognising this, we make it our practice to maintain the blood pressure by the administration of ephedrine prior to the introduction of the spinal anæsthetic.

Oliguria, or deficiency of renal secretion, when this arises from backward pressure, presents an important surgical problem. Three common causes of bilateral backward pressure are stricture of the urethra, prostatism, and vesical tumours. Backward pressure in such cases may lead to a marked hydronephrosis and hydroureter with pronounced atrophy of the renal cortex. The two former can now be clearly demonstrated by excretion urography and the consequence of the renal atrophy rendered evident by the altered blood and urine chemistry. The gravity of the illness thus having been recognised, the treatment can be directed accordingly. There is, however, a more subtle form of renal impairment, not so demonstrable by excretion urography or by blood chemistry, with no evident renal atrophy but with a kidney whose functional activity has been markedly impaired. It is met with especially in the silently grossly over-distended urinary bladder in certain cases of simple prostatic hypertrophy. Here the kidneys have been accustomed for long to function against a high ureteral pressure. The renal function appears efficient, but the renal reserve is destroyed so that if backward pressure be suddenly relieved and completely removed, this removal is followed by a period of marked hypersecretion and later by a diminished secretion which may lead ultimately on the third or fourth day to complete anuria and death. The important problem in such a case is the gradual and accurate decompression of the bladder that is necessary to restore the kidney to normal functional activity.

Oliguria due to persistent vesical systole. At present the recognised treatment of renal tuberculosis is considered in the majority of cases to be the removal of the diseased organ and the ureter. This is advocated on several grounds. Only one I would refer to just now, and it is the effect of the disease on the opposite healthy kidney. As regards this organ, it is not infection that we dread: it is the silent destruction of it by the constant backward pressure of the urinary bladder in persistent systole. It is generally recognised that over 70 per cent. of all cases of tuberculous disease of the kidney come to the surgeon at a stage when the ureter on the affected side and the bladder

have become involved in the disease, the capacity of the latter being reduced sometimes to only a few ounces. Nephrectomy therefore only removes the primary source, the infected bladder later undergoing a natural cure, the diseased mucous membrane healing and the normal bladder capacity being restored. Occasionally the tuberculous infection, or a pyogenic infection, remains and the bladder continues in a state of persistent systole with consequent serious backward pressure on the healthy kidney above, pronounced dilatation of the ureter and renal pelvis resulting, with atrophy of the renal secreting tissue and deficient renal secretion in consequence. The ultimate result may be most serious. In two such cases a fatal result followed from oliguria and a terminal anuria from this cause four and five years respectively after nephrectomy for tuberculous disease. Another patient (L. R.) suffers from it to a pronounced degree seven years after the operation, and in another (V. O.) a similar change has taken place. A young boy, aged 12 (A. T.), is at present an inmate of our wards undergoing treatment for this complication.

A variety of surgical procedures has been adopted in these cases to relieve the backward pressure :—(1) temporary drainage of the pelvis ; (2) temporary drainage of the ureter ; (3) denervation of the lower end of the ureter ; (4) presacral neurectomy ; (5) vesical exclusion with transplantation of the ureter into the pelvic colon. The last operation, which was recently performed on the young boy mentioned above, is naturally the most serious and most drastic, but it gives promise of being the most efficient method of treating this serious complication.

The problem that it presents, where a single damaged kidney exists, is that which confronts the surgeon in many cases of ureteral transplantation for vesical exclusion.

This operation has been carried out by us for a number of conditions :—(1) where the bladder is permanently incontinent from a congenital malformation, that is, vesical exstrophy ; (2) where it is permanently incontinent from accident—from a vesico-vaginal fistula incurable by plastic operation ; (3) where total cystectomy is indicated in the treatment of malignant disease of the urinary bladder ; (4) where there has been complete obstruction of the outflow channel from the bladder and this channel cannot be restored, and a suprapubic drainage has been established which has been followed by infection and persistent systole of the bladder ; and (5) as has been mentioned,

where a single kidney remains and this is undergoing slow destruction from backward pressure, as in a case of tuberculous disease.

The essential problem in all cases is the prevention of congestive anuria which is liable to develop from the swelling and œdema at the site of the implantation. Various methods are employed to diminish this danger. None are certain preventatives. In cases of extroversion of the bladder and vesico-vaginal fistula, we consider the problem solved by doing the operation in two stages with a lengthy interval between them.

In malignant disease of the urinary bladder, such a practice is not advisable. The delay entailed contra-indicates the two-stage operation which would raise the number of operations the patient had to endure to four and thus impose an unwarranted strain on his strength and courage. Bilateral transplantation must therefore be carried out to diminish the number of operative interferences and to expedite the cure. In the class of case where ureteral transplantation is indicated and a persistent suprapubic sinus discharging urine exists, bilateral transplantation is again a necessity to obtain an aseptic technique which otherwise would be impossible; and, finally, when a single kidney exists, obviously all the eggs are in one basket and the operation is of necessity one-stage. To diminish the risk of anuria and lessen the amount of oliguria in these cases, we have employed various methods. We have inserted the catgut drain or wick through the site of the anastomosis, as Charles Mayo first advocated, and we have also previously drained one or both renal pelves, with results that have given some encouragement. It is only recently, however, that we have felt that we have reached firmer ground with these cases, and I, personally, consider that this is due to the assistance Mr Dick has been able to provide by his methods.

II. Mr Lawson Dick.

The problem with which we are confronted is how the kidney which is labouring under difficulties can best be aided to perform its function of elimination of nitrogenous and other waste products. Light can be thrown on this problem by a consideration of some of the known facts of renal physiology.

The kidney is a gland which removes waste products from the blood. This removal is effected by a process of active secretion and not by simple filtration. Energy must be expended in a secretory process, and this energy may be measured by the amount of oxygen which the tissue consumes. In the performance of its ordinary function, the work done by the kidney is almost as much as that done by the heart. Heart muscle during ordinary contraction uses ·054 c.c. of O_2 per gram per minute, and the kidney during ordinary activity uses ·05 c.c. of O_2 per gram per minute.[5] The kidney expends this energy in concentrating urine.

If two solutions be separated in a receptacle only by a semi-permeable membrane, water tends to pass through this membrane from the less concentrated to the more concentrated solution. The force which the concentrated solution exerts in drawing the water through the semi-permeable membrane is known as osmotic pressure. Renal epithelium, in addition to being an actively secreting tissue, is a semi-permeable membrane. The osmotic pressure of the blood is about seven atmospheres. The osmotic pressure of concentrated urine of specific gravity of about 1030 may be as much as forty atmospheres. In secreting urine of this concentration the kidney has to work against an osmotic pressure of over thirty atmospheres, or between four hundred and five hundred pounds per square inch. It is therefore a logical conclusion, which has been verified by experiment, that the kidney has to perform more work in secreting a small amount of concentrated urine than in secreting a large amount of dilute urine. One of the early signs of renal failure in nephritis is the inability of the kidney to concentrate urine, as evidenced by the large quantity of dilute urine secreted overnight in place of the normal small amount of concentrated urine.

Although the exact mechanism of renal secretion is still in some doubt, the manner of the kidney's action is broadly this. There is passed into the capsule of Bowman through the glomerular tuft a filtrate composed of all the non-colloid constituents of the plasma. These non-colloid substances, such as urea, chloride, sugar, and others, are in exactly the proportion in which they are found in the plasma. As the filtrate passes down the tubules it is elaborated into urine. According to the theory of Cushny, the elaboration is effected entirely by the reabsorption of water and threshold substances in the tubules.[2] Starling and his co-workers have recently put forward

evidence that, under certain circumstances, there is active secretion in the tubules in addition to reabsorption, but the point is not of great importance in the present argument.

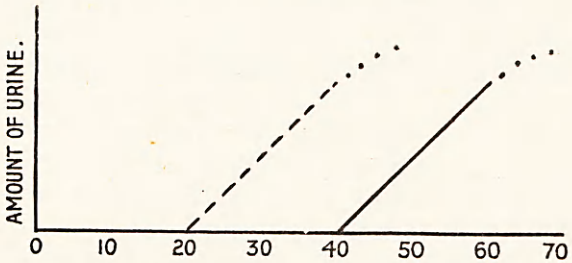
Whichever theory is held, glomerular filtration is the starting point of renal secretion. This filtration is resisted by the osmotic pressure of the plasma colloids which tends to hold the water in the glomerular capillaries. Filtration is made possible by the blood pressure in the capillaries of the glomerular tufts. The blood pressure in the capillaries of the glomerular tufts is about two-thirds of the arterial blood pressure, or about 80 mm.Hg. The osmotic pressure of the plasma colloids resisting filtration is about 30 mm.Hg. There is therefore normally a positive filtration pressure in the glomerular tuft of about 50 mm.Hg, which is necessary for proper renal function. This filtration pressure is equal to the pressure in the capillaries of the glomerular tuft less the pressure in the renal tubules and in Bowman's capsule. This last pressure is normally zero or very near to it, but in pathological states it may be raised. Glomerular filtration pressure can be reduced by (1) lowering of the blood pressure, or pre-renal anuria; (2) post-renal obstruction causing a rise in ureteric pressure which is transmitted to the glomeruli, or post-renal anuria; (3) renal congestive anuria. This last is a component of the two preceding types. By some damage, a condition of congestion and œdema is produced in the kidney. This has a two-fold effect—it interferes with the blood flow and produces a fall in the glomerular capillary pressure, and it causes a post-glomerular obstruction by pressure on the tubules.

Verney and Starling [8] showed that when the blood pressure falls to about 50 mm.Hg renal secretion ceases. They further showed that the addition to the circulating blood of a solution of urea or salts has the effect of making urine secretion possible at a lower blood pressure. Their results suggest that the diuretic action of urea and salts is that shown in Fig. 1.

Renal secretion ordinarily commences only when the blood pressure reaches about 50 mm.Hg, and thereafter increases in amount in proportion with increase of the blood pressure. The effect of the addition of urea or salts is to displace this curve to the left without alteration of its shape. Thus in a case of anuria if the blood pressure be adequate for renal secretion, and if no post-renal obstruction can be demonstrated, the anuria

must be intra-renal in origin, and the most favourable circumstances for the occurrence of urine secretion are produced by the action on the kidney of urea or salts. In most cases of anuria, urea is already present in excess in the blood without producing a diuresis. The action of salts remains to be considered.

Salts in solution injected into the blood act as diuretics by keeping water in the circulation. This produces a dilution of the plasma colloids which favours glomerular filtration. Water injected alone does not act in this way. Water injected directly into the circulation produces no diuresis because it produces no hydræmia. The injected water immediately leaves the blood



Glomerular Pressure in mm.Hg.

——— Normal urine secretion.

– – – – – Urine secretion after injection of sod. sulph.

FIG. 1.

and enters the body cells, principally those of the muscles and skin, whence it is only slowly released. Water so injected even produces damage to body cells as evidenced by laking of the blood and the appearance of hæmoglobin in the urine after the injection.

The diuretic effect of solutions of different salts varies. It was first shown by Magnus[6] that the intravenous injection of sodium sulphate produces a diuresis which is more abundant than that produced by injection of sodium chloride in similar amounts. The secretion of urine after the injection of sulphate increases more rapidly and attains its maximum sooner. The maximal diuresis is greater, and secretion regains the normal rate more slowly. This can be explained by the fact that sulphate is a salt foreign to the body in large amounts and completely non-threshold to the kidney. Baird and Haldane[1] showed that quite large amounts of sodium chloride can be

stored in the tissues, and that once the storage is effected the chloride is only slowly given up again. There is no evidence of the storage of sodium sulphate. Therefore while sodium chloride and its solvent water may leave the plasma and pass into the tissues and thus cease to exercise any diluent effect on the plasma colloids, sulphate after injection tends much more to remain in the plasma until it is excreted by the kidney. The dilution of the plasma effected by the injection of sodium sulphate is therefore longer continued in its action on the kidney than that induced by sodium chloride. Further, sodium sulphate is a non-threshold salt. Any sulphate that appears in the glomerular filtrate must be passed to the exterior. It cannot be reabsorbed by the tubular epithelium as can sodium chloride.

An experiment of Cushny's is of interest in this connection.[4] A rabbit was anæsthetised with urethane. A cannula was inserted into each ureter. One ureter was left free and the other was subjected to a pressure of 20 mm.Hg. A mixture of sulphate and chloride was injected intravenously. The urine from each ureter was collected in five-minute periods. The urine from the obstructed ureter was naturally less in amount and the amount of chloride and of sulphate excreted was reduced. The percentage reduction in amount, chloride, and sulphate, is shown in Table I.

TABLE I.

Percentage Reduction in Secretion from Obstructed Ureter in Five-minute Periods.

Minutes.	Amount.	Chloride.	Sulphate.
0-5	33	47	1
5-10	37	44	23
10-15	38	46	24
15-20	47	56	34
20-25	59	75	42
25-30	46	92	27
30-35	69	100	68

The secretion of chloride is interfered with by ureteral obstruction to a much greater degree than is the secretion of sulphate. This experiment suggests that, in the presence of ureteral obstruction, a solution of sodium sulphate is a more powerful diuretic than a solution of sodium chloride.

An investigation of the diuretic action of sodium sulphate in the human subject was made in two cases. In each case the patient was given a diet which was carefully regulated as to

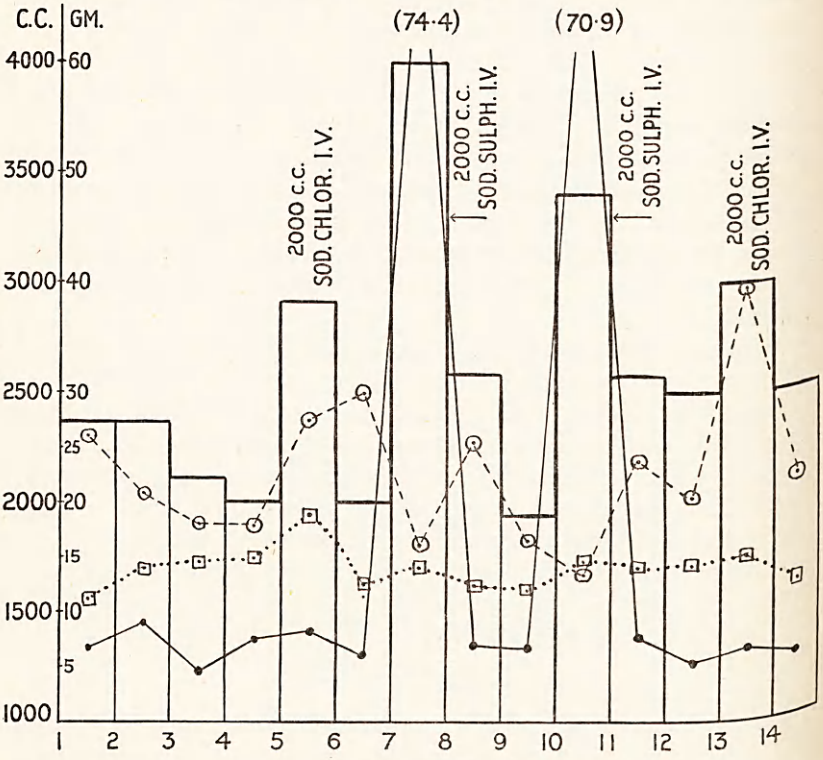


FIG. 2.

KEY TO FIGS. 2 AND 3.

Total amount of urine.

Total sulphate output.

Total chloride output.

Total nitrogen output.

(1) fluid intake, (2) nitrogenous content, and (3) chloride content. On some days during the administration of the diet the fluid intake was augmented by the intravenous injection of two litres of isotonic sodium sulphate solution or two litres of

isotonic sodium chloride solution. During the course of the experiment the urine was collected and the following observations were made: (1) total amount of urine voided in twenty-four hours, (2) total content of (*a*) chloride, (*b*) sulphate, and (*c*) nitrogen. The results are expressed graphically in Figs. 2 and 3. In the case recorded in Fig. 2 the daily fluid intake was about 2300 c.c. and the daily nitrogen intake was about 13·1 gm. In the case recorded in Fig. 3 the daily fluid intake

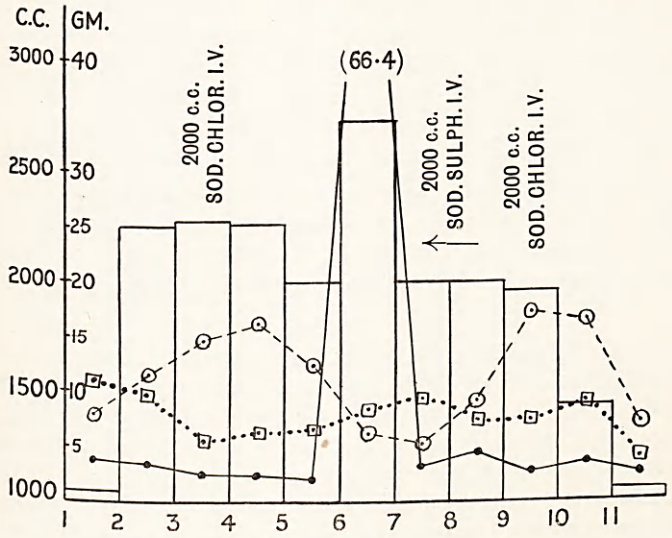


FIG. 3.

was about 1800 c.c. and the daily nitrogen intake was about 8·2 gm.

The diuresis induced by sodium sulphate is in every case greater than that induced by sodium chloride. In no case is there any evidence of storage of sodium sulphate in the body after intravenous injection. In the case of all injections of sodium chloride except the last recorded in Fig. 2 there is evidence of storage of the sodium chloride injected, in that the rise in chloride excretion extends over more than one day. The increase in nitrogenous excretion in response to the diuresis is slight. This is because both of the subjects were in nitrogen equilibrium with no retention of nitrogenous substances. According to Cushny[3] the effect of diuresis in the normal animal is to produce a profound fall in the percentage

of solids excreted, but this is associated with a slight rise in the total amount of solids excreted. He goes on to say, "Further, water, circulating in the blood and lymph, washes out the waste products, so that the plasma becomes enriched with them, and the kidney responds by eliminating them in larger quantities than usual."

On these grounds it is considered that the intravenous injection of sodium sulphate is of value in stimulating diuresis, and it has been used in several cases. The sulphate is injected in the form of an isotonic solution of sodium sulphate. The preparation used is ordinary hydrated sodium sulphate, Na_2SO_4, $10\,H_2O$, or Glauber's salt. This is the most stable of the forms in which sodium sulphate is obtainable. 42·85 grams of Glauber's salt dissolved in one litre of water give an isotonic solution, and this strength has been used throughout.

The first case in which this mode of treatment was used is of interest and has already been referred to by Professor Johnstone at a meeting of the Obstetrical Society.

Mrs L. H., aged 44. Eight weeks before admission, patient was delivered of a full-time child, her fifth, by a precipitate but otherwise normal labour. She was sent in to the Royal Infirmary, Edinburgh, to Professor Johnstone's wards, with a history of hæmaturia of one week's duration. Some days after her admission to hospital urine secretion ceased. On the second day of anuria, Mr Wade was asked to see her. The blood pressure was 130/85 mm.Hg, therefore the anuria was not pre-renal. The passage of ureteral catheters to the full extent met with no obstruction, therefore the anuria was not post-renal. During this time the patient was drinking large amounts of water, which were retained. On the third day of her anuria sickness began to develop, which materially reduced the amount of her oral fluid intake. On the fourth day of the anuria, two litres of isotonic sodium sulphate were given intravenously together with one litre of isotonic sodium chloride. No diuresis ensued, and this dose was repeated on the fifth day. Now the sickness was persistent and troublesome, the patient was very drowsy, and several attacks of uræmic twitching of the face, hands and arms were seen. Some hours after completion of this injection the patient began to pass urine, and in the next twenty-four hours 8400 c.c. of urine were voided. Coincident with the onset of the diuresis, the patient's condition showed an immediate clinical improvement, no further twitchings were observed, the sickness ceased, and the drowsiness and confusion vanished. The record of the urine secretion and of the blood chemistry is shown in Table II.

TABLE II.

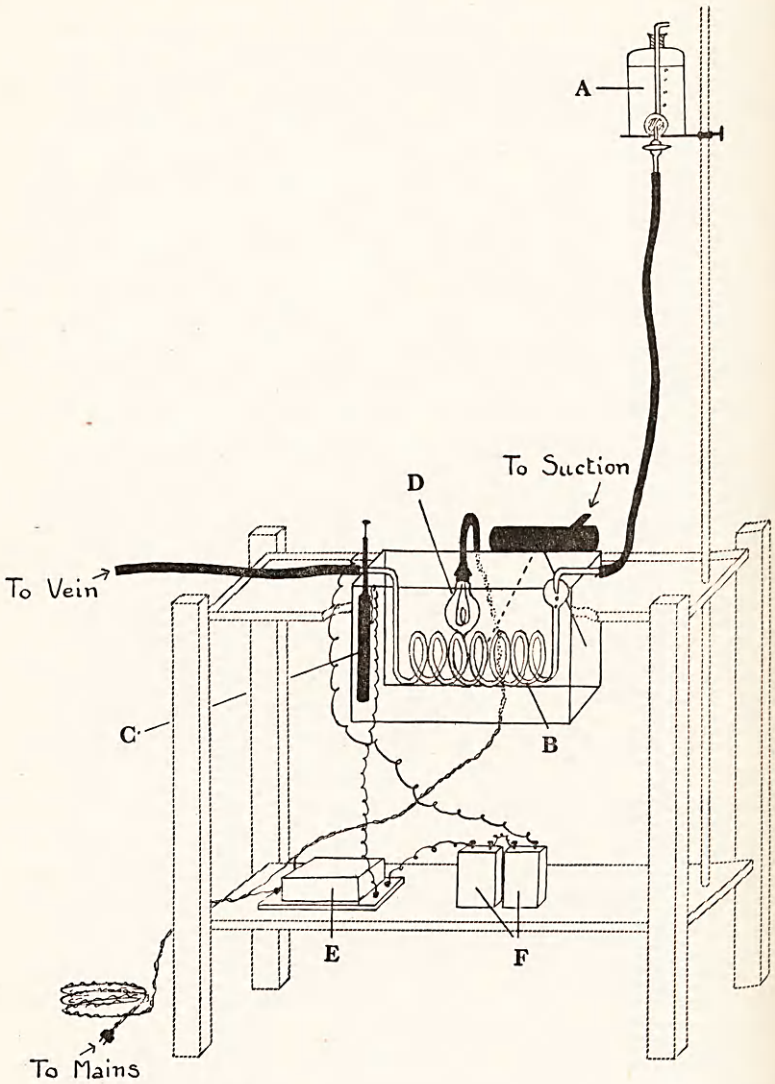
Day.	Urine.		Blood.			
	Amount in c.c.	Percentage of Urea.	Urea.	N.P.N.	Creatinine.	CO_2 Comb. Power in vols. per 100 c.c.
			in mgm. per 100 cm.			
1	...	...	...	60	4·0	61
2	...	...	...	71	4·0	60
3	...	...	122	90	4·2	50
4	...	...	154	105	5·6	40
5	8,400	0·5	147	100	4·4	44
6	5,100	0·8	101	64	...	69
7	3,300	1·1	51	45	2·9	69
8	3,000	0·9	...	...	...	...
16	1,800	1·5	28	31	2·7	70

Sixteen days after the onset of anuria the patient's blood chemistry had returned to normal. On her discharge from hospital a renal function test showed that her kidneys had an efficiency of over 70 per cent. of the normal. She was last seen three months ago, well and symptomless.

In order to avoid the administration of a large bulk of fluid at one time, a method was devised whereby a continuous flow of warmed fluid can be run slowly into a vein. The apparatus consists of a Marryat bottle which delivers the fluid at a constant rate. The fluid is conducted through a glass coil and thence to a venous cannula. In the glass coil there is incorporated a dripper whereby the rate of flow can be ascertained. The glass coil is immersed in a water-bath which is thermostatically controlled and maintained at a constant temperature. The fluid is warmed in its passage through the glass coil, and the temperature in the bath can be adjusted so that the fluid is delivered into the vein at 37° C. By this means fluid can be run slowly into a vein for any desired period—for a week or more.

The details of three of the cases in which this form of treatment was used are appended. They typify the method of use and the result.

Case VI.—Mrs M. F., aged 37. Patient referred to Mr Wade with a history of increased frequency of micturition associated with dysuria and strangury and a constant gnawing pain. Three years before, patient had had a carcinoma of the cervix treated by radium implantation. On cystoscopic examination a diagnosis was made of



A. Marryat Bottle.
B. Glass Coil.
C. Thermostat.
D. Heating Lamp.
E. Relay from Mains.
F. Batteries operating Thermostat.

FIG. 4.

involvement of the base of the bladder with malignant disease spreading up from below. Bilateral ureteral transplantation was carried out in one stage, and a tube was passed up the rectum to the site of the transplants. Immediately after the operation continuous intravenous administration of sodium sulphate solution was started, at a rate of about 100 c.c. per hour. During the first ten hours 600 c.c. of urine drained from the rectal tube, and in the subsequent six days the amounts of urine secreted were 2100 c.c., 3420 c.c., 1980 c.c., 2400 c.c., 2760 c.c. and 2640 c.c. Thereafter the infusion was discontinued. In this case the infusion overcame the dangerous and possibly fatal post-operative anuria which would almost certainly otherwise have supervened.

Case VII.—W. A., aged 45. Mr Wade performed a nephrectomy for a tumour of the kidney. During the first seven days after operation the urine secretion averaged 1500 c.c. About midday on the eighth day the patient ceased passing urine. Catheterisation twenty-four hours later, during which time no urine had been voided, showed that the bladder was empty. Fluid intake by mouth during this time had been encouraged, and the patient co-operated well, drinking about 3000 c.c. There was no sickness. Eight hours later, as secretion had not recommenced, the continuous intravenous administration of isotonic sodium sulphate was begun. The rate of the infusion was about 200 c.c. per hour for the first twenty-four hours and thereafter about 100 c.c. per hour. During the first six hours 1440 c.c. of urine containing 1 per cent. of urea was secreted. In the following four days the amounts of urine voided were 5400 c.c., 3000 c.c., 3000 c.c. and 3360 c.c. respectively, and the average urea content was about 0·7 per cent. Thereafter the infusion was stopped, and the patient made an uninterrupted recovery.

No cause for the anuria was discovered. There was at this time a slight fever, and a suggestion of post-renal obstruction due to a ureteritis or of renal congestive anuria might be supported. Whatever the cause of the anuria, it yielded rapidly to intravenous sodium sulphate.

Case VIII.—D. B., aged 10. This was a small boy admitted in a critical condition due to congenital vesical sphincteric stenosis. This is a condition of achalasia or dysfunction of the musculature of the bladder neck, whereby normal emptying of the bladder is interfered with, and a condition of backward pressure is produced analogous to that of prostatism. On admission the bladder was grossly overdistended, reaching up above the umbilicus. Both kidneys could be felt as enormous hydronephrotic sacs. Renal function was found to be very poor—the blood urea was 139 mgm. per 100 c.c., and no shadow was seen on either side following the intravenous injection of

uroselectan B. After very careful consideration the operation of presacral neurectomy was decided upon, and was performed by Mr Wade under gas and oxygen anæsthesia. On the day after operation the amount of urine voided fell to 150 c.c., and during this night and up to 11 A.M. on the following day no urine was voided. Catheterisation showed the bladder to be empty. Up till midday on this day three uræmic fits were observed, and the patient was becoming very confused and drowsy. The continuous intravenous administration of sodium sulphate was commenced at midday, the rate of the injection being about 100 c.c. per hour. During the next twelve hours 1200 c.c. of urine were voided, containing 0·8 per cent. of urea. A uræmic fit occurred during the insertion of the cannula. Three more occurred during the subsequent ten hours, when they ceased. It was not possible to collect all the urine even by means of frequent catheterisation because the patient was incontinent, but during the next four days the amounts collected were 780 c.c., 1920 c.c., 2940 c.c. and 1880 c.c., with an average urea content of 0·8 per cent. On this day the blood urea was down to 84 mgm. per 100 c.c. and the infusion was stopped. Unfortunately the boy later succumbed to infection of his urinary tract, but at this time a critical stage was overcome.

Conclusions.

The four cases which have been described recovered from anuria. In the opinion of the authors the recovery was largely brought about by the intravenous injection of sodium sulphate solution.

The experimental evidence which suggested this method of treatment has been discussed, and it was concluded that the intravenous injection of a solution of sodium sulphate is the best method of producing a diuresis. This conclusion has been justified by clinical and experimental results.

An important objection to a general application of the method to cases of uræmia is that there is no guarantee that a sodium sulphate diuresis will increase the output of nitrogenous products to the same extent as it increases the total urinary output. This objection is largely met by the results recorded in Table II., which show that sodium sulphate diuresis produced in three days in a case of anuria a fall of blood urea from 154 mgm. to 51 mgm. per 100 c.c., a concentration almost within normal limits. Furthermore, in the cases of D. B. and L. H., uræmia was actually present, and during the diuresis induced by sodium sulphate the uræmia disappeared. In the

cases described, however, the kidneys were not suffering from an irreversible injury. In cases of anuria of similar types spontaneous recovery is not unknown. In the authors' opinion the damage produced to the kidney by chronic prostatic retention is not dissimilar to that produced by chronic interstitial nephritis. There is, however, this important distinction. In chronic interstitial nephritis the damage is an irreversible one. In almost all cases of chronic prostatic retention drainage of the bladder with adequate precautions results in a restoration of renal function towards normal in greater or less degree. In a few cases, however, the damage produced by the prostatic retention may have progressed so far that like that of chronic interstitial nephritis it has become irreversible. In these cases the same efficiency of sodium sulphate as a diuretic cannot be expected. The success of the method obviously depends on the presence of an adequate number of potentially functioning renal units.

I thank Dr C. P. Stewart for carrying out the biochemical investigations, the Dietetic Department for arranging and supplying the diets, and the nursing staff of Mr Wade's wards for their generous and careful help. I also thank Professor Clark for much advice and encourgement throughout the investigation.

REFERENCES.—[1] Baird and Haldane, *Journ. Physiol.*, 1922, lvi., 259. [2] Cushny, *The Secretion of the Urine*, 2nd ed., 1926, chaps. vii. and viii. [3] Cushny, *ibid.*, p. 30, 1926. [4] Cushny, *Journ. Physiol.*, 1902, xxviii., 431. [5] Clark, *Applied Pharmacology*, 5th ed., 1933, p. 412. [6] Magnus, *Arch f. Exp. Path. u. Pharm.*, 1900, xliv., 68, 396. [7] Starling and Verney, *Proc. Roy. Soc.*, series B., 1924, xcvii., 321. [8] Verney and Starling, *Journ. Physiol.*, 1922, lvi., 353.

DISCUSSION.

Professor Wilkie spoke.

Mr R. Leslie Stewart said—The problem of anuria is a difficult one; from the clinical standpoint perhaps the most interesting type of case is the unexplained anuria to which Professor Wilkie has referred. I have two slides here which illustrate types of anuria which were dealt with by surgical measures.

The first patient was a woman aged about 50, who was operated on in August 1931, having the right kidney removed for a condition of infective hydronephrosis. Mr Wade carried out the operation. Just before going on holiday, I happened to be in charge of the wards temporarily while he was away. The patient did perfectly well for

some days, then she developed, on 3rd September, an anuria with pyrexia and left-sided pain. We looked up the notes and found that her left kidney urine had been found—at the time of her urological investigation—to be infected. We carried out the usual treatment, catheterising the left ureter on 4th September, and got off 12 oz. of urine. We did not leave the catheter in but catheterised again the following day, 5th September, when there was nothing but a few drops of blood-stained fluid obtained. On 6th September she was definitely uræmic and looked extremely ill. She was taken to the operating theatre and the left kidney was cut down upon and found to be extremely congested. The renal pelvis was slightly dilated and there was blood-stained urine in it. A drainage-tube was put in and the excretion very quickly rose to about 150 oz. in the day. The tube was left in until 14th September—*i.e.*, for one week—then it was removed. Some secretion came away from the loin until 18th September, when she began to pass urine from her bladder again. One noticed a very marked polyuria following the resumption of secretion, the secretion going up to nearly 200 oz. in the day. This patient is still under treatment. Her condition was an infected kidney on the left side, and the cause of her anuria appeared to be an acute infection associated with inflammatory obstruction at the uretero-pelvic junction. It is now three years since the operation and the left kidney is somewhat hydronephrotic, but she is carrying on fairly well.

The second patient was a man aged 58, who came in as an emergency case with anuria of a few days' duration and acute pain in the left side. X-ray showed no calculus. We immediately cut down on his left kidney, and found it to be extremely congested, the pelvis containing a little blood-stained fluid. The renal pelvis was drained. He was cystoscoped the following day to see if we could get anything from his right kidney, but only a very small amount of urine was obtained from the ureteral catheter. There was a fairly normal output at first from the left side, some coming *via* the bladder, but later there was nothing passed from the bladder at all and we simply continued to get secretion from the left kidney drainage-tube. We then carried out a nephrotomy on the right kidney, and an interesting point in this was that when we exposed the right kidney it was found not congested but rather pale and hydronephrotic, a different picture to that obtaining at the operation on the left side. After draining for some days he began to pass urine from his bladder. Both the openings in his loin closed up and he developed a polyuria as in the other patient. The explanation of this case was somewhat difficult. We thought it was due to a congestive type of anuria, chiefly post-renal. The only thing of special interest in his after-history was the fact that he died of a carcinoma of the stomach about nine months later, and

the question arises as to whether this had anything to do with his attack of anuria.

I cannot say much about the scientific problems that have been discussed to-night, but the condition, clinical and scientific, must continue to be of great interest. From the clinical point of view, with a patient with anuria, the main difficulty may be to decide whether to treat him by non-operative measures or by operation.

Mr Struthers spoke.

Dr J. D. S. Cameron said—Mr Wade almost convinced me that the interest of the surgical kidney cases was as great as that of the medical cases. I might recall to Mr Struthers one case similar to those here dealt with. Within the last two years, Dr Matthew transferred to him a man admitted to the wards as a case of acute nephritis. On admission there was a condition of anuria, there were no symptoms suggestive of a nephritic condition, and as all the biochemical investigations were against a diagnosis of nephritis, he was transferred to Mr Struthers's ward. At operation a condition of bilateral congestion was found. Both pelves were drained, and in the matter of a week the condition had returned to normal. In connection with the physiology of renal function, we have to consider the matter of the blood flow through the kidney. Most probably, the fact that there is not a sufficient blood flow is accountable for the anuria or oliguria which is present in cardiac failure cases. There we have a kidney substance which is more or less normal, though certainly congested, there is a very high intercapillary pressure and high venous pressure, and yet with these factors we do not have a sufficient blood flow through the kidney. We can ascribe the anuria or oliguria of cardiac failure to the effect of that insufficiency.

Mr David Band said—We are accustomed to recognise clinically two types of uræmia, the first occurring where there is obstruction to both ureters or to one ureter, the other kidney being functionless. There you have the patient who, with anuria of sudden onset, develops a high blood urea in a few days with remarkably little clinical evidence of uræmia, very little gastro-intestinal upset, very few head or mental symptoms, and no convulsions, until towards the end of a week, when these symptoms set in and very shortly death follows. In that type of case there is a rise in the blood urea before the clinical signs of uræmia present themselves. In the second type of uræmia, we have the individual who, perhaps from backward pressure from the prostate, or from chronic interstitial nephritis, has a high blood urea, which remains high over a long period, and only very gradually do signs of uræmia develop. It struck me in listening to these papers, that perhaps the therapeutic value of sodium sulphate, combined with

skilled surgery, might throw some light on the site of the lesion in these two types of renal disease leading to uræmia. For instance, I have the impression that the sulphates are secreted from the tubules, along with urea, *i.e.*, the Starling-Verney theory of renal secretion has rather supplanted the filtration and reabsorption theory of Cushny. It would seem that, if these tubules are able to secrete, then the administration of sodium sulphate to the blood stream will stimulate them very strongly and perhaps just tip the balance between anuria and renal secretion. On the other hand, if one looks at the chronic case, as where the kidney has been damaged by backward pressure over a long period, one finds—at least in my experience—that sodium sulphate will produce a considerable secretion for a period of days, which, however, is not urine, in that it does not contain a sufficient percentage of urea and does not bring the patient through his uræmia.

The suddenly obstructed kidney developing anuria, properly relieved by surgical measures and stimulated by sodium sulphate, completely recovers. On examining the chronically obstructed cases at post-mortem, one is not surprised to find that the kidney could not carry through, because it is grossly diseased.

I would ask Mr Wade and Mr Dick to consider that, if sodium sulphate is a stimulant to a healthy kidney recently put out of action, it might not help us to distinguish that type of kidney from the chronically obstructed kidney from long-standing backward pressure.

Dr R. A. Fleming said—I have had experience of a single case of the type that has been mentioned. A gentleman, a little over eighty, had, some years ago, an attack of influenza followed by broncho-pneumonia. I saw him at the beginning of his bad illness—about five weeks before the incident which I am going to mention—and I suggested to the doctor who was looking after him that although the patient had a good deal of incontinence, there was an element of either uræmia or anuria—more correctly uræmia in his case. However, the doctor declined to listen. Five weeks later I had occasion to be in the South again and I saw the old gentleman. His own son, a doctor just home from abroad, agreed with me that the patient could not live more than twenty-four hours unless something was done. I suggested once again this uræmic theory, and at that time it certainly looked like a renal anuria. I suggested that we might try pituitrin, as we could not give anything by the mouth because he was almost unconscious. On the Friday night the old gentleman had $\frac{1}{2}$ c.c. of pituitrin; on the Saturday he had another $\frac{1}{2}$ c.c.; and on the Sunday his health was so satisfactory that we decided to get him home—nearly three hundred miles, partly by road and partly by rail—and he arrived in fairly good condition. He only had one other $\frac{1}{2}$ c.c. of pituitrin. Now the problem is, how did the pituitrin produce the flow of urine which

apparently was the cause of his recovery? An additional point I should mention is that his arteries were those of an individual of about thirty, and he is still alive and verging on ninety.

Mr Henry Wade.—On behalf of Mr Dick and himself Mr Wade expressed appreciation of Professor Wilkie's remarks, particularly with reference to the possibilities that this new line of treatment offered in dealing with certain serious surgical problems.

Mr Leslie Stewart had raised the question as regards the position of the operating surgeon in treating these different cases of anuria and the circumstances in which operative interference was indicated. We considered that when organic obstruction, such as an impacted calculus, is revealed, naturally it should be treated by operation at once and the obstruction relieved. Similarly, where ureteral catheterisation reveals organic obstruction and no permanent relief is obtained by the catheterisation, operation again should be performed.

The difficult problem arises in the class of case where on ureteral catheterisation you find the pelves empty, and there is no obvious organic blockage and no failing of blood pressure. In such a case we feel prepared to try the effect of twenty-four hours' continuous infusion before operating, if this should ultimately be found to be necessary.

Mr Struthers raised the question as to whether it is necessary to have an apparatus so scientifically exact as the one that was made for us by Mr Condon. The patients we have to treat are critically ill, and we feel certain that it is advisable to instil the fluid at a constant and regular blood temperature and carry out the treatment with a relatively scientific exactitude.

Mr Lawson Dick, in reply, said—I am sorry that I am not prepared to offer to the President any suggestion as to the mode of action of pituitrin in the case which he detailed. The action of pituitrin on renal secretion is a complicated one, and I do not think that anyone could answer the question within the necessarily limited scope of this reply.

In regard to the mode of action of sodium sulphate which was raised by Mr Band, I was this week-end in personal touch with Dr F. R. Winton of Cambridge, who began with Starling and Verney in 1922 in their work upon kidney transfusion experiments and who has been working on these lines since. He gave it to me as his opinion, although he could not offhand give me any definite experimental proof, that the action of sodium sulphate in producing a diuresis is almost solely, if not solely, due to the fact that it keeps water in the tubules after the water has been filtered through the glomerulus. Sodium sulphate is a salt which does not easily pass

through body membranes and which therefore exerts in the renal tubules a high osmotic pressure. Chloride, on the other hand, penetrates body membranes easily, and urea easily. The result is that either of these may be readily reabsorbed in the tubules if there is any delay in the passage of the fluid through the tubules, but the absorption of sodium sulphate is much less likely to occur. Dr Winton also offered it as his opinion, although again he could not offer any experimental proof, that a diuresis produced by sodium sulphate is likely to bring with it, through the kidney, urea and other waste substances.