THE FUNCTION OF THE KIDNEY WHEN DEPRIVED OF ITS NERVES.*

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PLATES 81 TO 83.

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The question as to what may be the function of a kidney excluded from all nervous influences is not settled at present, in spite of many experimental attempts by various observers. The reason for this lies in the fact that none of the methods employed to solve the question have been free from criticism. That the kidney is plentifully supplied with nerves is well known; but that these have any further function than that of vasomotor control has not been proved. Attempts to demonstrate secretory fibers to the kidney in either the vagus or splanchnic nerves or their branches have given only conflicting evidence.

Removal of all the nerve filaments at the renal hilus by dissection would exclude the kidney from the nervous system, so that its function could be compared with that of a normal organ. But on examining the situation more closely one finds that such method of nerve removal has been found most uncertain in its results.¹ This is due to the fact that the nerve filaments supplying the organ not only lie in a network closely applied to the renal vessels, but also run partly within the walls of these vessels. It has therefore been suggested to use some chemical means of destruction, such as painting with carbolic acid after the dissection. But even under these circumstances one is never absolutely sure that all nerves have been removed. Also, in such thin walled vessels as the renal vein, car-


bolic acid extensively used may cause a local reaction leading to thrombosis. For these or other reasons, none of the evidence thus far brought forward in regard to the function of such kidneys is convincing.

It has been shown by workers on the methods and possibilities of blood vessel suture that a kidney removed from the body of an experimental animal, and later reimplanted by restoration of the circulation, is able to support life in a presumably normal fashion. With one exception, however, all such investigators have been engaged in demonstrating the possibility of the operation, and have not concerned themselves with the detailed physiological function of the organ.

In the present investigation it was desired to examine in detail the function of a kidney which had been removed from the body and subsequently replaced. By this method it is certain that the organ is entirely outside the sphere of all nervous influences for a time at least, if not permanently. Furthermore, the response of such a kidney to the various functional tests gives at least indirect evidence on the question of secretory innervation.

HISTORICAL.

Asher\(^2\) is one of the most recent investigators to attempt the demonstration of secretory nerves to the kidney. With his coworkers, Pearce and Jost, he has made observations which seem to show that the vagus nerve carries secretory fibers, while the splanchnic carries inhibitory ones; at least so far as the water output of the kidney is concerned. Jungmann and Meyer,\(^3\) after cutting the splanchnic, found an increase of urine and of sodium chloride delivered from the kidney on the same side as the severed nerve. Rhode and Ellinger,\(^4\) however, obtained different results, which led them to believe that the splanchnic has an inhibitory action. The difficulty seems to lie in the fact that in the methods

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employed to elucidate the problem, the circulatory effects of vagus or splanchnic stimulation completely mask other possible effects.

More recently Pearce⁶ has employed the method of Barcroft in which the oxygen consumption of the kidney is used as the index of cellular activity, and he has been unable to confirm his previous work done with Asher.

Transplantation or reimplantation of the kidney has been found surgically possible by Carrel, Stich, and a few others.⁹ The most recent worker on this subject has been Lobenhoffer. His is the only work which attempts in any detailed way to study the function of a kidney so treated. He united the severed renal vessels to those of the spleen in dogs, and was successful in ten instances. After removal of the other kidney, the water and salt output, as well as that of lactose and sugar caused by phloridzin, was studied. His results show that such a kidney is able to meet not only the ordinary demands of life, but also the excessive ones set up by the experimental injections. Further details of his work will be discussed later.

Zaaijer⁷ has recently reported the survival and complete health of a dog bearing a single kidney, which had been transplanted to the iliac vessels 6 years previously.

Method.

The experiments were carried out on large dogs of both sexes. After examination of the various regions where the kidney might be placed, it was decided not to transplant the organ, but to reunite it to its own severed vessels; for in this way the nearest approach to normal physiological conditions is secured.

Although the left kidney of the dog is somewhat more accessible than the right, and has slightly longer vessels, the renal artery on the left is often bifurcated, or even may leave the aorta as two separate vessels. This reduces the caliber of the arteries and doubles the amount of time spent in sewing. The right side was chosen, therefore, in nearly all instances.

Ether was used by the intratracheal method in all the experiments. This method of administration is important, because by its use the respiratory movements can be reduced to a minimum, or even abolished. A motionless field is thus obtained which is of great aid in accurate and speedy sewing.

The animals were prepared for operation by shaving over the abdomen and far down onto the flanks. This area was then made sterile by soap and water, alcohol, ether, and tincture of iodine. A catheter was placed in the bladder, and in the case of male dogs, was carried off to the left side where it remained during the operation. The surgical asepsis was in every respect as strict as possible; gowns and gloves were worn, although during the actual suture of the blood vessels the gloves had to be removed, following which the hands were carefully coated with sterile vaselin.

**Transverse Abdominal Incision.**—Incision is made transversely across the abdomen just above the level of the umbilicus, and extending from the outer border of the left rectus abdominis across the right side down to the erector spinae group of muscles (Fig. 1). This is well shown in the illustrations. Failure to prolong the incision far enough towards the posterior wall of the abdominal cavity prevents easy access to the whole kidney region, and makes the suture difficult or impossible.

The abdomen is entered in layers, careful attention being paid to hemostasis. After incision of the skin and subcutaneous tissues, the fascia of the external oblique is picked up on the right, at the outer border of the rectus. It is lifted up, incised, and the incision prolonged well toward the flank. The internal oblique is similarly treated. The rectus is dissected bluntly from its underlying sheath as far as the middle line, when it is cut through. The left rectus is similarly divided. After entering the abdomen through the linea alba, the transversalis can be quickly cut down in either direction (Fig. 2). The wound gapes widely and needs no retraction. All the intestines

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*This method of entrance to the abdominal cavity is of great aid in the performance of other operations, such as Eck fistula and those involving the biliary passages or adrenal glands. It is illustrated not because the procedure is in any way new, but because I have found that its value is not generally recognized by laboratory investigators.*
except the duodenum and descending colon, are then lifted out of
the abdomen to the left, where they lie covered by silk handkerchiefs
impregnated with liquid vaselin (Fig. 3).

Preparation of Kidney and Renal Vessels for Suture.—After
section of the peritoneum about the kidney, it is lifted out and turned toward
the middle line of the body where, surrounded with gauze, it is gently
held by the assistant. In this position the renal artery comes first
to view, and it is carefully cleaned as far as the aorta of all surrounding
tissue and nerves. This is done by blunt dissection and by
wiping with dry gauze. The kidney is allowed to fall back into place,
and the vein is similarly cleaned as far as the vena cava. The ureter
is next stripped downward for about 6 or 7 cm. The field is then
carefully washed with salt solution, every bleeding point caught
and tied, and after drying, the whole is coated with liquid vaselin,
including the kidney and its vessels. The two rubber-covered
serrefines are then placed on the artery, two others on the vein, and
the vessels are cut between them. The ureter is cut long. The
kidney is then removed from the body and placed on a clean gauze
pad. The gloves are now removed.

Vessel Suture.—The ends of the severed vessels are washed
quickly with salt solution from a bulb pipette, till every trace of
blood is removed. They are then coated with liquid vaselin. The
adventitia is removed from the ends of the arteries in the usual way,
after which the whole field within the abdomen is covered with vase-
lined silk handkerchiefs leaving only the stumps of the renal vessels
protruding. These handkerchiefs are held in place by brass clips
used by stationers, called “O.K. paper fasteners.”

The most exacting and important part of the vascular suture
lies in placing the three primary guide or tension stitches. This is
made much easier by using a suture armed with two needles, one at
either end. In this way the suture can always be passed from within
the vessel outward. The circumference of the vessel ends must be
accurately divided into thirds by these tension sutures.

The artery, being behind the vein, is sewed first, using an over-
and-over stitch. This is followed by suture of the vein. The serre-
finite clamps are then removed from the vein and the vessel is allowed
to fill under moderate pressure, rolling it a bit between the thumb
and finger. The artery is next freed while held between the thumb and finger so as partially to control the tension during the first few moments of blood flow. After the vascular suture is ended, the ureter is reunited by the invagination method of Van Hook. Following this, the operative field is cleaned of blood, and the peritoneum readjusted by a few interrupted sutures about the periphery of the kidney. Special pains should be taken to see that the kidney is replaced high enough toward the liver so that there is no angulation of the vein.

Closure of the Abdomen.—The next step consists in closing the abdomen after the bowels have been replaced. This is made certain by using first a mattress suture of stout silk placed in the linea alba. After tying this, the severed abdominal muscles can easily be approximated in layers. A continuous suture is used for the transversalis, including at the same time the peritoneum. Mattress stitches are used for the recti, while the obliques are held by interrupted sutures. Closure of the subcutaneous tissue and skin completes the operation. Silk is used throughout the operation, both for ties and sutures.

The dog is placed in a metabolism cage so that the urine can be accurately collected and measured.

The operation is a difficult one, but after some experience it was found possible to restore the circulation in about an hour following its interruption. Forty-three dogs were subjected to operation, of which sixteen survived in suitable condition for further physiological observations.

Examination of the Renal Function.

The operated animals were divided into two series. In the first, the function of the reimplanted kidney was compared with that of the intact one, at periods varying from 2 days to 3 weeks after the primary operation. For this purpose the animal was anesthetized with paraldehyde, each ureter brought out onto the flank through

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lumbar incisions, and the urines were compared. This method has been described in a previous communication.10

The dogs of the second series were subjected to removal of the unoperated kidney at times varying from 5 to 14 days after the primary operation. The work of their remaining, reimplanted kidney was later examined and compared with that of control dogs, in whom a single nephrectomy had been done.

Series I.

Two typical protocols will suffice to show the results of this series.


June 18. Has made a good recovery. Blood urea is 0.302 mg. per liter.11 Excretion of phenolsulphonephthalein given intravenously is 51 per cent in 2 hours.11

June 19. Given paraldehyde,11 1.7 cc. per kilo of body weight, by stomach tube, followed by 200 cc. of water. Ureters exposed in loins, and cannulae introduced delivering into test-tubes. Carotid blood pressure recorded on kymograph.

11.10 a.m. Urine appears without delay from each side. Collected for 1 hour.

12.10 p.m. 5.0 gm. of sodium chloride in 20 cc. of water given intravenously. Good diuresis from each side; urine collected for 1 hour.

1:10 p.m. Animal killed. The blood pressure during the experiment varied from 128 to 138 mm. of mercury, except just after the injection of the hypertonic salt solution. The sutured vessels were free from obstruction.

Microscopic examination of the reimplanted kidney showed the capsular spaces wide for the most part, and the glomerular tufts containing a considerable amount

11 As was shown in the communication noted above (Quinby and Fitz10) the two most dependable tests of renal function are the excretion of phenolsulphonephthalein and the estimation of the blood nitrogen or blood urea. The urease method of Marshall (Jour. Biol. Chem., 1913, xv, 487) was used. By this the normal amount of blood urea of the dog is found to lie between 0.200 and 0.380 or 0.400 mg. per liter. The phenolsulphonephthalein excretion was estimated by the method of Rowntree and Geraghty (Jour. Pharmacol. and Exper. Therap., 1909–10, i, 579). Paraldehyde was used, because in proper dosage it causes neither diuresis nor lowered blood pressure. It must be used fresh, however, because it loses strength on exposure to the air, thus making the dosage uncertain.
of blood. The cells and nuclei of the tubules were well preserved except in a very few areas where a small amount of cellular desquamation had taken place. The blood vessels were everywhere dilated, but no evidence of thrombosis or infarction could be found. A considerable number of hyaline bodies were seen in the collecting tubules, evidently casts. The uninvolved kidney was normal in all respects. Its capsules showed active diuresis, but the blood vessels were not so evidently dilated as were those of the operated organ.

<table>
<thead>
<tr>
<th></th>
<th>Amount of urine</th>
<th>Percentage of NaCl</th>
<th>Amount of NaCl.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st hr.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before diuresis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>5.0</td>
<td>0.90</td>
<td>0.045</td>
</tr>
<tr>
<td>Left</td>
<td>2.5</td>
<td>0.55</td>
<td>0.013</td>
</tr>
<tr>
<td>2nd hr.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After diuresis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>60.0</td>
<td>0.95</td>
<td>0.570</td>
</tr>
<tr>
<td>Left</td>
<td>22.0</td>
<td>0.95</td>
<td>0.209</td>
</tr>
</tbody>
</table>

* The chlorides were determined by the Volhard method at first; later by that of McLean and Van Slyke (Jour. Biol. Chem., 1915, xxi, 361).

We see that here the kidney without nerves shows an increased function over the normal one, both before and after diuresis.

11.05 a.m. Flow from right kidney begins a little later than from left which started immediately on delivering ureter. Urine collected for 1 hour after flow from each was established.
12.16 p.m. 5.0 gm. of sodium chloride in 20 cc. of water injected intravenously. Marked diuresis.
1.20 p.m. Animal killed. Blood pressure average was 133 mm. of mercury. Renal vessels without trace of clot, though there were a few adhesions about the kidney. A sample of blood drawn just before death showed 0.354 mg. of urea per liter.
Microscopic examination showed that both kidneys were normal in all respects except that in the one previously reimplanted a few mitotic figures could be found in the tubular cells after careful search. These were evidently the sequel of previous cellular degeneration.
In this experiment the operated kidney has a function about the same as that of the normal side.

These two protocols fairly represent the findings in this first series which comprised eleven dogs. For a period following operation varying from 10 to 14 days the denervated kidney shows an increased absolute function both for fluid and salt, as compared with the normal kidney. At times this increase is relative as well. This is true of the unstimulated organ, and especially so of the one subjected to the diuretic action of sodium chloride. Beyond this period, however, the balance is regained, so that each organ, operated and intact, divides the labor in very nearly equal parts.

We see here also that absence of the renal nerves abolishes the temporary inhibition of flow so often seen normally after the handling of the ureters necessary for their exposure in the loin. Urine from the denervated side always flowed immediately on section of the ureter; but in some instances the normal side showed an inhibition lasting for as long as 5 minutes. This is analogous to the temporary inhibition occasionally seen on passage of a ureteral catheter in man.

Series II.

The following is a typical protocol.
Nov. 23, 1915. Has made a good recovery; eats well and does not vomit.
Dec. 4, 1915. Ether. Lateral incision in left flank through which the kidney was removed after ligation of its vessels with silk. Wound closed in layers.
Dec. 7, 1915. Has made an excellent recovery. Passes 320 to 340 cc. of urine daily. Blood urea, 0.456 mg. per liter. Phenolsuphonephthalein, 60 per cent in
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2 hours. Urinary sediment shows a rare blood corpuscle; no casts; a few leukocytes. Sugar and albumin absent.

Dec. 11, 1915. Animal well. The 24 hour amount of urine has fallen somewhat and its concentration has increased.

Dec. 14, 1915. Has a rather marked balanitis, and does not urinate until the demand is imperative. After about 48 hours during which no urine was passed, voided a little over 700 cc.

Dec. 18, 1915. Balanitis has responded to irrigation with boric acid and animal is now well. Output of phenolsulphonephthalein, 50 per cent in 1 hour. No albumin or sugar.

Dec. 22, 1915. Intravenous injection of 500 cc. of normal (0.8 per cent) salt solution. Urine withdrawn by catheter at 30 minute intervals showed the following:

<table>
<thead>
<tr>
<th>Amount</th>
<th>NaCl per liter</th>
</tr>
</thead>
<tbody>
<tr>
<td>cc.</td>
<td>gm.</td>
</tr>
<tr>
<td>1st half hr.</td>
<td>83</td>
</tr>
<tr>
<td>2nd &quot; &quot;</td>
<td>62</td>
</tr>
<tr>
<td>3rd &quot; &quot;</td>
<td>48</td>
</tr>
<tr>
<td>4th &quot; &quot;</td>
<td>11</td>
</tr>
</tbody>
</table>

The urine before diuresis contained 19.10 gm. of sodium chloride per liter. It is thus seen that the kidney responds quickly to diuresis and regains its equilibrium within a normal time limit.

Jan. 31, 1916. Given 2 gm. of lactose intravenously. At the end of 5 hours 1.72 gm. were found in the urine.

Feb. 7, 1916. The 24 hour amount of urine has been measured for 65 days, giving an average of 180 cc. It contains neither albumin nor casts.

Feb. 9, 1916. Blood urea 0.320 mg. per liter. 61 per cent of phenolsulphonephthalein is excreted in 1 hour. Animal seems to be perfectly normal.

Four other animals of this series were killed after having shown normal kidney function for a month or longer. In each instance the kidney showed microscopic evidences of some hypertrophy of the elements, which usually occurs after unilateral nephrectomy. In two instances the kidney also showed a small depressed scar in the cortex with sclerosis of the normal elements and infiltration by connective tissue. These areas seemed to be the result of small focal necroses caused by interruption of the blood supply during operation. They were never of any considerable size, so that the function of the organ remained uninfluenced.
The results of this second series show that the life of dogs having a single reimplanted kidney is maintained in a normal manner, as estimated by renal functional tests as well as by other more general methods of observation.

DISCUSSION.

The experiments of the first series show that the immediate effect of loss of nerve control over the kidney is a period of overaction. This occurs in all cases, and in the presence of apparent health, as judged by the general condition of the animal, by the normal content of the blood in urea, and by a normal output of phenolsulphonephthalein. This period exists for a varying time, but balance has always been restored by the end of 2 weeks. The kidney recently deprived of its nerves is without vasomotor control; the organ is tense and appreciably enlarged; its vessels are dilated, and following the increase of blood flow there is an increase of function over that of the normal organ. Resumption of tone on the part of the blood vessels brings again normal function.

The results here would seem to be analogous to those vasomotor changes occurring in the splanchnic area after section of the cord. Following this operation there occurs a marked dilatation of the mesenteric vessels, but in a short time vasomotor control is again established. Vascular tone may be resumed through the intervention of other more peripheral nerve ganglia, or the smooth muscle fibers of the vessel wall may possibly regain their tone without such intervention. Also, in the kidney there are ganglion cells, especially in the region of the renal sinus, which may be responsible for the resumption of vasomotor control. Although we know that fibers of the sympathetic type are able to regenerate much more quickly than are those of the peripheral nerves, that they should be able to grow to the renal blood vessels and resume control over them within 2 weeks after section seems improbable. Certainly nerve control by the normal pathways could never have been regained in Zaaijer's dog whose kidney was sutured to the iliac vessels, or in those of Lobenhoffer who used the splenic vessels.

The time variation in regaining normal function is probably to be explained by the greater or less degree of surgical insult in the indi-
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No kidney showed normal function after being excluded from the circulation for longer than 1 hour and 20 minutes. The second series of observations indicates that a single kidney which has been removed from the body and subsequently reimplanted, can maintain normal life for apparently indefinite periods. Also such a kidney is able to respond to the excessive demands made on it by the injection of various test substances. My results in this group of experiments fairly coincide with those of Lobenhoffer, except in a few details. He found that the 24 hour amount of urine passed by his dogs varied between 1,500 and 2,000 cc. This is quite unusual. Normal cage dogs in a large number of observations made by us, are found to pass from 200 to 450 or 500 cc. of urine daily, having a specific gravity of about 1.030. Of course this is but a rough average, since all our animals had water continuously at hand, and must have taken varying amounts from day to day. Their diet was of meat. I feel, therefore, that the continuous excretion of such large amounts of urine tends to suggest the absence of complete return to normal conditions.

Again, in the three infusion experiments reported by Lobenhoffer, his animals put out amounts of water and salt which varied widely, though the quantities infused were the same. In the few infusions done by me the resulting outputs were all within 10 or 12 per cent of each other.

The observations on the relative values of the different methods used for testing renal function made by Quinby and Fitz showed that the estimation of the blood nitrogen, or that part of it composing the blood urea, and the output of phenolsulphonephthalein, together form the best means of measuring renal function. Further experience with these tests in clinical work by many observers has confirmed this opinion. I have therefore been content to follow the dogs of this second series by means of these tests, rather than by phloridzin or lactose, as did Lobenhoffer.

The above results, though they throw no direct evidence on any possible secretory function of either the vagus or splanchnic nerves, seem to suggest that if this exists it must play a minor and infrequent part. Under all the conditions produced both by my experiments and by those of Lobenhoffer, the denervated kidney has been
seen to react in an entirely normal manner. One may ask, therefore, if secretory nerves to the kidney are assumed to exist, under what conditions they are manifest; for no lack of such action seems to be demonstrable. Added to the inability of the present observations to show any failure of kidney function which might be ascribed to lack of secretory nerve influence, is the recent work of Cow, who finds in the duodenal mucosa some substance which has a definite diuretic effect on the kidney by means of a hormone action.

It is probable that vasomotor conditions in the kidney, added to the chemical and hormone action of substances contained in the circulating blood, will be found entirely adequate to explain all variations and types of normal renal function.

SUMMARY.

1. By means of vascular suture it is possible to remove the dog's kidney from the body and later to restore it to its former position.
2. Such a kidney is removed from the control of the nervous system, at least for a time.
3. Examination of the function of a kidney so treated shows an initial period of overaction, as compared with that of the normal kidney.
4. This is followed by balanced action.
5. The more recent tests of renal function show that a single, re-implanted kidney is able to maintain normal life indefinitely.
6. The results of these experiments, together with the evidence already at hand, suggest strongly that secretory nerves to the kidney do not exist.

EXPLANATION OF PLATES.

PLATE 81.

Fig. 1. The transverse abdominal incision extending from the outer border of the left rectus muscle well down into the right flank.

PLATE 82.

Fig. 2. The oblique muscles and both recti have been divided and the abdomen is being opened by incision of the transversalis in a direction parallel to its fibers.

\[^{12}\text{Cow, D., } Jour. Physiol., 1914–15, xlix, 441.\]
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PLATE 83.

Fig. 3. The intestines have been withdrawn for the most part from the abdomen, and lie to the left covered by silk handkerchiefs. The kidney, with its vessels and ureter, lies well exposed. Above the kidney is seen a portion of one of the lobes of the liver. At its inner side lie the inferior vena cava, and the pancreas enclosed by a portion of the duodenum.
FIG. 1.

(Quinby: Kidney Deprived of Nerves.)
Quinby: Kidney Deprived of Nerves.
FIG. 3.

(Quinby: Kidney Deprived of Nerves.)