EXPERIMENTAL ATRESIA OF THE URETER.

BY TORALD SOLLMANN, W. W. WILLIAMS AND C. E. BRIGGS.

(From the Pharmacological Laboratory of Western Reserve University, Cleveland, Ohio.)

The effects of the complete and permanent occlusion of one ureter have been studied by numerous investigators. The older literature, which is summarized by Lindemann, bears mainly on the morphological changes occurring in the kidney, the ureter of which was ligated. The more recent experiments have dealt particularly with the changes observable in the opposite kidney, with the object of investigating the existence of auto-nephrotoxins. The functional changes produced in the kidney by ligation of its ureter have been touched upon only incidentally. This last condition suggested the present research, but in the course of this study we also controlled the morphological observations of previous investigators.

OPERATIONS AND MORPHOLOGICAL CHANGES.

Operations.—Four dogs were operated on August 7, 1903, and the right ureter ligated about 5 centimeters from the pelvis of the kidney. Dog (1) died after 31 days. Dog (2) sickened about the 72d day, and was killed on the 74th day. On the 107th day dogs (3) and (4) were re-operated under ether, and urinary fistulae were established with the right kidneys. Dog (4) died 9 days later, or 116 days after the primary operation. Dog (3) was killed on the 185th day (the 78th day after the second operation).

The kidneys of all dogs showed more or less similar gross and microscopic changes with the exception of (4), in which the lesions were masked by a generalized renal infection.

Operated Kidneys.—The kidneys on the ligated side were enlarged and the pelvis contained from 88 to 250 c.c. of fluid. Minus

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the fluid, the weight of the operated kidney was only one-fourth to two-thirds of that of the sound kidney. The capsule of the kidney as well as Bowman's capsule were slightly thickened. Most of the glomeruli were shrunken and many were replaced by fibrous tissue. The epithelial cells of the convoluted tubules showed cloudy swelling, necrosis and pressure atrophy. Most of the tubules were obliterated. The collecting tubules ran generally parallel to the cortex and showed slight dilatation in places. The interstitial tissue was increased, with slight round-cell infiltration. The arteries showed various degrees of endarteritis and periarteritis.

Sound Kidneys.—The kidneys on the non-ligated side were always slightly enlarged and microscopically showed slight cloudy swelling and moderate congestion especially of the medulla.

PROTOCOLS.

Dog 1.—The right ureter was ligated 5 cm. from the kidney on August 7, 1903. The dog, without apparent cause, died October 7, 1903 (31 days).

Autopsy.—Putrefactive odor. Very small external scar. Internally small adhesions. Left kidney seems normal. Pelvis of the right kidney distended. Right ureter dilated to about 1 cm. in diameter.

Sound kidney weighs 31 grams.
Operated kidney weighs 124 grams with liquid.
Operated kidney weighs 21 grams without liquid.

Therefore, 103 grams of liquid.

The right kidney consists of a sac with walls about 2 mm. in thickness.

Microscopic Examination.—Right kidney: The capsule is slightly thickened. The glomeruli show moderate thickening of Bowman's capsule. The capsular spaces are not dilated. Some tufts are considerably shrunken, with increased growth of fibrous tissue; and an occasional tuft is replaced by fibrous tissue. The convoluted tubules are for the most part obliterated, although there are occasional normal ones and others are lined with only a small fringe of ragged protoplasm containing apparently healthy nuclei. The collecting tubules are all pressed to one side and their general direction is parallel to the kidney capsule. Most of them have slightly flattened epithelial cells with nuclei in good condition. There is apparently slight dilatation of some. The blood vessels show moderate congestion. The arteries show slight internal thickening and more marked
periarteritis. The interstitial tissue is increased throughout, with a few small areas of round cell infiltration.

Left kidney shows slight cloudy swelling and moderate congestion especially of the medulla.

Dog 2.—The right ureter was ligated 5 cm. from the kidney on August 7, 1903. Reported sick on October 21. On October 23, dog receives morphin at 8:15 A.M. and ether at 8:45. Weight 10 kg. Cannula placed in left ureter at 9:24. Cannula placed in right ureter at 9:40. Urine flowed very slowly from the right kidney and ceased entirely at 10:15. At 10:30 A.M. 100 c.c. of 10 per cent. crystallized sodium sulphate was injected slowly into femoral vein. Dog died suddenly without assignable cause. Lived 74 days.

Sound kidney weighs 42 grams.
Operated kidney weighs 150 grams with liquid.
Operated kidney weighs 20 grams without liquid.

Therefore, 130 grams of liquid.

The pelvis of right kidney is markedly dilated.

Microscopic Examination.—Right kidney. The capsule is slightly thickened. The glomeruli show slight thickening of Bowman's capsule. Many capsular spaces are dilated and the tufts occupy one-third to one-half the space, the remaining portion filled with finely granular material. Some of the tufts are shrunken and many are obliterated. Nearly all of the convoluted tubules are obliterated or represented by a mass of nuclei surrounded by a little granular protoplasm. A few are considerably dilated and lined with large cuboidal epithelial cells. The collecting tubules run more or less parallel to the cortex. Many are obliterated and the majority of the remaining ones show varying degrees of dilatation. Many are filled with casts. The interstitial tissue is everywhere increased with small areas of leucocytic infiltration. There are a few small areas in the cortex that look like healed infarcts. The arteries show slight intimal and more marked adventitial thickening. Slight congestion. The pelvic lining is thickened and consists of several layers of rather large polygonal cells.

Left kidney as in dog No. 1.

Dog 3.—The right ureter was ligated 5 cm. from the kidney on August 7, 1903. On November 25 (107 days after the primary operation) a second operation was performed and 88 c.c. of urine were gently squeezed out and a urinary fistula was established. On the next day the dog was fairly lively. No food was given until November 30. On December 4 the skin was gaping, but the dog was lively. Ureter fistula was not patulous to a probe which could
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be introduced only 5 cm. On February 11, 1904 (185 days after the primary operation and 78 days after the second) the dog was very well, although the abdominal wound was not quite healed. The fistula was moist. Could pass probe to kidney. 9:10 A. M. 2 c.c. 4 per cent. morphin, 9:30 ether. Right kidney found shrunken and empty. Cannulae were placed in the ureters. The right remained perfectly dry; the left showed good secretion, as follows:

From 10:45 to 11:07 the average secretion of urine was 0.2 c.c. per minute.

From 11:07 to 11:10 225 c.c. of 5 per cent. cryst. sodium sulphate at 40° C. was injected into the femoral vein.

From 11:07 to 11:15 average secretion of urine was 1.75 c.c. per minute.

From 11:15 to 11:25 average secretion of urine was 3.6 c.c. per minute.

The right cannula remaining dry, it was reinserted nearer the kidney. It filled with a little bloody serum which could not have been more than 2 or 3 c.c. and no fluid was secreted during the experiment.

From 11:25 to 11:37 average secretion of urine was 2.6 per minute.

From 11:37 to 11:42 average secretion of urine from the left kidney almost ceased, being 0.2 c.c. per minute (probably due to shock).

From 11:42 to 11:44 second injection of 200 c.c. sodium sulphate solution. Left kidney starts secreting at once.

From 11:45 to 11:50 average secretion of urine was 2.5 per minute.

From 11:50 to 11:55 average secretion of urine was 2.5 per minute.

From 11:55 to 12:06 average secretion of urine was 2.5 per minute.

The left ureter was clamped at 12:08. Between 12:10 and 12:12 a third injection of 200 c.c. sodium sulphate solution was made. At 2 P. M. only 2 drops had escaped from the right ureter. The dog was killed.

Sound kidney weighs 43.2 gm.
Operated kidney weighs 9.6 gm.; about 4.5 mm. thick.

The right kidney is small, measuring 30 mm. in length, 16 mm. in breadth, and 8 mm. in thickness. On section it is very dense and the pelvis contains no fluid. The left kidney measures 41 mm. in length, 31 mm. in breadth, and 21 mm. in thickness.

Microscopic Examination.—Right kidney. The capsule is somewhat thickened. The glomeruli show slight thickening of Bowman's capsule. Many capsular spaces are dilated and the tufts are shrunken. A few glomeruli are obliterated and replaced by fibrous tissue. The convoluted tubules are mostly obliterated, some are represented by a confused mass of epithelial cells with their nuclei showing varying degrees of degeneration. In small discrete areas, usually near the cortex, are a few tubules lined with large epithelial cells and apparently in good condition. The collecting tubules are mostly obliterated and some of the remaining ones are dilated and contain casts. The interstitial tissue is increased throughout with a few small hemorrhagic and scattered areas of leucocytic infiltration in it. The blood vessels are moderately congested and show marked adventitial thickening. The pelvic epithelium is thickened and consists of several layers of large cells.

Left kidney. The glomeruli are larger than normal; the tubules are apparently larger, with normal epithelial cells. Moderate congestion.

Dog 4.—The right ureter was ligated 5 cm. from kidney on August 7, 1903. On November 25 (107 days after the primary operation) a second operation was performed and 88 c.c. of urine were gently squeezed out and a urinary fistula established. On the next day the dog was fairly lively. No food was given until November 30. The dog gradually became sick and at noon of December 4 was comatose and died in the afternoon (116 days after the primary operation and 9 days after the second). The dog was kept frozen and was autopsied on December 7, 1903. No peritonitis. Right kidney was enormously enlarged with very thin walls and the pelvis was distended with 225 c.c. of reddish, turbid fluid, containing some pus. No sufficient cause of death could be assigned.

Microscopic Examination.—Right kidney. The capsule is much thickened and numerous vessels connect it with the cortex. Bowman's capsule is also considerably thickened. Most of the glomeruli are replaced by fibrous tissue, although a few tufts remain which are much shrunken and encroached upon by fibrous tissue. Practically no tubules are to be seen. The interstitial tissue is increased. The arteries show varying degrees of endarteritis and several rather large ones are thrombosed. There are a few small hemorrhages. The greatest part of the sections is composed of necrotic tissue with here and there indefinite remains of glomeruli and tubules and everywhere marked infiltration with polymorphonuclear leucocytes predominating although no definite abscesses are to be seen.
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CHEMICAL EXAMINATION OF THE FLUIDS IN THE OCCLUDED URETERS.

The results of these examinations are presented in Table I, the analytical methods appearing in the appended notes. Column III gives a summary of the fluid obtained after the first operation in the four dogs. The fluid from the left ureter of the congenital atresia reported by Dr. Allen is also included in this table.

1. Duration of the Atresia in the Human Case (see page 82 of the Journal).
   - In the thirteen years which elapsed since the establishment of the right kidney fistula, no urine was voided from the bladder, so that the left ureter must have been completely occluded for at least this period of time. It is probable, however, that the atresia was congenital, i.e., that it persisted for 16 years.

2. Quantity of Fluid.—The quantities are only approximate, generally somewhat too low.

3. Color of Human Fluid.—After the precipitation of the proteid, the fluid has a light straw, serum color, which is slightly darkened by nitric acid and by heating with soda.

4. Color of Dogs' Urine, 3 and 4.—This is not altered by precipitating the proteids.

5. Color of Second Accumulation of Fluid in Dog 4.—This is fairly deep red, with an abundant slimy grayish red precipitate. The filtrate, after the removal of the proteids, is very faintly colored.

6. Odor of Human Fluid.—This is faint, somewhat like serum, on heating. It is not urinous, even on boiling with soda.

7. Specific Gravity.—This was taken with a picnometer in the human case, with areometers in the dogs.

8. Depression of Freezing Point.—Determined by Beckmann's apparatus, $\Delta = 0.86$ in the human case.

9. Total Solids.—10 c.c. dried at 110° C.

10. Ash.—Incineration of 10 c.c. This is apt to show a trifle higher than it should, if the incineration is incomplete.

11. NaCl.—Incineration of 5 to 10 c.c. with NaNO$_3$ and Na$_2$CO$_3$ solution in HNO$_3$ to neutralization; titration with AgNO$_3$. Chromate indicator.

12. Non-chloride Ash.—Difference between total ash and NaCl. This is apt to be too high, see (10).

13. SO$_3$.—Gravimetrically with barium, in 20 c.c.

14. P$_2$O$_5$.—The determination of SO$_3$ and P$_2$O$_5$ is not very exact on account of the small quantity.

15. Organic Solids.—Difference between total solids and ash.

16. Total Coagulable Proteid.—10 to 50 c.c. of the fluid are acidulated with acetic acid and boiled with an equal volume of saturated sodium sulphate or chlorid. The precipitate is washed with water, alcohol and ether, dried at 110° C and weighed.

*See page 82, this number of the Journal.
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### TABLE I

**Analytical Data of the Fluids Obtained from the Ligated Kidney.**

<table>
<thead>
<tr>
<th>Column I.</th>
<th>II.</th>
<th>III.</th>
<th>IV.</th>
<th>V.</th>
<th>VI.</th>
<th>VII.</th>
<th>VIII.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time between occlusion of ureter and collection of fluid.</strong></td>
<td>At least 13 years (1).</td>
<td>31 to 107 days.</td>
<td>31 days</td>
<td>74 days.</td>
<td>107 days.</td>
<td>107 days.</td>
<td>78 days.</td>
</tr>
<tr>
<td><strong>Quantity of fluid (2).</strong></td>
<td>200 c.c.</td>
<td>88 to 130 c.c.</td>
<td>103 c.c.</td>
<td>130 c.c.</td>
<td>88 c.c.</td>
<td>88 c.c.</td>
<td>225 c.c.</td>
</tr>
<tr>
<td><strong>Sp. gr. (7).</strong></td>
<td>1.060</td>
<td>1.069</td>
<td>1.068</td>
<td>1.069</td>
<td>1.065</td>
<td>1.088</td>
<td>1.018</td>
</tr>
<tr>
<td><strong>Depression of freezing point.</strong></td>
<td>0.754°C (8)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Total solids (g).</strong></td>
<td>—</td>
<td>1.8 to 2.1</td>
<td>2.115</td>
<td>2.035</td>
<td>1.800</td>
<td>5.805</td>
<td></td>
</tr>
<tr>
<td><strong>Ash (10).</strong></td>
<td>0.85</td>
<td>0.5 to 0.95</td>
<td>0.936</td>
<td>0.850</td>
<td>0.845</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Cl as NaCl (14).</strong></td>
<td>0.83</td>
<td>0.68 to 0.75</td>
<td>0.72</td>
<td>0.65</td>
<td>0.72</td>
<td>0.68</td>
<td>0.59</td>
</tr>
<tr>
<td><strong>Non-chloride ash (12).</strong></td>
<td>0.065</td>
<td>0.085 to 0.206</td>
<td>0.065</td>
<td>0.085</td>
<td>0.065</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>SO₄ (15).</strong></td>
<td>0.046</td>
<td>0.033 to 0.065</td>
<td>—</td>
<td>0.033</td>
<td>0.065</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Organic solids § (15).</strong></td>
<td>0.055</td>
<td>0.939 to 1.230</td>
<td>1.159</td>
<td>1.230</td>
<td>0.955</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Total Usable Protein § (16).</strong></td>
<td>0.06</td>
<td>0.95 to 0.85</td>
<td>0.75</td>
<td>0.697</td>
<td>0.860</td>
<td>0.390</td>
<td>3.973</td>
</tr>
<tr>
<td><strong>Non-protein Nitrogen § (21).</strong></td>
<td>—</td>
<td>0.086 to 0.766</td>
<td>0.080</td>
<td>0.126</td>
<td>0.056</td>
<td>0.126</td>
<td>—</td>
</tr>
<tr>
<td><strong>Urea § (22).</strong></td>
<td>0.044 (24)</td>
<td>0.02 to 0.065</td>
<td>0.082</td>
<td>0.125</td>
<td>0.056</td>
<td>0.126</td>
<td>—</td>
</tr>
<tr>
<td><strong>Non-urea nitrogen § (26).</strong></td>
<td>—</td>
<td>0.025 to 0.0054</td>
<td>0.025</td>
<td>0.0054</td>
<td>0.053</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Reducing substance.</strong></td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Sediment.</strong></td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Round cells of various types, largely degenerated.</strong></td>
<td>A few blood and other cells (leuco - cytes?) largely degenerated.</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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</tr>
</tbody>
</table>

All the dogs' urines have a slightly alkaline reaction.
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17. Globulin.—Addition of equal volume of saturated ammonium sulphate.
19. The percentage of albumin is obtained by subtracting the globulin from the total proteid.
22. Urea Nitrogen.—Folin's method on filtrate of (16).
24. Urea in Human Fluid.—This was not determined by Folin's method, but by estimating the nitrogen in the boiled filtrate. This gave a small precipitate with phosphotungstic acid; some proteid had therefore probably escaped precipitation, and the figure for urea is too high, and unreliable. The presence of urea was shown qualitatively by the effervescence of a hypobromite solution.
25. Qualitative Tests for Urea were Positive.
26. Non-Urea Nitrogen.—Difference between (21) and urea nitrogen.

SUMMARY, DISCUSSIONS OF THE RESULTS, AND CONCLUSIONS.

Previous investigators have found that complete occlusion of the ureter may lead either to hydronephrosis or to atrophy. In Lindemann's series of six dogs, for instance:

Two animals showed simple hydronephrosis, three animals showed simple atrophy, and in one animal the kidney was slightly enlarged and the ureter and pelvis dilated, but fluid was absent. In his series of four rabbits, all showed hydronephrosis.

The result, whether hydronephrosis or atrophy, is evidently not determined by the time elapsing after the operation. Lindemann found that the intrapelvic pressure resulting from the ligation obliterates the lumen of the vessels, first of the veins and subsequently of the arteries; but that this is compensated by an increase of the collateral blood supply through the capsule, the degree of this compensation determining the presence or absence of hydronephrosis. If the blood supply is free, the fluid after tapping will accumulate again and again.

It is somewhat remarkable that all of our dogs showed hydronephrosis after the first operation. The results of establishing a urinary fistula differed in the two cases in which it was tried: The fluid did not re-form in Dog 3 even when sodium sulphate was
injected; whereas in Dog 4, a very abundant quantity of fluid re-
accumulated spontaneously; but it differed notably in composition
from the original fluid, having more the character of a purulent
inflammatory exudate.

The histological changes consist in necrosis of the renal cells,
obliteration of the glomeruli, increase of connective tissue, and
endarteritis and periarteritis. Different areas in the same kidney are
affected in very different degree, some areas appearing almost nor-
mal. The glomeruli are generally less altered than the tubules.
The collecting tubules are generally displaced so as to run parallel
to the surface; many are dilated. The changes correspond closely
to those described by Lindemann.

The sound kidneys showed slight hyperaemia and hypertrophy,
but no necrosis. This corresponds with the findings of Pearce
and of Ames.

The uniformity in chemical composition of the fluid obtained,
after the first operation, from the four dogs, as shown by Column
III of Table I, is very striking, and points to a uniform origin by
a process which is but little affected by the interval elapsing after
the operation. The specific gravity, total solids and proteids corre-
spond to those of a very dilute lymph, being but a trifle above those
of cerebro-spinal fluid and aqueous humor, and much lower than
those of serum, lymph and most cystic fluids (the proteid content of
the latter being generally from 2 to 6.5 per cent.). The human fluid
(Column II) which had remained in the kidney for a very long time
had a particularly low proteid percentage; while that of the second
fluid of Dog 4 (Column VIII) was very much higher; this last
fluid having a pronounced inflammatory character and being of
recent formation.

The absence of notable amounts of the specific urinary constitu-
ents is particularly important. Odorous principles are entirely

4 The research was originally undertaken at the suggestion of one of us
(Briggs), to decide whether it would be possible to re-establish the function of
the kidney after temporary ligation of the ureter. The answer must be in the
negative, at least when a considerable interval elapses before the establishment
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absent. Urinary pigments appear to be present in the four dogs' urines, but absent from the human case, and after the second operation in case of the dogs. It seems fair to assume that the pigments were secreted shortly after the ligation, when the kidneys were still functional, and that they were reabsorbed with extreme slowness.

Urea was present in all the fluids, but its quantity was very small in the dogs, and probably in the human case. It is on the whole somewhat greater than in the serum (0.103 per cent., in place of 0.05 per cent.), but the difference may be within the analytical error. The same applies to the ammonia, phosphates and sulphates.

An important difference between these fluids on the one hand and blood serum, lymph and ordinary exudate on the other, lies in the higher contents of chlorid, and the consequently greater molecular concentration. The ordinary chlorid content of body fluid varies between 0.55 and 0.70 per cent., mean about 0.6 per cent (as NaCl), while that of the first kidney fluid, in the dogs, varied between 0.68 and 0.75 per cent., mean 0.725 per cent.; that of the human fluid was 0.83 per cent., that of the second fluid of Dog 4 only 0.52 per cent. The depression of the freezing point in the human case was 0.715 ° C., as against the normal value, for human serum, of 0.491 to 0.562. (Possibly the blood of this patient had a higher concentration than normal, since uremia existed.)

The high chlorid percentage has evidently no relation to the length of time during which the fluid sojourned in the kidney. It is probably to be explained by the relatively slow absorption of this ion from the kidney pelvis. It is also to be remarked that cerebrospinal fluids generally have a somewhat high chlorid content (0.573 and 0.6 per cent.), but this never reaches the height of these ureteral fluids.

Conclusion.—The fluid accumulating in the kidney, after unilateral ligation of the ureter, consists in the main of a transudate,

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5 Lindemann (l. c.) and Starling (Schaefer's Text-book of Physiology, 1898, i, 650) state that the fluid in atresia of the ureter is of light color, low specific gravity, and very low urea content.

poor in proteids, but somewhat enriched in chlorids and perhaps in urea, phosphates and sulphates. A small quantity of pigment is also retained. The fluid is probably formed by filtration through a filtering surface which is not freely permeable to proteids. A process of reabsorption also goes on simultaneously, in such a manner that the soluble solids are somewhat increased (perhaps to counterbalance the osmotic value of the serum proteids). There is no evidence that the remaining specific renal elements play any part in the formation of this fluid, although this part is not excluded.

We are indebted to Dr. Wm. T. Howard, Jr., for the preparation of the histological material and for valuable criticism.