RENAL FUNCTION IN EXPERIMENTAL HYDRONEPHROSIS.

By REUBEN A. JOHNSON, M.D.

(*From the Department of Pathology and Bacteriology of the University of Minnesota, Minneapolis.*)

PLATES 17 TO 21.

(Received for publication, March 28, 1918.)

The object of this investigation is the study of the function of kidneys in the early stages of experimental hydronephrosis by means of the phenolsulfonephthalein test of Rowntree and Geraghty (1). The anatomic changes in hydronephrosis have been thoroughly studied by other observers and will be discussed here only as they pertain to the main purpose of the paper.

Anatomic Changes in Hydronephrosis.

The anatomic changes after complete obstruction of the ureter will be discussed in stages corresponding in duration to the experiments given below.

During the first 3 days only slight changes are noted. Suzuki (2) found a considerable dilatation of the collecting and distal convoluted tubules, but only a slight dilatation of the proximal convoluted tubules at this stage. Fabian (3) noted a slight general dilatation of the tubules as early as 3 hours after ligature of the ureter. In a kidney with hydronephrosis of 3 days' duration I noted a considerable dilatation of the collecting tubules and those portions of Henle's loops lined by flattened epithelium, in both cortex and medulla. The proximal convoluted tubules, however, showed no definite change. The renal pelvis was moderately dilated.

In hydronephrosis of about a week's duration much more pronounced changes develop. Suzuki, in a hydronephrosis of 9 days' duration, found marked dilatation of the capsular spaces and the collecting tubules, and moderate dilatation of the distal convoluted

tubules and both limbs of Henle's loops. The proximal convoluted tubules showed slight or no dilatation. A few casts were found distal to the first convoluted tubule. Casts in the medulla are mentioned by Ponfick (4). Scott (5) found collapse of some tubules in the apical portion of the pyramid, but my observations do not confirm this. In a hydronephrosis of 7 days' duration I observed marked dilation of the ureter and pelvis, and the kidney was distinctly pale. The cortex was thinner in the portions lateral to the sinus than elsewhere. The collecting tubules everywhere are dilated (Fig. 3). The proximal convoluted tubules are unchanged or slightly reduced in size in all parts of the kidney except in the portions lateral to the sinus where they are, for the most part, markedly reduced in size. Numerous casts are found in the collecting tubules in some parts of the kidney.

In hydronephrosis of about 2 weeks' duration the changes have become very pronounced. Suzuki described a narrowing of the parenchyma, most marked in the portions adjacent to the hilus. There was dilatation of the collecting and the distal convoluted tubules. The proximal convoluted tubules and the loops of Henle were usually collapsed, showing beginning atrophy. The atrophy was much more pronounced in the portions adjacent to the hilus than in the mid-sagittal portions. Occasionally a proximal convoluted tubule showed dilatation with a thinned epithelium. Very few casts were noted. In my control animal with a hydronephrosis of 2 weeks' duration the kidney was very pale. The pelvis and ureter were markedly dilated. The parenchyma was thinned, especially in the parts lateral to the sinus. The collecting tubules were all considerably dilated. The proximal convoluted tubules usually showed collapse with a moderate amount of atrophy. Some of these tubules were moderately dilated and had a thin epithelium (Fig. 8). In the portions lateral to the sinus of the kidney the dilatation of the tubules was pronounced and the atrophy of the proximal convoluted tubules was also much greater than in other portions of the kidney. Very few casts were to be seen (Fig. 9).

My observations agree with those of Suzuki that the portions of renal parenchyma lateral to the sinus of the kidney are much more severely injured than other parts of the kidney. The collecting tubules draining these lateral portions of the kidney are entirely col-

lapsed. Suzuki's explanation of this phenomenon seems entirely satisfactory. He points out that the collecting tubules draining these portions of the kidney are subjected to much greater pressure than in other parts of the parenchyma.

In hydronephrosis of about 3 weeks' duration Suzuki noted marked atrophy of the proximal convoluted tubules and dilatation of the collecting tubules. The atrophic changes were much more pronounced in the lateral than in the mesial parts of the renal parenchyma. My observations on a hydronephrosis of 19 days' duration are essentially the same as Suzuki's. In the lateral portions of the kidney the proximal convoluted tubules are in a state of advanced atrophy with relative or absolute increase of the intervening connective tissue. The atrophy of the tubules in the mesial portions of the kidney is not nearly so pronounced. Collecting tubules are everywhere dilated. Only a few casts are to be seen.

Some authors mention areas of lymphocytic infiltration in hydronephrotic kidneys but these were not found in my experimental animals except where tubular atrophy was extreme. Probably most of these lymphocytic infiltrations mentioned by various authors are examples of spontaneous nephritis which is common in rabbits.

Anatomic Changes in Temporary Hydronephrosis with Subsequent Drainage.

The investigators mentioned above studied the changes in hydronephrosis without drainage. Others removed the obstruction to the ureter after suitable intervals, established drainage, and studied the subsequent changes.

Rautenberg (6) ligatured the ureter close to the bladder to produce a hydronephrosis. At a second operation an anastomosis was made connecting the dilated ureter and the bladder, and at a third operation the sound kidney was removed. In this manner the changes which were produced in the period of obstruction plus those occurring in the period of drainage could be studied. The duration of hydronephrosis in his experiments varied from 2 to 6 weeks with subsequent drainage even as long as 6 months. He summarized his results as follows: Temporary ligature causes atrophy of the epithelial cells, especially in the convoluted tubules of the cortex. The degree of atrophy varies directly with the duration of obstruction and the injury is not uniformly distributed through the kidney. New connective tissue fills the space left by shrinkage of the tubules.

Some of the atrophic tubules return to normal size with a corresponding decrease of the new connective tissue. The extent of the recovery varies directly with the length of the drainage period. The recovery varies markedly in distribution and degree, sharply contrasted areas of atrophic and normal tubules being found in close association. He believes that the recovery is not permanent. The epithelial cells do not functionate normally, regressive changes again prevail, and eventually complete atrophy of the entire tubule results. The finding of increased blood vessel anastomoses between the kidney and surrounding tissue, claimed by Lindemann (7), was not confirmed by Rautenberg.

Bradford (8) ligatured the ureter on one side in dogs, and after intervals of from 11 to 40 days brought the dilated ureter to the abdominal surface and established a urinary fistula. The animals were kept for 7 to 51 days following the second operation. In three of the experiments a pyonephrosis developed, but the other nine remained free from infection. She found that after the second operation the kidney returned to its normal shape but was reduced to a third or half of its normal size. The ureter remained thickened and dilated. Microscopically there was no general increase of connective tissue, except along the blood vessels. The renal tubules were crowded together, many had disappeared, especially in the cortex, and the epithelial cells were much smaller, with a distinct loss of granulation. These factors accounted for the decrease in the size of the kidney.

The changes in temporary hydronephrosis have been described also by Corbett (9) and by Amos (10).

Functional Studies in Kidneys with Hydronephrosis.

The studies made of the functional capacity of kidneys with hydronephrosis may be divided into two groups. In the first group hydronephrosis was produced by a complete, sudden blocking of the ureter and functional studies were made at the completion of the desired period of dilatation. In addition, some of the experimenters of this group removed the obstruction, established drainage, and were able to make functional studies during the period of drainage. In the second group hydronephrosis was produced by a constant partial obstruction, sufficient to impede but not to stop the flow of urine.

Hydronephrosis Produced by Complete Obstruction without Drainage.—Suzuki studied the function of hydronephrotic kidneys by determining their ability to excrete indigo carmine. The dye was injected shortly before the animals were killed. Judging by the presence of carmine masses in the lumina and carmine granules in the cells of the tubules, he concludes that there is a progressive decrease of function with the duration of the hydronephrosis. In early stages the

function is fairly good, but after 3 weeks it is greatly reduced and is apparently limited to a few convoluted tubules in the medial part of the kidney.

Boetzel (11) produced a unilateral hydronephrosis by ligaturing the ureter close to the bladder, then injected toluidine for functional study, and killed the animals 7 hours following the injection. Toluidine is eliminated by the convoluted tubules. After a dilatation of 6 days' duration no coloring matter was found in the pelvic fluid. After 21 days scarcely any granules, and after 30 days no dye granules were found in the renal cells. If the pressure is released in from 21 to 30 days the kidney excretes some of the dye in the urine, and after some time granules appear in the tubules. From this he concludes that accumulation of dye granules in the cells and excretion are independent, and that in Suzuki's experiments the carmine casts found are due to an abnormal secretion of tubules injured by the carmine itself. He agrees with Rautenberg that kidneys dilated 4 weeks or longer are injured beyond functional power and does not think that all the compressed tubules can recuperate.

Lindemann (12) found an impaired output of indigo carmine from a kidney the ureter of which had been ligatured for only $1\frac{1}{2}$ hours.

Pfaundler (13) obstructed the ureter on one side for periods varying from 15 minutes to 6 hours and analyzed the fluid obtained. He compared the urine from both kidneys and found an increased volume of urine but a decreased concentration of urea and sodium chloride on the obstructed side.

Bainbridge (14) made a unilateral hydronephrosis in cats by ligaturing the ureter. After varying periods of dilatation he measured the pressure of the retained fluid and then analyzed it. After emptying the pelvis he collected the secretion from the two sides simultaneously, using salt as a diuretic. He found a steady diminution in the amount of water and solids excreted by the dilated side, decreasing directly with the duration of the hydronephrosis. The acidity was also diminished. The power of excretion was not entirely lost even when the hydronephrosis had lasted 2 months.

Heidenhain (15) tied one ureter and injected indigo carmine 24 hours later. The animal was killed as soon as the dye appeared in the urine from the normal kidney. The obstructed kidney differed from the normal in showing less color grossly and in the absence of dye granules in the cells of the convoluted tubules. Both kidneys showed carmine in the lumina of the tubules.

Kawasoye (16) ligatured the ureter on one side in nine rabbits and produced hydronephrosis varying from a few hours' to 9 months' duration. 20 minutes before killing the animals he injected indigo carmine. In the shorter periods of dilatation, up to 24 hours, he found a decreased amount of the dye in the tubular epithelium, but after 48 hours no dye whatever was found.

Hydronephrosis Produced by Complete Obstruction with Subsequent Drainage.—The studies given above were limited to a determination of the functional capacity of kidneys at the conclusion of a period of dilatation. Other observers drained the dilated kidneys and made subsequent functional observations. Rautenberg, in the series of experiments given previously, drained the dilated kidney into the

bladder after desired periods of dilatation, and at a still later date removed the normal kidney. Seven rabbits with a preliminary hydronephrosis of 42 days and an interval of drainage of from 34 to 155 days died of renal insufficiency a few days after removal of the normal kidney. A similar result was obtained with two rabbits in which the duration of hydronephrosis was 28 and 29 days respectively. However, in a series of three rabbits with hydronephrosis of 3 weeks' duration and a period of drainage of from 22 to 31 days before removal of the normal kidney, two were still living a year later. The third rabbit died of a pyelonephritis. Albumin in small amounts and casts were found in the urine of both the living animals even after a year's time. In a second series of three rabbits with a shorter period of dilatation (about 2 weeks) and nephrectomy after a drainage period of from 14 to 19 days, two died. One was living 39 days after the nephrectomy but it was weak and emaciated. He concludes from these results that there is great individual variation in rabbits. The only functional test which Rautenberg applied was the ability to maintain life and this was lost in kidneys obstructed longer than 3 weeks. That there was still some unhealed renal lesion was shown by the presence of albumin and casts in the urine a year after the removal of the normal kidney.

Kawasoye determined the functional capacity with indigo carmine in a series of seven rabbits in which the obstruction was removed after varying intervals of dilatation. He found a complete restoration of function after a 4 day period and an incomplete restoration after a 7 to 14 day period. No restoration of function whatever, as shown by indigo carmine, was found in kidneys obstructed 21 days.

Corbett tied a ligature around the ureter just tight enough to produce complete obstruction without cutting through the tissues. After desired intervals the abdomen was again opened and the ligature loosened, allowing the urine to flow into the bladder. The normal kidney was removed at the same operation. The functional capacity of the injured kidney was then determined by a study of the total nitrogen and chlorides in the urine. He concludes that kidneys obstructed longer than 10 days do not excrete these substances in normal amounts.

Sollmann, Williams, and Briggs (17) produced a unilateral hydronephrosis of 107 days' duration and then made a urinary fistula for the dilated kidney. During 78 days of drainage no urine was excreted and only two drops were found in the shrunken kidney at autopsy.

Hydronephrosis Produced by a Partial Obstruction.—Keith and Snowden (18) tied a rubber band around one ureter to produce partial obstruction. The opposite kidney was removed at the same time. A hydronephrosis resulted in all cases with the fluid under a pressure of from 12 to 30 cm. of water as measured at autopsy. They noted a polyuria, a low specific gravity, and a trace of albumin, in the urine continuously after the operation. The phlorhizin test showed a moderate delay. The blood nitrogen showed a sharp rise at first and then maintained a fairly constant level to within a few days of death, when there was a great increase. The phthalein test was very sensitive and showed a slowing of excretion in the early stages, and in the later stages a progressive reduction in the total excre-

tion when the rise in blood nitrogen occurred. The development of a pyelonephritis is only a question of time in animals operated on by this method.

Hermann (19), Lépine and Porteret (20), and Lindemann determined the effect of a constant back pressure on the kidney secretion by analyzing the urine. In addition to chemical analysis Schwarz (21), Cushny (22), and Filehne and Ruschhaupt (23) noted the effects of diuretics. Similar work on the effect of back pressure on kidney secretion was done by Brodie and Cullis (24) in decerebrated dogs. All are agreed that the flow of urine decreases with high and increases with a low back pressure. With the exception of Brodie and Cullis they found a decreased concentration of solid constituents. For a review of the literature on this phase of the question the reader is referred to Keith and Snowden.

In a recent article Keith and Pulford (25) describe the results obtained in experiments in which bilateral partial obstruction of the ureters was produced by ligaturing with rubber bands. The degree of obstruction obtained was not the same in all the experiments. In five animals definite functional impairment was shown after obstruction lasting about a week and the bands were then removed. Normal function returned in a few days. In another experiment the animal died shortly after removal of the obstruction, but in this case a pyelonephritis complicated the picture. Removal of the bands after 143 days of obstruction, in one experiment, failed to improve the impaired renal function, but observations were continued for only a week.

EXPERIMENTAL.

Method.

The animals used in the experiments were male rabbits, and all experiments were performed under ether anesthesia. To eliminate all animals in which an already existing renal lesion was present a careful urinalysis and a preliminary phthalein test were made. All rabbits showing any abnormalities in the urine or a phthalein output of less than 65 per cent for 2 hours were discarded. The average phthalein output in the rabbits used was higher than 65 per cent.

The rabbits were operated on in three stages. The preliminary operation consisted in the division and suturing of the ureter in the bladder wall. With all necessary aseptic surgical precautions and under ether anesthesia a median suprapubic incision about 4 cm. long was made exposing the bladder and lower portion of the ureter. The right ureter was then freed at its lower end close to the bladder, care being taken not to injure the blood vessels, ligatured doubly, and sectioned between. An incision about 2 cm. long was

then made in the posterior wall of the bladder through the peritoneal and muscular coats down to the mucosa. The mucosa was separated from the muscular coat for a short distance on both sides and the ligatured ureter was then buried between the mucosa and the muscular coat by suturing the edges of the incision together. The abdomen was then closed.

At the second operation, after varying intervals of time, depending on the duration of hydronephrosis desired, the abdomen was again opened, under ether anesthesia, by an incision close to the first incision and parallel to it. An incision was made through the anterior wall of the bladder. The dilated end of the ureter, buried beneath the mucosa at the previous operation, was clearly visible as an elevation. The mucosa of the bladder over the elevated area was incised and the end of the ureter brought through and opened. The fluid from the dilated ureter then gushed forth into the bladder and drainage was established. The anterior wall of the bladder and abdomen were then sutured.

At the third operation, usually about 1 month after the establishment of drainage, under ether anesthesia, a nephrectomy through a dorsal incision was made on the left side, leaving the hydronephrotic kidney to perform the function alone. The animals were then kept in metabolism cages and the quantity of daily urine was measured. The urine was examined at frequent intervals. A record was kept of the weight. As often as it was deemed necessary phthalein tests were made. When the test returned to normal the animals were killed and the kidneys studied grossly and microscopically. The tissues were fixed in Helly's fluid, embedded in paraffin, and stained with hematoxylin and eosin.

A great many of the experiments were not successful. In a few cases infection from the operation, especially when it was necessary to operate at short intervals, resulted. Sometimes when the abdomen was opened for the second operation it was found that the ligature had slipped off and no hydronephrosis had resulted. Epidemics in the animal house caused the death of many of the experimental animals. In the series reported only those rabbits are included in which it was absolutely certain that the obstruction of the ureter was complete for the length of time indicated.

In order to determine the changes which occurred in the kidneys during the period of drainage, the ureter was ligatured in a number of control rabbits with normal urinary findings. These animals were killed after periods of dilatation corresponding to the duration of the hydronephrosis before drainage in the above experiments. By comparison the extent of recovery during the drainage period was determined.

The phthalein test was made by injecting 1 cc. of the dye into the lumbar muscles. 2 hours later, with aseptic precautions, a No. 10 French, soft rubber catheter was introduced into the bladder. Catheterization is easily performed on male rabbits. The kidney and ureter were then gently pressed to expel as much urine as possible and the bladder was washed out with sterile salt solution. The reading was made in the usual manner in an Autenrieth-Königsberger colorimeter.

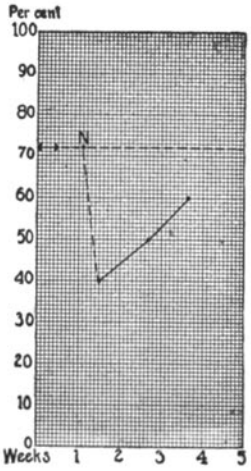
Experiment 1. Complete Obstruction of the Ureter for 3 Days.—Male rabbit. Preliminary phthalein 72 per cent. Urine normal. Right ureter ligatured. 3 days later, at the second operation when the ureter was opened, a smoky, brownish fluid gushed into the bladder. 5 days after the second operation the left kidney was removed. The phthalein test was 40 per cent on the 2nd, 50 per cent on the 10th, and 60 per cent on the 17th day after the nephrectomy (Text-fig. 1). A moderate amount of albumin and a few erythrocytes were present for a few days after the nephrectomy, but later the urinary findings were normal. The rabbit died 23 days after the nephrectomy from intestinal obstruction.

The right (hydronephrotic) kidney weighs 6.3 gm. The pelvis and ureter are slightly dilated. Fluid from the pelvis at autopsy shows numerous hyaline and granular casts and one cast of a renal tubule. The lining surface of the pelvis is smooth and shiny. No pus is present. The fluid in the bladder shows a small amount of pus but there is no marked congestion of the bladder wall. The only important difference between the right and left kidneys is the slight dilation of the right pelvis with a corresponding slight thinning of the renal parenchyma anteriorly and posteriorly. Microscopically no important differences are seen.

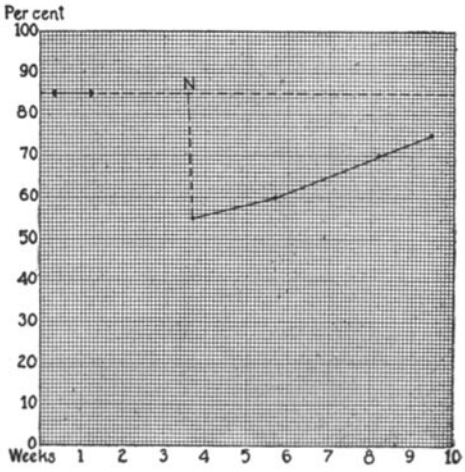
Experiment 2. Complete Obstruction of the Ureter for 7 Days.—Male rabbit. Preliminary phthalein test 85 per cent. Urine normal. Right ureter ligatured. 7 days later at the second operation the ureter was found well dilated, about the size of a small goose quill. When it was opened a thin, brownish fluid gushed out under tension into the bladder. Loss of weight between first and second operations 150 gm. 16 days after the second operation left nephrectomy was performed. The phthalein test rose gradually from 55 per cent the day following nephrectomy to 75 per cent 40 days later when the animal was chloroformed (Text-fig. 2). The kidney function had returned to the average normal although not so high as the

original test. The rabbit had increased in weight 280 gm. during the experiment. The urine showed a faint trace of albumin continuously after the nephrectomy but there were no casts, erythrocytes, or pus cells.

The right kidney (hydronephrotic) weighs 6.6 gm. Grossly it shows several linear scars on each side of the pelvis radiating out from the hilus as a center, gradually becoming less distinct and disappearing about two-thirds of the distance to the convex border. They do not cross the rounded convex border. On section these linear scars are seen to correspond to small lateral evaginations of the



TEXT-FIG. 1. Function of a kidney obstructed for 3 days (Experiment 1).



TEXT-FIG. 2. Function of a kidney obstructed for 7 days (Experiment 2).

The ordinates indicate percentage of phthalein, and the abscissæ the time measured in weeks. The horizontal dotted line indicates the level of the preliminary phthalein test. The solid portion of this line indicates the period during which the ureter was tied off. N indicates the point at which the normal kidney was removed, and the phthalein readings are indicated by dots on the charted line.

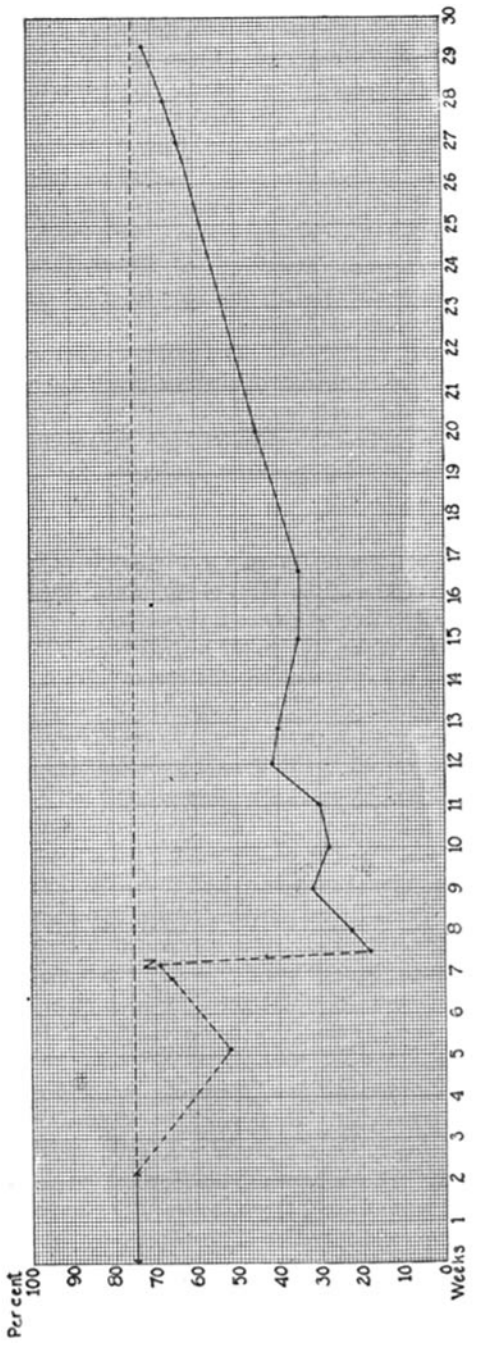
pelvis. The cortical tissue in the linear areas is atrophic, apparently a permanent destruction of the renal tissue due to the hydronephrosis. The cortex shows a uniform thickness of about 4 mm. The microscopic structure of the renal parenchyma is practically normal (Fig. 1) except in the linear scars mentioned above which show atrophy of tubules, small collections of lymphocytes, and increase of connective tissue (Fig. 2). Fig. 3 shows a kidney obstructed by ligature of the ureter for 7 days, and, in all probability, represents the condition of the right kidney of this experiment at the time when drainage was established.

Experiment 3. Complete Obstruction of the Ureter for 14 Days.—Male rabbit. Preliminary phthalein test 75 per cent. Urine normal. Right ureter ligatured. 14 days later at the second operation the ureter was found well dilated, about the size of a large goose quill. Brownish fluid gushed out under pressure when it was opened. The phthalein test was 52 per cent 21 days after the second operation, and 66 per cent 30 days after, which was the combined function of the normal and the hydronephrotic kidneys. 35 days after the second operation left nephrectomy was performed. A few erythrocytes, leukocytes, and hyaline and granular casts appeared in the urine for a few days. The phthalein test rose gradually from 18 per cent 2 days after the nephrectomy to 72 per cent 152 days later, when the animal was chloroformed (Text-fig. 3). The phthalein test had returned to within 3 per cent of the original test. The rabbit was active, well nourished, and normal except for a very faint trace of albumin which had been continuously present in the urine since the nephrectomy.

The right kidney (hydronephrotic) weighs 6.8 gm. It presents striking changes grossly. On both the anterior and posterior aspects of the kidney the mesial portion which forms the wall of the sinus is atrophic and depressed, not unlike an old infarct, while the lateral portion along the rounded border is hypertrophied and elevated. The two portions are sharply marked off from each other along a definite line, somewhat irregular at the limits of the pelvis. On section the parenchyma forming the lateral walls of the sinus is very thin and atrophic, apparently a permanent lesion in this region due to the hydronephrosis. The parenchyma along the convex border is hypertrophied, the cortex being 6 mm. in thickness, apparently a compensatory change. The pelvis is dilated and the ureter seems to be the same size as at the second operation 7 months previously.

Microscopic sections show practically normal structure along the convexity of the kidney. Anatomic recovery in this portion is apparently complete (Figs. 4 and 5). A few mitotic figures are seen. There is no increase of connective tissue except in a few small areas. But there is a sudden transition to atrophic tissue where the convex portion joins the flattened lateral walls of the sinus as described in the gross specimen. These lateral portions consist of numerous lymphocytes, markedly atrophic tubules, dilated capsular spaces with atrophic glomeruli, and diffusely distributed fibrous tissue (Figs. 6 and 7). Fig. 8 shows the mesial and Fig. 9 the lateral portion of a kidney obstructed for 14 days, and probably represent the condition of the corresponding portions of the right kidney of Experiment 3 at the time when drainage was established.

Experiment 4. Complete Obstruction of the Ureter for 17 Days.—Male rabbit. Preliminary phthalein 70 per cent. Urine normal. Right ureter ligatured. 17 days later at the second operation the ureter was found well dilated, about the size of a large goose quill. A thick brownish fluid gushed out under tension when it was opened. Loss of weight was 200 gm. between the first and second operations. 14 days after the second operation left nephrectomy was performed. The phthalein test was 3.5 per cent on the 3rd day following nephrectomy. The daily



TEXT-FIG. 3. Function of a kidney obstructed for 14 days (Experiment 3).

output of urine increased gradually from 60 cc. on the day following nephrectomy to 250 cc. on the 6th day and remained at about this level. A large amount of albumin, a few erythrocytes, leukocytes, and hyaline and granular casts were constantly present in the urine. The rabbit was very weak and inactive during the entire period and was found dead 9 days after the nephrectomy. The cause of death was apparently renal insufficiency, as no lesions aside from the kidney changes were found at autopsy.

The right kidney (hydronephrotic) weighs 7 gm. There is no evidence of pyelitis or pyelonephritis either grossly or microscopically. The finer structure cannot be studied well because of postmortem autolysis. There are no marked differences between this kidney and one obstructed for the same period without drainage.

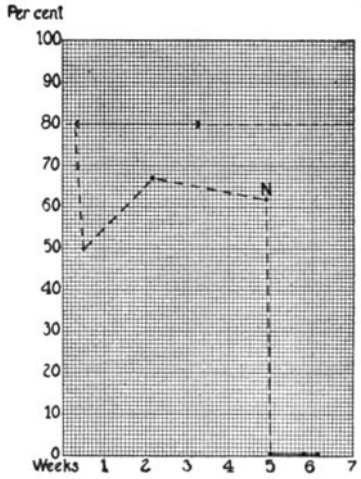
Experiment 5. Complete Obstruction of the Ureter for 19 Days.—Male rabbit. Preliminary phthalein 75 per cent. Urine normal. Right ureter ligatured. 19 days later a ureterocystostomy was performed as the preliminary operation was not the usual one but consisted of only ligature and section of the ureter. The ureter was dilated to the size of a large goose quill. A large amount of dark brownish fluid gushed out under tension. Loss of weight of 150 gm. between first and second operations. 18 days after the second operation the rabbit weighed 50 gm. more than at the beginning of the experiment and a left nephrectomy was performed. On the day following nephrectomy the phthalein test was 0. On the 2nd day 20 cc. of urine were excreted showing a tinge of phthalein, a moderate amount of albumin, but no erythrocytes, leukocytes, or casts. The rabbit became very weak and died 3 days after nephrectomy. The urine in the bladder at autopsy showed a minute trace of phthalein. There was no obstruction at the ureteral orifice in the bladder wall. No lesions aside from those in the kidney were found, and death was due apparently to renal insufficiency.

The right kidney (hydronephrotic) weighs 9.1 gm. The pelvis and ureter are markedly dilated. There is no evidence of infection. There are no important changes present, grossly or microscopically, other than those ordinarily found in a simple hydronephrosis of like duration.

Experiment 6. Complete Obstruction of the Ureter for 19 Days.—Male rabbit. Preliminary phthalein 70 per cent. Right ureter ligatured. 19 days later at the second operation the ureter was about ¼ inch in diameter and filled with a brownish fluid under tension. 3 days after the second operation left nephrectomy was performed. The phthalein test was 3 per cent on the 2nd day following the nephrectomy. The daily output of urine increased from 40 cc. on the day following nephrectomy to 80 cc. on the 4th day. Urinalysis showed a trace of albumin, a few leukocytes, and a few erythrocytes. The rabbit became very weak and died on the 4th day. At autopsy, besides the renal changes, there was found a small, circumscribed, inspissated abscess in the lower lobe of the right lung. Apparently the cause of death was renal insufficiency, as the lung condition was well walled off and chronic.

The right kidney (hydronephrotic) weighs 12.8 gm. A few subcapsular petechiæ are present. The pelvis and ureter are markedly dilated. There is no evidence of infection. No striking microscopic differences between this kidney and one dilated for a similar period of time without drainage are to be noted.

Experiment 7. Complete Obstruction of the Ureter for 21 Days.—Male rabbit. Preliminary phthalein 80 per cent. Urine normal. Right ureter ligatured. The phthalein test was 50 per cent the day following, and 67 per cent on the 13th day after ligature of the ureter. 21 days after the first operation the ureter was found dilated to about ½ inch in diameter and a dark smoky brown fluid gushed out when the opening was made into the bladder. The phthalein was 62 per cent 10 days after the second operation, which was the combined function of the normal and the hydronephrotic kidneys. 11 days after the second operation left



TEXT-FIG. 4. Function of a kidney obstructed for 21 days (Experiment 7).

nephrectomy was performed. The phthalein test was 0 on the day following nephrectomy, but minute traces were present in the urine during the next few days. On the 5th day the phthalein test showed only a faint trace (Text-fig. 4). The amount of urine increased from 2 cc. on the day following the nephrectomy to 100 cc. on the 8th day. A large amount of albumin, with a few erythrocytes, leukocytes, and hyaline casts was continuously present. The rabbit was found dead on the 9th day apparently from renal insufficiency, as no other lesions were present at autopsy.

The right kidney (hydronephrotic) weighs 11.6gm. The pelvis and ureter are markedly dilated. There is no evidence of infection. No marked changes other than those usually found in a simple hydronephrosis of 21 days' duration are present (Fig. 10). A kidney with such extensive changes is unable to function sufficiently to maintain life.

DISCUSSION.

Hydronephrosis of 3 days' duration causes considerable dilatation of the collecting tubules and the portions of Henle's loop lined by flattened epithelium. No anatomic changes are recognizable in the convoluted tubules. The kidney of Experiment 1 returned to about normal function, as measured by the phthalein test, in 15 days. The only abnormality seen in the kidney after functional recovery is a slight dilatation of the renal pelvis and a slight thinning of the renal parenchyma on the lateral aspects of the renal sinus.

When hydronephrosis has been present for 7 days there is a marked dilatation of the pelvis with considerable thinning of the parenchyma laterally. The dilatation of the collecting tubules is more marked than in the 3 day stage and there is some reduction in size of many of the convoluted tubules, those in the portions lateral to the sinus being especially compressed. The kidney of Experiment 2 had an initial phthalein excretion of 55 per cent and returned to normal function in about 40 days. After functional recovery the kidney showed a dilated pelvis with thinning of the parenchyma laterally. The lateral portions of the kidney showed a few scars due to complete atrophy of small portions of the cortex. Elsewhere the anatomic picture was about normal.

A kidney with hydronephrosis of 14 days' duration shows more dilatation of the pelvis and ureter and greater thinning of the renal parenchyma, especially in the parts lateral to the sinus, than in the 7 day stage. The collecting tubules are considerably dilated and the proximal convoluted tubules are collapsed with some atrophy. The supporting connective tissue is increased. The lateral portions of the kidney show the maximum dilatation of the collecting tubules and maximum atrophy of the proximal convoluted tubules. The initial phthalein output of the kidney in Experiment 3 was 18 per cent, which returned to normal only after 152 days. The pelvis and ureter were still dilated after functional recovery. The portion of renal parenchyma forming the wall of the sinus was completely atrophied. As already stated, Suzuki's explanation of the greater injury sustained by this portion of the kidney seems satisfactory; *i.e.*, the collecting tubules draining this portion, owing to their longer and more indirect course to the papilla are subjected to greater pressure

than those draining the central portion. The destruction of these collecting tubules results in atrophy of their convoluted tubules and glomeruli. The parenchyma along the convex border of the kidney was almost normal, the convoluted tubules having regained their normal size and appearance.

In the kidneys with hydronephrosis longer than 14 days (17, 19, 19, and 21 days) there is marked dilatation of the ureter and pelvis. The proximal convoluted tubules are in a state of advanced atrophy with relative or absolute increase of connective tissue. The collecting tubules are markedly dilated everywhere. No kidney of this group was able to secrete over 3.5 per cent of phthalein. No improvement in secretory power was obtained and no rabbit lived sufficiently long after drainage to develop any notable renal changes other than those seen in simple hydronephrosis of equal duration.

It is to be noted that the ureter and pelvis showed no tendency in any of the experiments to return to normal size. No evidence of secondary infection was seen in the pelvis, ureter, or kidney parenchyma.

If a nephrectomy is performed on a normal animal the remaining kidney excretes, a few days later, nearly as much phthalein as the previous output of both kidneys. The atrophy produced by hydronephrosis greatly reduces this ability until compensatory hypertrophic changes can occur. The kidney with hydronephrosis of 3 days' duration required 15 days to recover 20 per cent of function, or 1.33 per cent per day. The one with hydronephrosis of 7 days' duration required 40 days to recover 20 per cent, or 0.5 per cent per day. The one with hydronephrosis of 14 days' duration required 152 days to recover 54 per cent, or 0.35 per cent per day. It can be readily seen, therefore, that the longer the period of dilatation the slower is the rate of recovery after drainage. The delayed recovery of function in the more prolonged cases of hydronephrosis is apparently due to the greater degree of atrophy of the convoluted tubules. The more advanced the atrophy the slower seems to be the return to normal. The destruction of collecting tubules is not the cause of the atrophy of the convoluted tubules except in the lateral portions of the kidney.

In view of the slow recovery after complete hydronephrosis for 2 weeks it is not surprising that Keith and Pulford noted no appreciable

improvement in a week in a hydronephrosis obtained by partial obstruction of the ureter for 143 days. The rapid recovery noted by them in other experiments after partial obstruction for about a week, when secondary pus infection did not complicate the picture, is also in accordance with the above results.

The contention of Rautenberg that the regeneration after drainage is not permanent and that eventually complete atrophy ensues is not borne out by my experiments. The presence of albumin in the urine in Experiment 3 even at the end of the experiment indicated renal disturbance; but the high phthalein excretion and the autopsy findings showed no evidence of a secondary atrophy.

Rabbits with hydronephrosis longer than 14 days did not live long after removal of the normal kidney. In this group the greatest phthalein output was 3.5 per cent. They all died apparently of renal insufficiency. One may conclude from these results that when a hydronephrotic kidney shows so low a phthalein excretion it will be unable to maintain the life of the individual. The question arises whether such a hydronephrotic kidney would improve sufficiently to maintain life if the normal kidney were not removed until 6 months or more after the establishment of drainage. My observations do not determine this point.

Another point, likewise not determined by the above experiments, is whether the hydronephrotic kidney would recover functionally as it did in Experiment 3 if the normal kidney had not been removed; *i.e.*, whether the stimulus of compulsory function is necessary for recovery.

In the above experiments kidneys obstructed longer than 14 days did not recover; but Rautenberg had two rabbits with hydronephrosis of 3 weeks' duration that lived a year after removal of the normal kidney. This probably means, as Rautenberg suggests, that there is considerable individual variation in rabbits.

SUMMARY.

Complete obstruction of the ureter causes atrophy of the renal parenchyma, especially marked in the portions lateral to the renal sinus. The longer the duration of the obstruction, the greater is the degree of atrophy.

If the obstruction is removed within 2 weeks the kidney may regain its normal structure except for a varying amount of atrophy in the lateral portions.

Kidneys obstructed for 2 weeks or less may regain their normal function, as measured by the phthalein test.

The longer the period of obstruction, the slower is the rate of recovery. A hydronephrosis of 7 days' duration required 40 days, and one of 14 days' duration required 152 days to recover normal function.

I wish to express my indebtedness to Dr. E. T. Bell for criticisms and suggestions during the progress of this work.

BIBLIOGRAPHY.

1. Rowntree, L. G., and Geraghty, J. T., The phthalein test. An experimental and clinical study of phenolsulphonephthalein in relation to renal function in health and disease, *Arch. Int. Med.*, 1912, ix, 284.
2. Suzuki, T., Zur Morphologie der Nierensekretion unter physiologischen und pathologischen Bedingungen, Jena, 1912.
3. Fabian, E., Die Niere des Kaninchens nach der Unterbindung ihres Harnleiters, *Biblioth. Med., Abt. Path. u. path. Anat.*, 1904, No. 18, 1.
4. Ponfick, E., Ueber Hydronephrose, *Beitr. path. Anat. u. allg. Path.*, 1910, xlix, 127.
5. Scott, G. D., Experimental hydronephrosis produced by complete and incomplete ligation of the ureter, *Surg., Gynec. and Obst.*, 1912, xv, 296.
6. Rautenberg, E., Die Folgen des zeitweiligen Ureterverschlusses, *Mitt. Grenzgeb. Med. u. Chir.*, 1906, xvi, 431.
7. Lindemann, W., Ueber Veränderung der Nieren infolge von Ureterunterbindung, *Z. klin. Med.*, 1898, xxxiv, 299.
8. Bradford, E. R., Observations made upon dogs to determine whether obstruction of the ureter would cause atrophy of the kidney, *Brit. Med. J.*, 1897, ii, 1720.
9. Corbett, J. F., Changes in the kidney resulting from tying the ureter, *Am. J. Med. Sc.*, 1912, cxliv, 568.
10. Amos, B. S., On the effect of ligature of one ureter, *J. Path. and Bacteriol.*, 1905, x, 265.
11. Boetzel, E., Experimentelle Untersuchungen über die Hydronephrose, *Beitr. path. Anat. u. allg. Path.*, 1913, lvii, 294.
12. Lindemann, W., Ueber die Wirkung der Gegendruckerhöhung auf die Harnsecretion, *Beitr. path. Anat. u. allg. Path.*, 1897, xxi, 500.
13. Pfaundler, M., Über die durch Stauung im Ureter zu Stande kommende Veränderung der Harnsekretion, *Beitr. chem. Physiol. u. Path.*, 1902, ii, 336.

14. Bainbridge, F. A., The effects of ligature of one ureter, *J. Path. and Bacteriol.*, 1906, xi, 421.
15. Heidenhain, R., Versuche über den Vorgang der Harnabsonderung, *Arch. ges. Physiol.*, 1874, ix, 1.
16. Kawasoye, M., Experimentelle Studien zum küntslichen Ureterverschluss, *Z. gynäk. Urol.*, 1911–1912, iii, 172.
17. Sollmann, T., Williams, W. W., and Briggs, C. E., Experimental atresia of the ureter, *J. Exp. Med.*, 1907, ix, 71.
18. Keith, N. M., and Snowden, R. R., Functional changes in experimental hydronephrosis, *Arch. Int. Med.*, 1915, xv, 239.
19. Hermann, M., quoted by Keith and Snowden (18).
20. Lépine, R., and Porteret, E., Sur la composition de l'urine sécrétée pendant durée d'une contre-pression exercée sur les voies urinaries, *Compt. rend. Acad.*, 1888, cvii, 74.
21. Schwarz, L., Ueber Harnveränderung nach Ureterbelastung, *Zentr. Physiol.*, 1902–03, xvi, 281.
22. Cushny, A. R., On saline diuresis, *J. Physiol.*, 1902, xxviii, 431.
23. Filehne, W., and Ruschhaupt, W., Beiträge zur Lehre von der Diurese. VII. Die Diurese bei Abflusserschwerung, *Arch. ges. Physiol.*, 1903, xcv, 409.
24. Brodie, T. G., and Cullis, W. C., On the secretion of urine, *J. Physiol.*, 1906, xxxiv, 224.
25. Keith, N. M., and Pulford, D. S., Jr., Experimental hydronephrosis. Functional and anatomic changes in the kidney following partial ureteral obstruction, *Arch. Int. Med.*, 1917, xx, 853.

EXPLANATION OF PLATES.

PLATE 17.

FIG. 1. Cortex of the kidney of Experiment 2, showing complete recovery after obstruction of the ureter for 7 days.

FIG. 2. Section through one of the linear scars occurring in the kidney of Experiment 2.

PLATE 18.

FIG. 3. Cortex of a control kidney with complete obstruction of the ureter for 7 days. Compare with FIG. 1.

FIG. 4. Cortex of the kidney of Experiment 3, from the convex border, showing almost complete recovery after obstruction of the ureter for 14 days.

PLATE 19.

FIG. 5. High power view of FIG. 4.

FIG. 6. Cortex of the kidney of Experiment 3, from the lateral wall of the sinus of the kidney, showing extreme atrophy after obstruction of the ureter for 14 days.

PLATE 20.

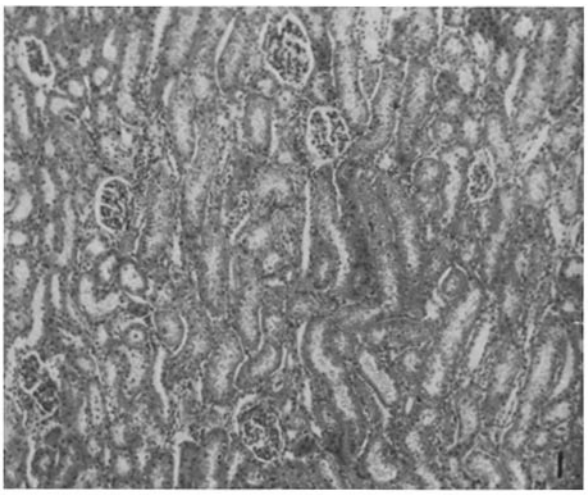
FIG. 7. High power view of Fig. 6.

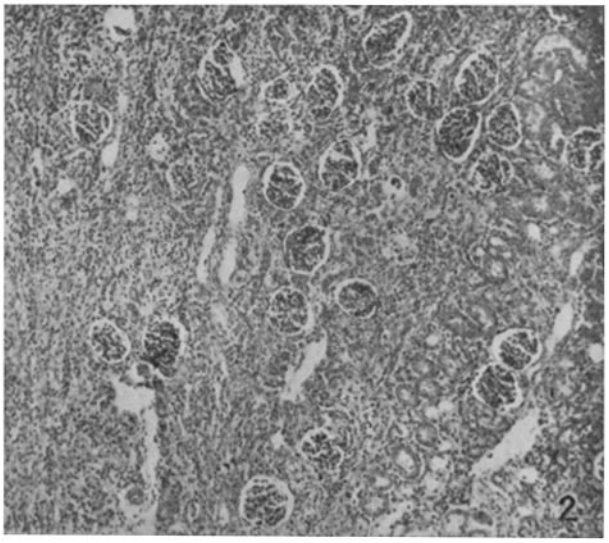
FIG. 8. Cortex from the convex border of a control kidney with complete obstruction of the ureter for 14 days. This portion of the kidney recovers after drainage. Compare with FIG. 4.

PLATE 21.

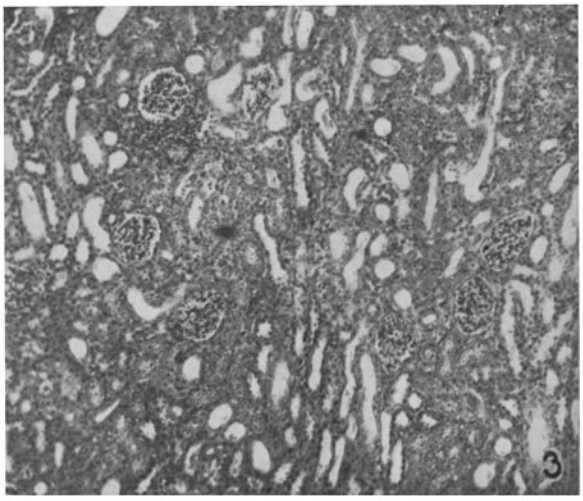
FIG. 9. Cortex from the lateral wall of the sinus of a control kidney with complete obstruction of the ureter for 14 days. This portion of the kidney does not recover after drainage. Compare with FIG. 6.

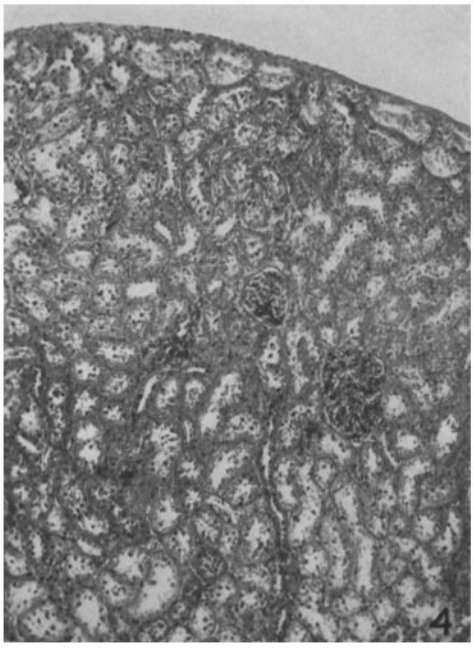
FIG. 10. Cortex of the kidney from Experiment 7 with complete obstruction of the ureter for 21 days.



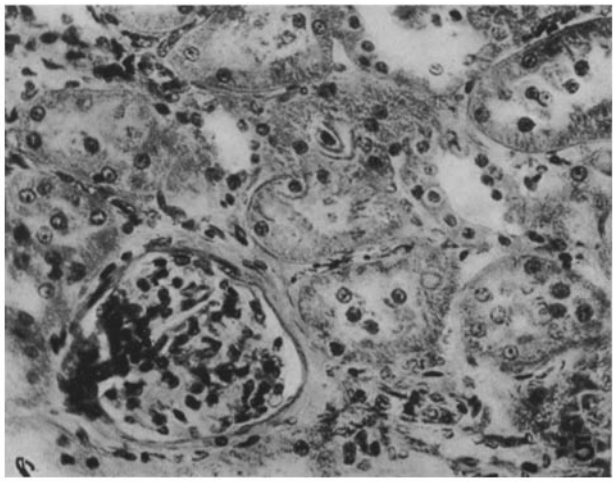


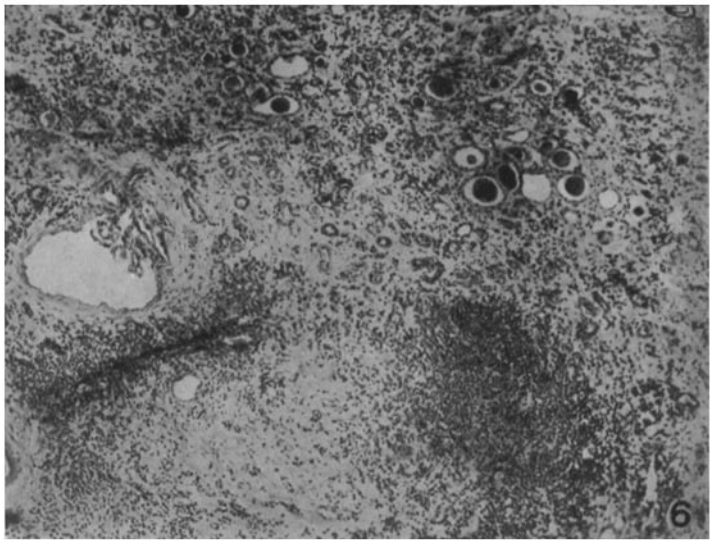
(Johnson: Renal function in hydronephrosis.)



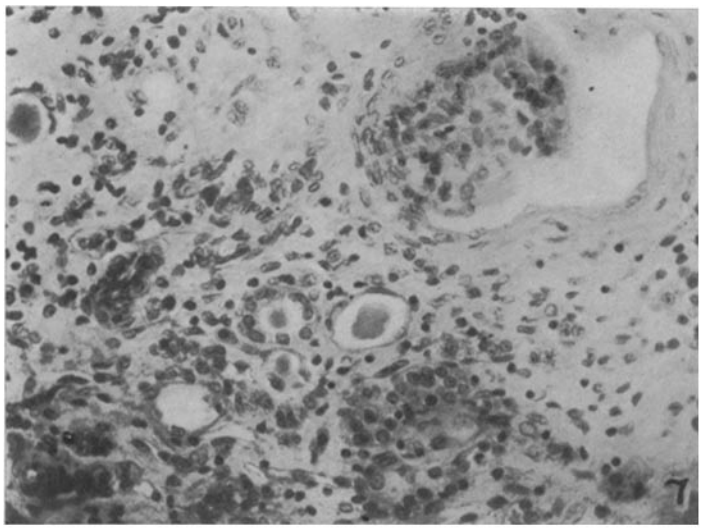


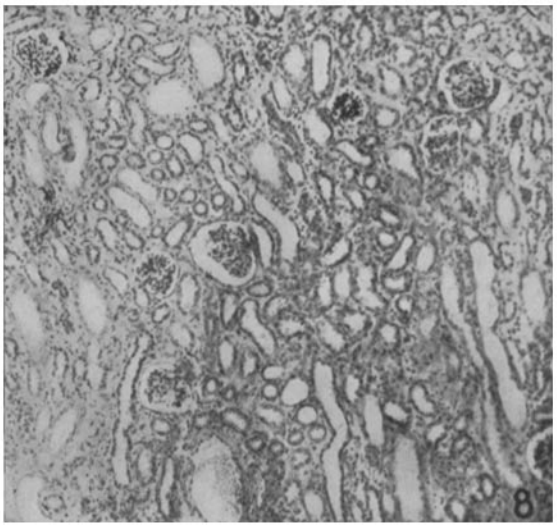
(Johnson: Renal function in hydronephrosis.



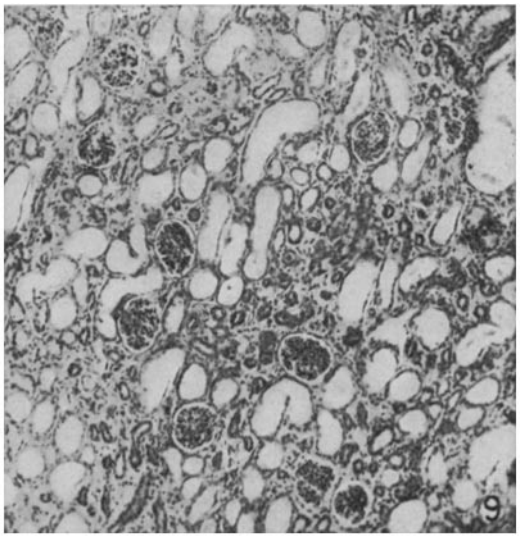


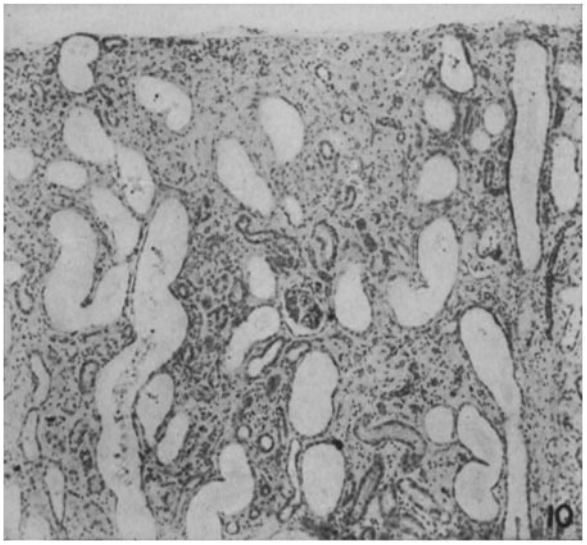
(Johnson: Renal function in hydronephrosis.





(Johnson: Renal function in hydronephrosis.)





(Johnson: Renal function in hydronephrosis.)