OBSERVATIONS ON THE BEHAVIOUR OF THE TRANSPLANTED KIDNEY IN DOGS

by

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TRANSPLANTATION OF TISSUES from one animal to another of the same species (homotransplantation) has for a long time interested surgeons and biologists; and no one more so than John Hunter[1]. Except for corneal and arterial homografts no real progress has been made but this may be due to the apparent hopelessness of the problem and consequently its receiving only sporadic attention.

Many theories have been formulated to explain the obscure biological incompatibility of host and homotransplanted tissues. Theories of nutritional and vascular defects have received no experimental proof; Loeb's[2] theory of a purely local cellular immunity has now been superseded by the systemic actively acquired immunity theory which has recently been elaborated by Medawar[3]. This obscure immunological reaction is the greatest barrier to any attempt at the clinical use of homotransplanted tissues.

What would be the clinical indications for transplanting kidneys once the immunological problem was solved? Lucien Brull[4] has investigated the possibilities of treating acute uræmia in dogs by means of the homotransplanted kidney. The investigations of his co-worker, Lefebvre[5], show clearly that the homotransplanted kidney can clear urea. But more is required of a kidney then mere excretion of urea—for instance, the maintenance of the composition of the extracellular fluid. However, the recent work of Borst and Bull and his co-workers[6] may render Brull's approach obsolete. Thus, it would have to be in the chronic group of renal diseases that surgical intervention might be indicated in the future.

In Fig. 1 is shown the typical behaviour of a homotransplanted kidney functioning as a third kidney in a dog. On the fifth day the urinary flow ceased from the homotransplant; the flow had been meagre and blood-stained during the fourth day. On the fifth day, along with the anuria in the homotransplanted kidney, other phenomena developed—the temperature rose sharply; the blood pressure rose to 180 mm. Hg.; anorexia was complete; and, an occasional vomiting episode interrupted an otherwise complete apathy. Removal of the homotransplanted kidney produced an equally dramatic improvement; the temperature and blood pressure fell to normal levels within 12 hours; in addition, the dog regained its previous appetite and general well-being. A similar course was found in most successfully homotransplanted kidneys. Other workers

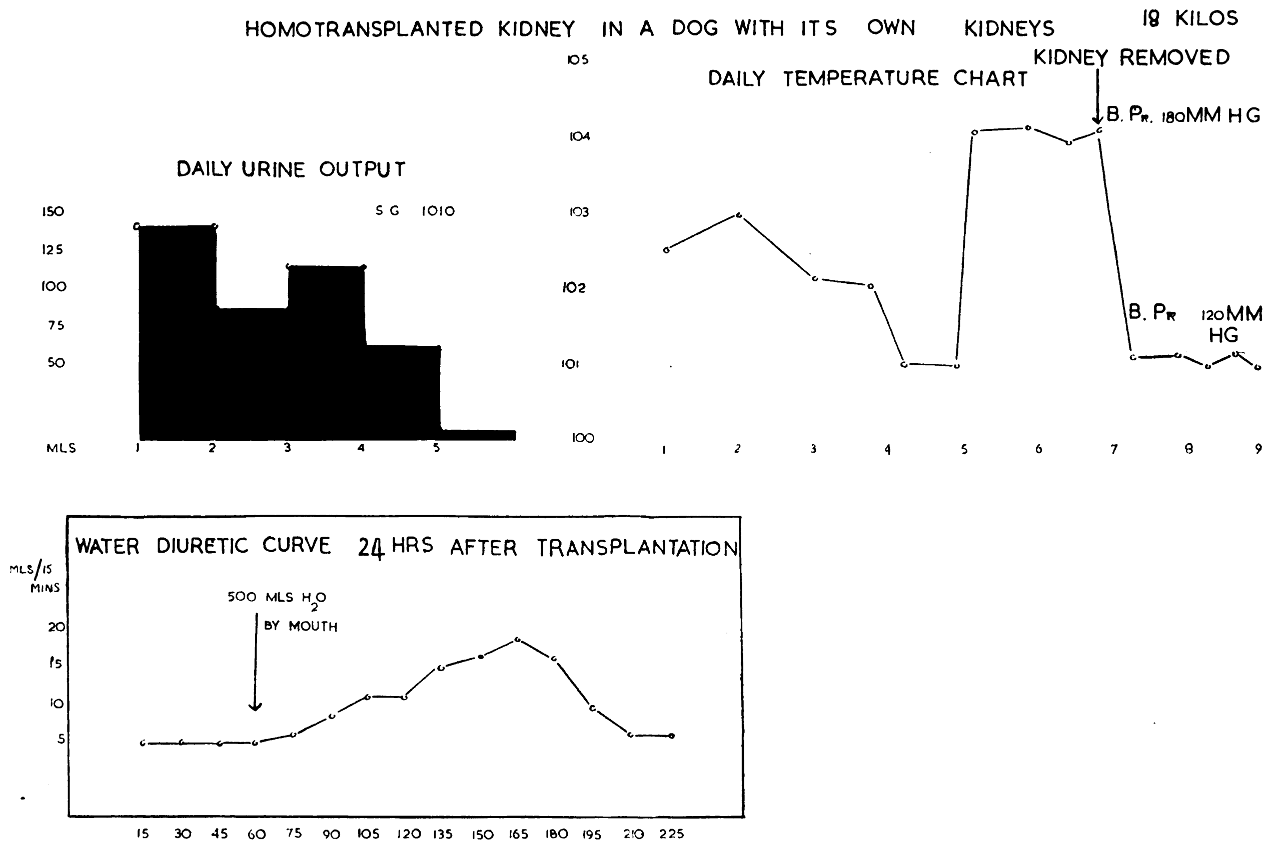

Fig. 1. A composite graph of the behaviour of a homotransplanted kidney in a dog with its own two kidneys intact. The graph shows the daily output and the low specific gravity. The diuretic curve shows a mild response to a water load 24 hours after operation. The temperature chart shows that as the kidney begins to disintegrate the toxic state associated sometimes with hypertension develops.

Fig. 2. A section of a homotransplanted kidney removed on the fifth day after operation. There is complete disintegration of the renal substance with massive round cell infiltration. H.E. X145.

have recorded similar end-results; no previous mention, however, has been made of what may be termed "the toxic syndrome" associated occasionally with hypertension which heralds the natural disintegration of the homotransplanted kidney.

Fig. 2 shows the histological features of a disintegrating homotransplanted kidney removed on the fifth day. Dr. I. Doniach reports as follows:

"The kidney is enlarged and its architecture grossly altered by oedema, hæmorrhagic and non-hæmorrhagic necrosis. Most of the glomeruli and many tubules appear necrotic. In addition to hæmorrhage, the interstitial tissue of the cortex and outer medulla is heavily infiltrated with polymorphs, lymphocytes, histiocytes and plasma cells. Most of the cortical arteries and veins are dilated and are involved in the necrotising process and a number are thrombosed. No organisms can be seen in a Leishmann stain. The sinus renalis is massively infiltrated with fibrin, red cells, polymorphs and lymphocytes and histiocytes."

Sufficient experiments have been carried out to make it quite clear that any attempt at homotransplanting kidneys in humans, at this stage, is doomed to failure and would be a dangerous procedure.

In Fig. 1 it will be observed that the daily output of urine was not maintained at its initial level and was of a low specific gravity; the specific gravity of normal dog's urine lies in the 1035-1050 range.

Numerous problems arise. What is the cause of the low specific gravity? Can the transplanted kidney respond normally to a given load of water? Is it sensitive to the posterior pituitary hormone? What is the basis of the toxic hypertensive state? Is the mere operative interference sufficient to explain at least some of these findings?

The results of previous observations on the behaviour of the auto-transplanted kidney (the dog being its own donor) have been limited in range and inadequately controlled. It was decided, therefore, to set aside the investigation of the behaviour of homotransplanted kidneys and concentrate on a detailed and systematic study of the behaviour of the autotransplanted kidney. The remainder of this communication will briefly deal, therefore, with the general results of short-term survival experiments, i.e., up to two months after autotransplantation. It is intended in this report to give an over-all picture of the behaviour of the autotransplanted kidney.

Historical Review:

It was only after 1902, when Carrel published his new technique of anastomosing blood vessels, that transplantation of kidneys for Carrel[7 8 9] and others[10 17] became a surgical feasibility. None of these distinguished surgeons of that period found this experiment an easy one. Only three workers recorded one long survival each—Carrel[9] almost one year, Zaaijer[11] six years, and Lexer[17] one year. Thus Zaaijer of Leiden holds the record by far—even to this day. It was thus realised from the outset that even the technique of transplanting a dog's own kidney involved many major problems; furthermore, the problems of transplanting whole organs would always be intimately bound up with those presented by vascular surgery. The same position obtains to-day.

The first approach to the problem of transplanting kidneys was really an investigation into the feasibility of such a procedure. By 1916, however, successes had been reported by many people and Quinby[17 18] now used the autotransplanted kidney, which is a truly denervated kidney, to demonstrate that the renal nerves had no control over the secretory function of the kidney. His impression was that for the first two weeks the autotransplant worked better than the normal! " . . . the function of the re-implanted kidney was greater than normal during the days immediately following operation until about two weeks had passed, when it was found normal "[18]. This statement must surely reflect the outlook of his time when mere volume was equated with good function. No record of the daily volume or specific gravity was kept.

In 1926, Williamson[20 21], Holloway[22], and Ibuka[23], repeated the previous work; they all reviewed the available literature up to that date. These three workers all testified that the function of the auto-transplant was almost normal. However, no records were kept of daily volume, specific gravity or method of collecting urine. Ibuka, it is true, trained his dog to lie for four hours while urine was collected into a test tube. This method has obvious fallacies. Actually, there are only three statements about the specific gravity in the whole of the available literature. Zaaijer[11] records it as 1017; Frey[24] gives a similar figure, and Lobenhoffer[16] gives a somewhat higher figure—1018-1030. As normal dog's urine lies in the 1035-1050 range, the figure of 1017, which coincides with what has been found in the present investigation, indicates a marked loss in the concentrating power (hyposthenuria).

The next phase in the history of transplanting kidneys followed Goldblatt's work on renal hypertension. The autotransplant was now used in an effort to elucidate the nature of the renal hypertensive state. Levy *et al*[25] transplanted kidneys distal to a Van Leersum loop around the carotid artery. In this way they were able to produce graduated constriction of the arterial supply to the autotransplanted kidney. Glenn *et al*[26 27] transplanted kidneys to the thigh and later produced graduated constriction of the femoral artery by means of a Goldblatt's clamp. Their conclusion is of interest:

" It is well-known that it is more difficult to produce a sustained hypertension in the dog after unilateral nephrectomy; it appears even more difficult to produce a sustained hypertension after unilateral nephrectomy and renal transplantation "[26].

Other work connected with hypertensive investigations has been confined to acute experiments[28 30]. In no investigation throughout this phase is there any reference to renal physiological details.

In recent years Malmejac *et al*[31 32] have investigated the effects of altitude on the autotransplanted kidney. From their reports the autotransplant behaved normally; however, there is no reference to data concerning specific gravity, daily output or method of collecting urine. Oudot[33 34] reported satisfactory results with " superpolyamide " tubes which are similar to the vitallium tubes of Blakemore and Lord. There is no record of specific gravity, daily output or method of collection of urine; survival periods, also, are not given.

The autotransplanted kidney has been observed to function in various sites in the body. Ullmann[10] was the first to use the carotido-jugular circulation; others have used the splenic vessels[16], the iliacs[11], and the femorals[26]. When the kidney has been transplanted to the thigh region, the ureter has been re-implanted into the bladder; when transplanted to the neck region, however, the ureter has been drawn out on to the skin surface as a ureterostomy.

The method of effecting vascular anastomosis has varied. The first method employed, of course, was suture, but this was found a difficult procedure and non-suture methods were sought after. But the non-suture methods have their disadvantages as well, when long-term survival work is the aim. Thus, Payr's cannulæ, the vitallium tubes of Blakemore and Lord, and the " superpolyamide " tubes of Oudot are by no means the answer; they all suffer from the common disadvantage that they do not allow of expansion of that portion of the artery to meet physiological demands.

The results of the present investigation will be presented in two sections:

1. The technical procedure and analysis of the causes of failure.
2. The study of renal function in temporarily successful autotransplants. The following will be briefly considered:—
   (*a*) Daily output, specific gravity and pH values.
   (*b*) Intravenous pyelography and dye excretion rates.
   (*c*) The renal blood flows and glomerular filtration rates.
   (*d*) The diuretic and anti-diuretic response.
   (*e*) The handling of electrolytes.
   (*f*) The investigation into the nature of hyposthenuria and polyuria.

1. The technique of transplantation

The site used has been the neck where the kidney has been interposed on the caritido-jugular circulation.

Greyhound bitches of weights varying from 25 to 30 kilos were used.

Anæsthetic: Nembutal 1/2 gr. per kilo of body weight intramuscularly.

With the dog in the supine position, an incision was made parallel to and below the right costal margin and then continued downwards for about 8 cms. The aponeuroses of the abdominal muscles were then incised in the line of the incision. At least two intercostal vessels and nerves were normally divided and ligated. The peritoneal cavity was opened and the right kidney quickly mobilised. The right kidney was the one of choice as the renal vessels on the left side were often anomalous. Having completely freed the kidney from its surroundings it was replaced in the belly and attention diverted to the neck where the future kidney bed was then prepared.

In the neck an incision of about 10 cms. was made parallel and medial to the right external jugular vein. This vein was mobilised in its lower half, ligated and divided obliquely below the ligatures; the vein was then flushed out with 1 per cent. heparo-saline. An intermuscular plane lateral to the sternocephalus was then sought for. On opening up this tissue plane fully, the carotid sheath with carotid artery, vagus and sympathetic nerves came into view. At the mid-point of the carotid artery its sheath was stripped for some millimetres, a bulldog clamp applied below and a ligature above; finally, the artery was sectioned between by a sharp razor blade. Any loose adventitia was removed from the upper two millimetres of the transected vessel. It is important to make quite sure that no minute portion of blood clot lies in the lumen of the artery; accordingly, this was flushed out with 1 per cent. heparo-saline. The neck region was now ready for the kidney.

Returning to the belly, the ureter was divided about 8 cms. from the pelvis of the kidney. Ligatures were applied to renal artery and vein which were then divided distal to those ligatures.

The kidney was then gently flushed out with 1 per cent. heparo-saline before anastomosis was attempted. When Blakemore-Lord tubes were used a 4 mm. tube was applied to the carotid artery and a 7 mm. to the external jugular vein before the kidney was removed from the belly. When suturing was employed the usual Carrel technique was followed; continuous over and over sutures were found satisfactory to effect an end-to-end anastomosis. The time taken to effect anastomosis, from the stage at which the renal artery was ligated to the stage at which the carotido-jugular circulation was opened up, varied from seven minutes (when Blakemore-Lord tubes were used) to 30 minutes (when suture was carried out).

Figs. 3 and 4 show the normal and transplanted ureter; the latter is obviously swollen. This swelling occurs within 30 minutes of ligating the ureter. It is important, therefore, that the kidney should be placed in the neck in its reverse abdominal position so that its ureter passes directly forwards on to the skin. If the kidney is placed in its normal position, the swollen ureter must course behind the renal vessels and, in doing so, may compress them. Dr. I. Doniach reports the histological features of the transplanted ureter thus:

" The transplanted ureter contrasts with the normal in the following features. The normal mucosal folds are lost as a result of distension of the lumen, the wall is thickened by oedema of the muscularis, the adventitia is the seat of an acute fibrinous inflammation, its vessels are dilated and it is ringed by a massive deposit of necrotic polymorphs."

Having completed the anastomosis, the clamps were removed from the carotid artery and external jugular vein. The renal artery was partly compressed so as not to allow too sudden a flow to the kidney. The kidney quickly resumed its normal colour and tension. The ureter, which quickly performs vermicular movements, was then catheterised with a portion of hard polythene tubing (1 mm. bore). Ligatures were then applied around the catheterised ureter; these ligatures stop the bleeding from the cut end of the ureter and also fix the catheter firmly in position in the pelvis of the kidney. The ureter was drawn out through an independent wound in the neck medial to the previous incision.

Having established complete haemostasis in the neck wound, the kidney was gently manœuvred into position and the skin edges brought together over it.

The flow of urine from the autotransplanted kidney usually occurred within 15 minutes of opening up the carotido-jugular circulation.

Penicillin in oil was continued for four days after the operation.

Analysis of Failure

Previous workers have not found this an easy procedure. Quinby[18] reported that out of 41 attempts only 16 came to the stage of physiological investigation. Wu and Mann[36], while investigating only histological changes, report as follows:

" Twenty-four transplantations with six complete failures. A series of six autotransplants resulted in: complete failure, 1; functioning for two days, 2; functioning for two to five days, 3. A series of 18 homotransplants

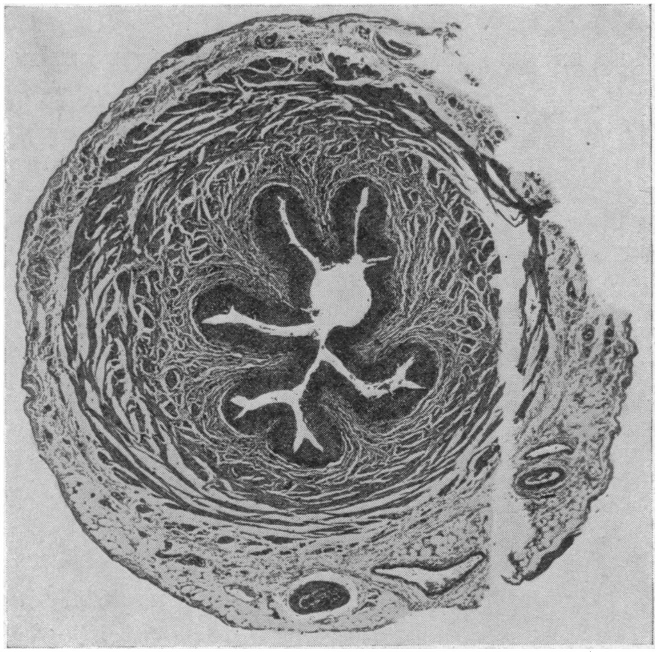

Fig. 3. A section of a normal ureter as seen in the abdomen before any operative interference. A catheter of 1 mm. bore can just be passed with some manipulation. H.E. X36.

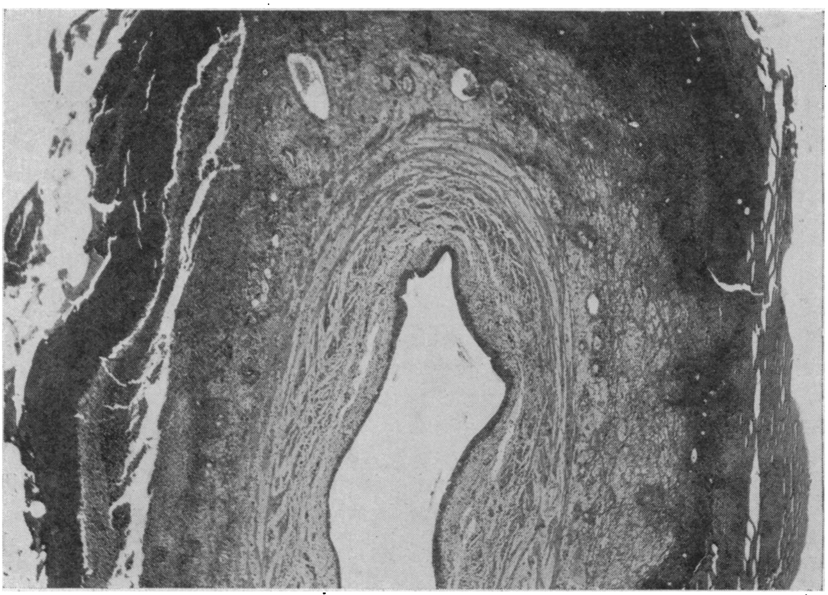

Fig. 4. A section of the ureter of an autotransplanted kidney 24 hours after transplantation. The lumen is so distended now that a tube of 2 mm. bore can be passed without any difficulty. H.E. X36.

resulted in: failed to secrete, 7; failed in 24 hours, 2; operative deaths, 2; functioned for two to five days, 6; functioned for one day, 1."

The failures of the present investigation will be presented in two sections: (i) Where Blakemore-Lord tubes were used. (ii) Where suture was performed.

The results are as follows:—

(i) Massive hæmorrhagic necrosis, 19; disengagement of the renal artery, 12; thrombosis of the renal artery, 4; fistula of the pelvis of the kidney, 1; pyelohydronephrosis, 1; stricture of the ureter, 1; anuria, 5.

(ii) Breakdown of the suture line at fifth day, 12; thrombosis of the suture line, 4; venous congestion of unknown origin, 8; massive hæmorrhagic necrosis, 26.

Of all these dogs only two survived for a period of eight weeks. Observations were carried out on 50 dogs in which the transplanted kidney secreted for periods varying from three days to eight weeks.

The renal artery became disengaged because the vitallium tube sloughed through the vessel wall usually about the tenth day after operation. No solution was found to counter this.

Massive hæmorrhagic necrosis presented an insoluble problem. How it occurs has never been determined. It is associated with exactly those symptoms which have already been pointed out as occurring in the disintegrating homotransplanted kidney. Fig. 5 shows a photograph of one type of massive hæmorrhagic necrosis which was encountered. It appeared that for the toxic state to develop a minimal circulation through the kidney was necessary. The hæmorrhagic necrosis may come on any time up to four days after operation. It is assumed that from the hæmorrhagic area some necrotoxic products are discharged into the bloodstream.

The five cases of anuria are of some interest. When these kidneys were removed the blood flow appeared normal. Histologically, they appeared normal, but it is possible that they were removed too soon for tubular damage to show up; the kidneys were removed at some period between 36 and 48 hours after operation. A photograph of a section of an anuric kidney is seen in fig. 6. This phenomenon is well recognised in experiments on the isolated kidney. Dr. I. Doniach reports as follows:

" Essentially normal architecture and vascularity; grossly hæmorrhagic capsule. A moderate number of Henle's loops and distal convoluted tubules are filled with eosinophilic cast material. The papillary pelvic submucosa is infiltrated with lymphocytes, polymorphs and plasma cells."

The kidneys removed after functioning for two months appear normal histologically. Dr. I. Doniach reports:

" Essentially normal kidney with healthy-looking glomeruli, tubules and blood vessels. The capsule shows a striking thickening by recently formed fibrous scar tissue."

Fig. 7 shows a section of an autotransplanted kidney removed after two months.

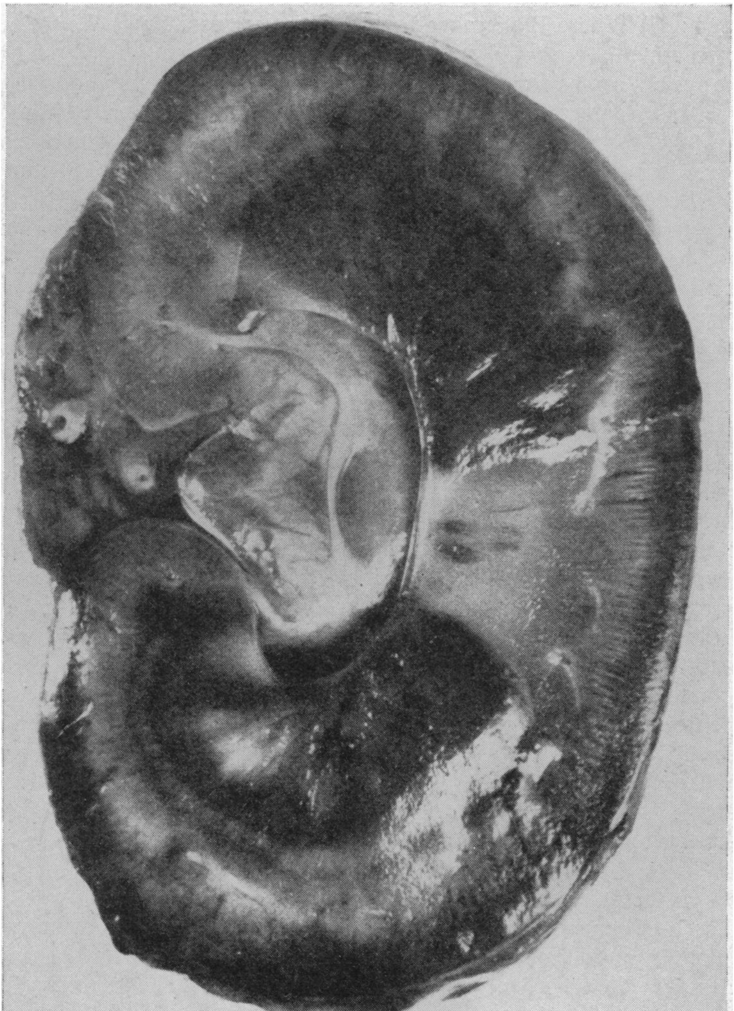

Fig. 5. A photograph of an autotransplanted kidney which was removed on the fourth day after transplantation. There are areas of massive hæmorrhagic necrosis at both poles with an intervening area of healthy kidney tissue.

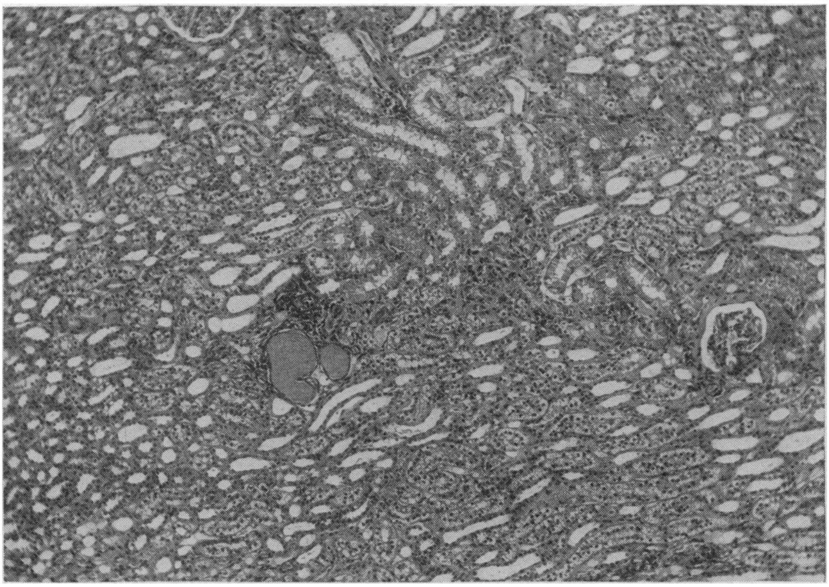

Fig. 6. A section of an anuric autotransplanted kidney removed 36 hours after transplantation. Except for a few casts in the tubules the renal tissue appears normal. H.E. X90.

2. The Daily Collection of Urine

When the dog left the table an apparatus as shown in fig. 8 was applied. This method of collecting urine is suitable for periods up to five days by which time the second ligature will have sloughed through the ureter. At this stage there is nothing to fix the catheter in position and it is now necessary to apply an apparatus as shown in fig. 9. This consists of a soft plastic indwelling catheter (bore 2 mm.) which can be kept in position permanently. Fig. 10 shows the apparatus in place in the dog's neck.

If this indwelling catheter is not kept in position the lumen of the ureter will become gummed up with serum and this will prevent the free flow of urine, resulting in hydronephrosis and infection. This has been the experience of past workers. Levy *et al* state " The results will not be given in detail because some degree of ureteral obstruction was present in all of the transplants "[25]. Simonsen and Sorensen, in a recent paper, declared : " The tendency of the ureteral ostium to sticky occlusion is considered the greatest technical difficulty in these experiments "[35]. Levy *et al* also state " The transplanted kidney was sometimes catheterised for the duration of the experiment but usually was not, since infection is apt to occur following such a procedure "[26].

In the present investigation it was considered that obstruction to a free flow of urine was much more liable to lead to infection than the use of a

Fig. 7. A section of an autotransplanted kidney removed two months after transplantation. The renal tissue appears normal throughout. H.E. X36.

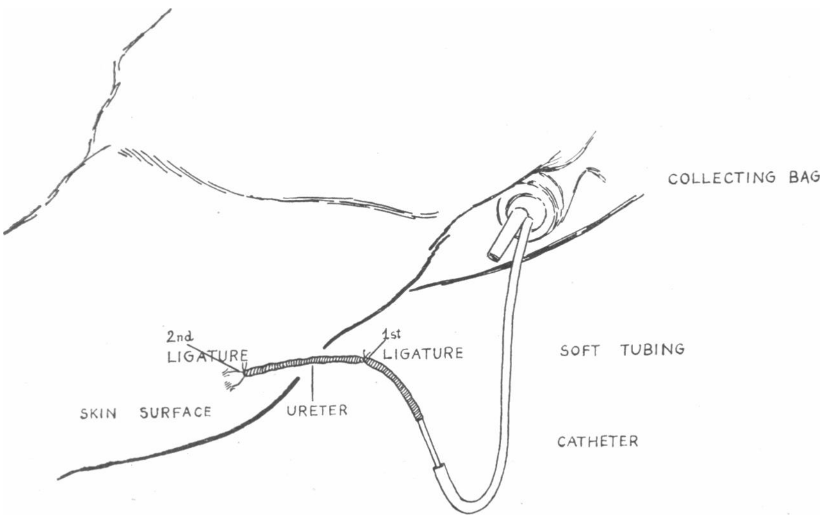

Fig. 8. The apparatus necessary for collecting urine in the immediate post-operative period. The polythene catheter is fixed in position by ligatures round the ureter. The distal end of the catheter is connected to plastic tubing which conducts the urine into a rubber bag slung on the belly of the dog.

permanently indwelling catheter. Hydronephrosis and infection occurred once and that in a dog in which difficulty was experienced in keeping the catheter in position. By means of the indwelling catheter hydronephrosis and infection can be prevented. It would appear that this is the only means whereby an accurate record of the daily output of urine can be obtained. Fig. 10 shows the indwelling catheter in position in the pelvis of the transplanted kidney.

(a) The Daily Output of Urine, Specific Gravity and pH Values

Fig. 11 shows the behaviour of a normal kidney before and after transplantation, the other kidney having been previously removed. Urine collections were taken at 12 hour intervals. It will be observed that after transplantation there develops a polyuria which continues unchanged in character throughout the period of observation. Associated with the polyuria is an inability to concentrate (hyposthenuria) and a polydipsia. At no time over varying periods of observation have other such transplants been able to stabilise themselves at their pre-operative levels. There was no progressive loss in weight in these animals.

The specific gravity is fixed at a low level usually at about 1010; thus this urine resembles closely a glomerular filtrate. This characteristic appears in the very first collection of urine.

Fig. 12 indicates that the pH of normal dog's urine is usually strongly acid at 5.9 and that of the transplant fed on the same diet is less acid at a

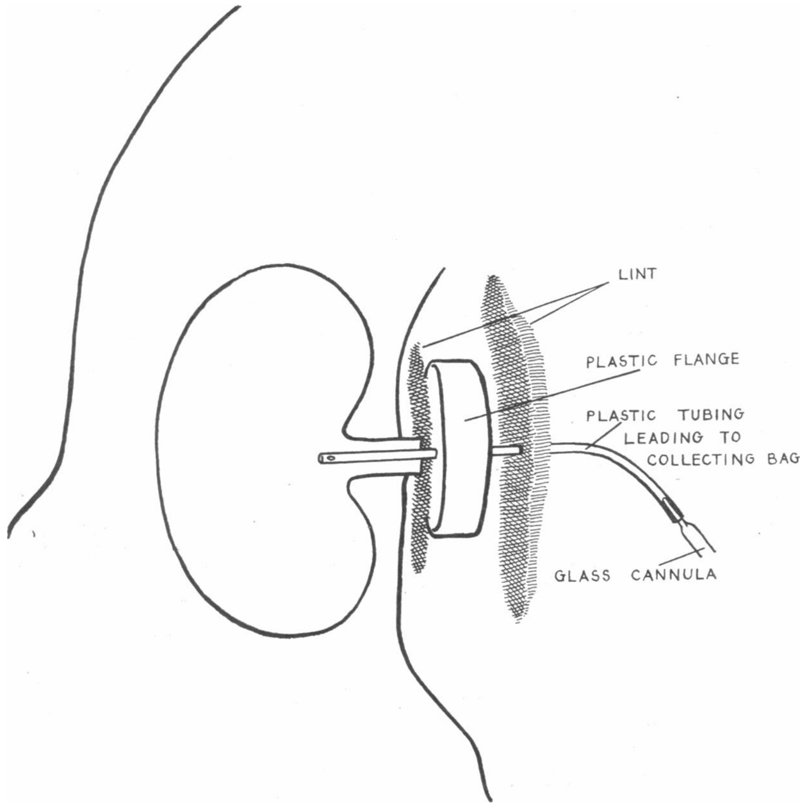

Fig. 9. The apparatus used for permanent urine collections. The catheter is now soft (2 mm. bore) plastic tubing which is cemented to the inside of the plastic flange. The plastic flange gains an upward lift by means of the lint held to the skin by mastisol.

pH of 6.7. The pH must be estimated with fresh urine from the catheter. The 12 hour collection in the rubber bag gives an entirely erroneous figure as urea-splitting organisms may push the alkalinity of the specimen up to the region of pH 8. On no occasion has the pH of the autotransplanted kidney ever approached the pH values of normal urine. The pH of the urine from the autotransplant during the first six hours following operation may rise to 7.62.

During diuresis, the pH of the autotransplant does not show the wide range of the normal kidney. It will be observed that in fig. 12, when the normal kidney reaches the peak of diuresis, the pH values of both autotransplant and the normal kidney approach one another. While the normal rarely reached a pH of 7 it was the usual behaviour of the autotransplant to rise well above a pH of 7.

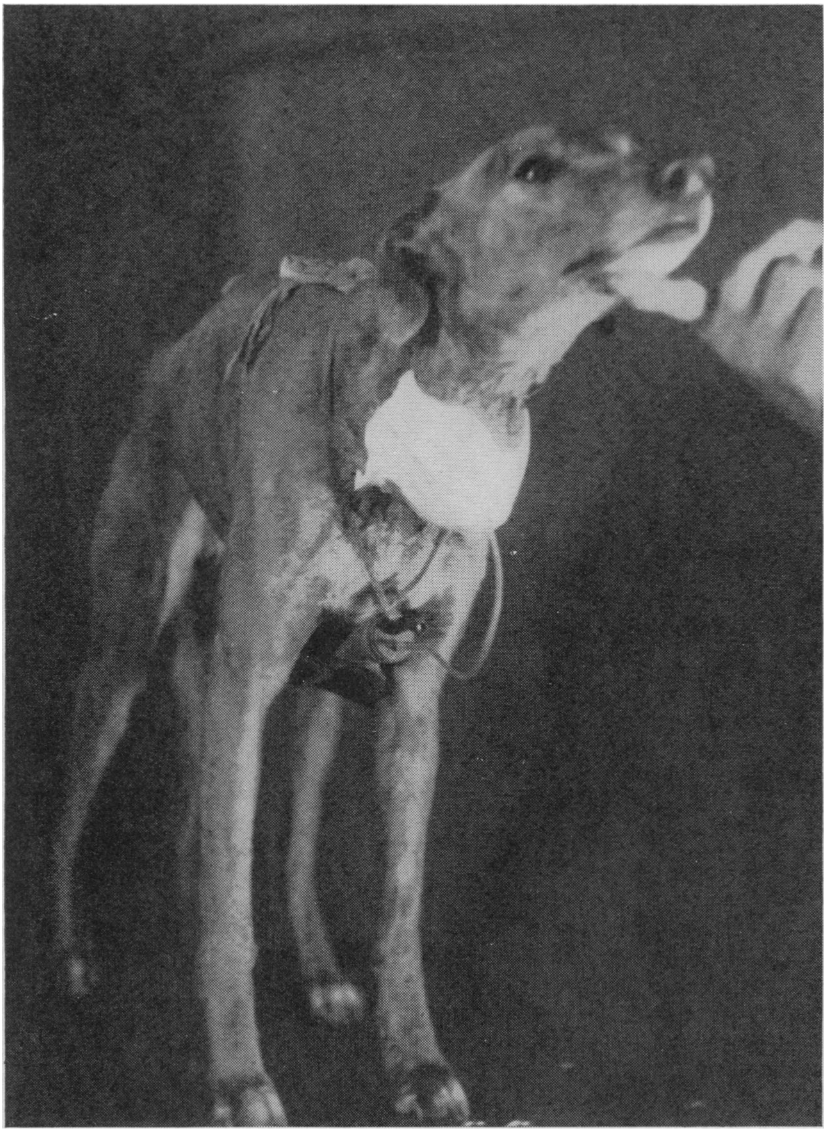

Fig. 10. The permanently indwelling catheter in position in the autotransplanted kidney in the dog's neck. This particular dog has no abdominal kidneys. This apparatus does not inconvenience the dog. If no such catheter is kept in position the urine trickles down the dog's neck and leads to great inconvenience.

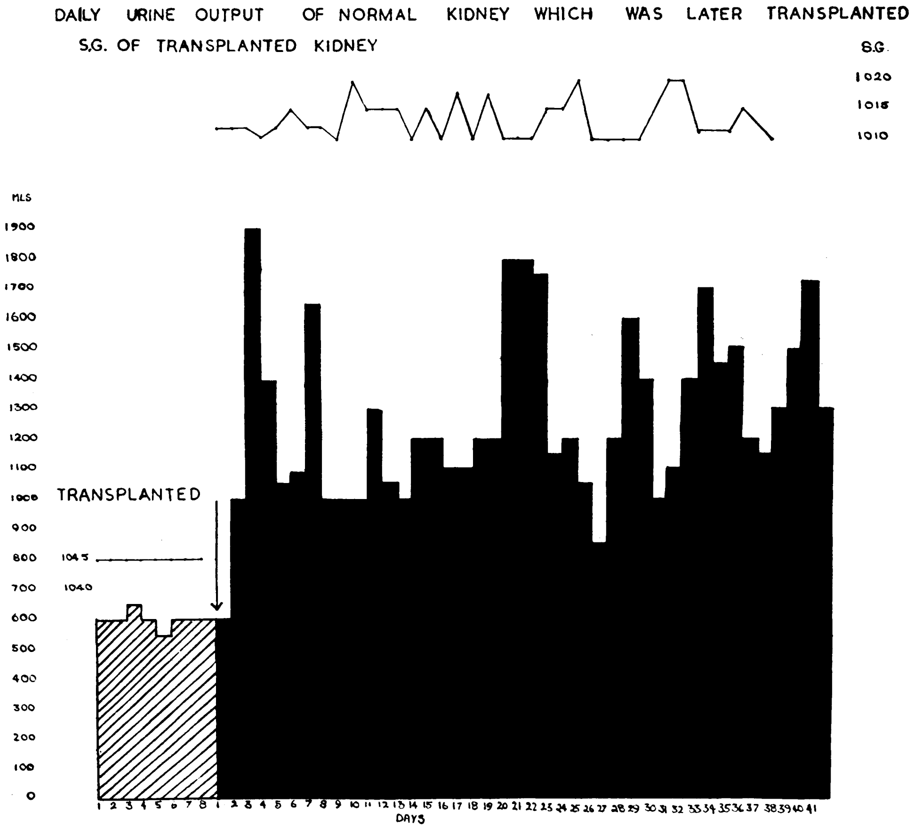

Fig. 11. The urine output of the same kidney before and after autotransplantation.

pH VALUES OF NORMAL AND TRANSPLANTED KIDNEYS

	Normal	Transplant
DAILY MEAN:	5·9	6·7
	(Range 5·9—6·2)	(Range 6·7—7·2)
DURING DIURESIS:	Normal	Transplant
	6·14	6·7
	6·36	6·78
	6·16	6·84
	6·38	6·72
	6·5	6·8
	6·6	6·78
	6·76	6·82
	6·82	6·9
	6·92	6·9
	6·9	7·4

Fig. 12. pH values of normal and autotransplanted kidneys in the same dog. The autotransplanted kidney is unable to acidify normally.

The urine of the autotransplanted kidney is sugar free; albumen is present for the first 48 hours in demonstrable amounts and then thereafter not detectable by ordinary boiling tests. There is always a heavy deposit of triple phosphates. Usually casts can be demonstrated but in no greater quantity than exist in a normal dog's urine.

(b) Intravenous Pyelography and Dye Excretion Rates

Fluid was restricted for six hours previous to intravenous pyelography. The dog was laid on its side, the catheter was clamped off and the injection of 35 per cent. pyelosil given. Signs of excretion of the opaque material were visible at four minutes and maximum at 12 minutes. No cases of iodine sensitivity were encountered. Figs. 13 and 14 show transplanted kidneys excreting pyelosil.

The appearance of opaque material in the pelvis in the four minute picture suggests a relatively normal function. The activity of the abdominal kidney was not followed for technical reasons. It is possible that, as the autotransplanted kidney is a subcutaneous organ, the opaque material is shown up more clearly than might otherwise be the case were the autotransplant in its normal position.

Indigo carmine was excreted by abdominal and autotransplanted kidneys in three minutes.

(c) Renal Blood Flows and Glomerular Filtration Rates

Herrick *et al*[37] found, using the thermostromuhr, that the renal blood flow through the autotransplanted kidney was normal on the third day after operation; no record of the daily output of urine, its specific gravity or method of collecting urine is given.

In collaboration with Mr. I. G. Graber a series of experiments was undertaken to determine, by means of the new renal investigating techniques, the effective renal blood flows and glomerular filtration rates.

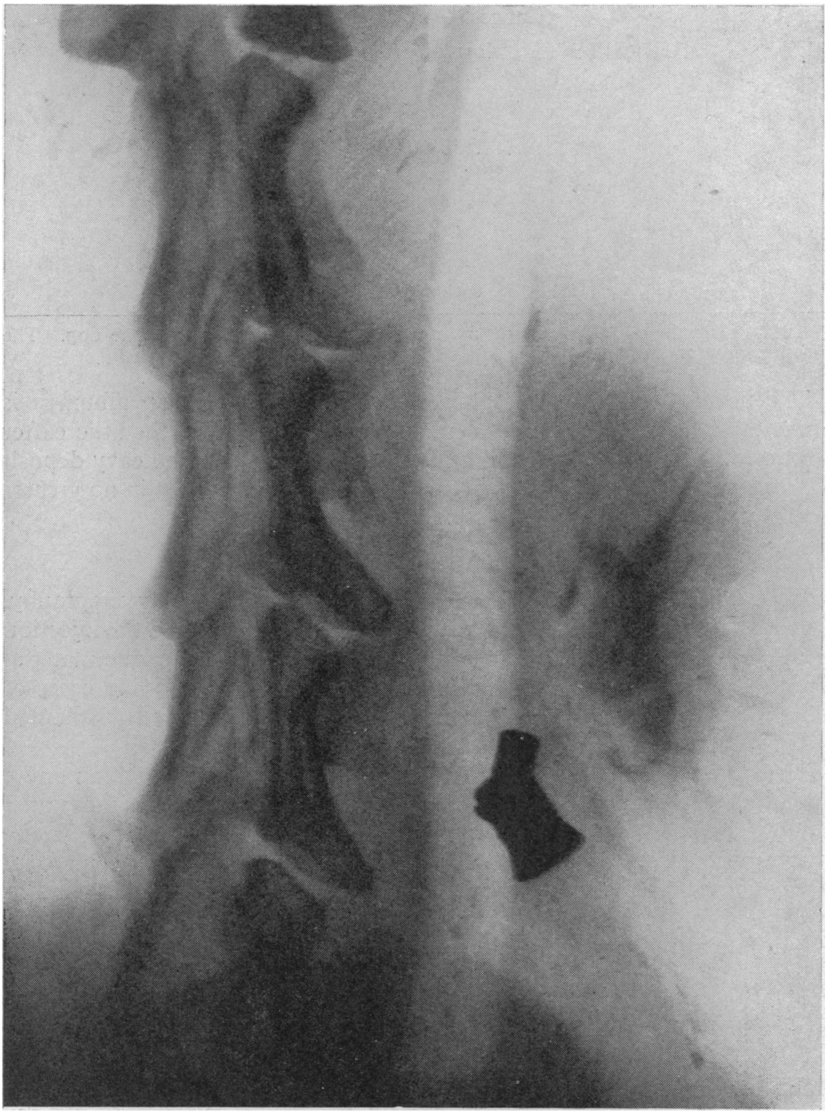

Fig. 13. A photograph of an X-Ray tåken 12 minutes after injection of 35 per cent. pyelosil. The Blakemore-Lord tubes are clearly visible.

Fig. 14. A photograph of an X-Ray taken 12 minutes after injection of 35 per cent. pyelosil. Anastomosis of the renal vessels in this case was by suture.

Two groups of results will be briefly considered here and presented in detail elsewhere:

Group I: Values when Blakemore-Lord tubes were used.

Renal blood flows of the autotransplanted kidney varied between 50 per cent. and 65 per cent. of the abdominal kidney; the glomerular filtration rates ranged between 50 per cent. and 93 per cent.

Group 2. Values when the vessels were sutured.

The blood flows varied between 53 per cent. and 95 per cent. of the abdominal kidney; the glomerular filtration rates ranged from 50 per cent. to 80 per cent. of the normal.

(*d*) *Diuresis and anti-diuresis*

The only previous reference to diuresis in the transplanted kidney is contained in the work of Holloway[22]. Although there is no evidence of controlled experiments, Holloway came to the conclusion that the autotransplanted kidney behaved normally. Other diuretic studies of the denervated kidney have not been associated with transplanted kidneys[38 41].

A brief outline of the findings will be given here and in detail elsewhere.

The experiments have been conducted in two groups.

Group 1. With one kidney previously removed, the remaining abdominal kidney was subjected to various diuretic and anti-diuretic measures. Then the abdominal kidney was transplanted.

Fig. 15 shows that the autotransplanted kidney has almost the same ability to respond to a given load of water as the normal kidney.

Group 2. The autotransplanted kidney has been made to compete against an abdominal kidney in the same animal.

Fig. 16 shows that when the autotransplanted kidney competes against the normal in the well-hydrated animal it cannot respond as efficiently. The first half of this diuretic curve indicates that the autotransplanted kidney can compete very well. This has often been misleading and it appears to be the result of previous dehydration. However, the second part of the curve shows that when a second water load is given, and the animal is now in a well-hydrated condition, the abdominal kidney has a far greater range. This phenomenon is rather difficult to interpret.

Fig. 17 indicates that the autotransplanted kidney can respond normally to emotional stress induced by faradic stimulation. Fig. 18 shows that the inhibition produced by emotional stress can be almost exactly paralleled by an intravenous injection of 1 mU Infundin. This adds further evidence to Verney's theory that emotional inhibition of water diuresis is brought about by a posterior pituitary hormonal mechanism.

(*e*) *The Handling of Electrolytes*

In collaboration with Dr. A. M. Joekes and Dr. A. A. G. Lewis an attempt has been made to evaluate just how the autotransplanted

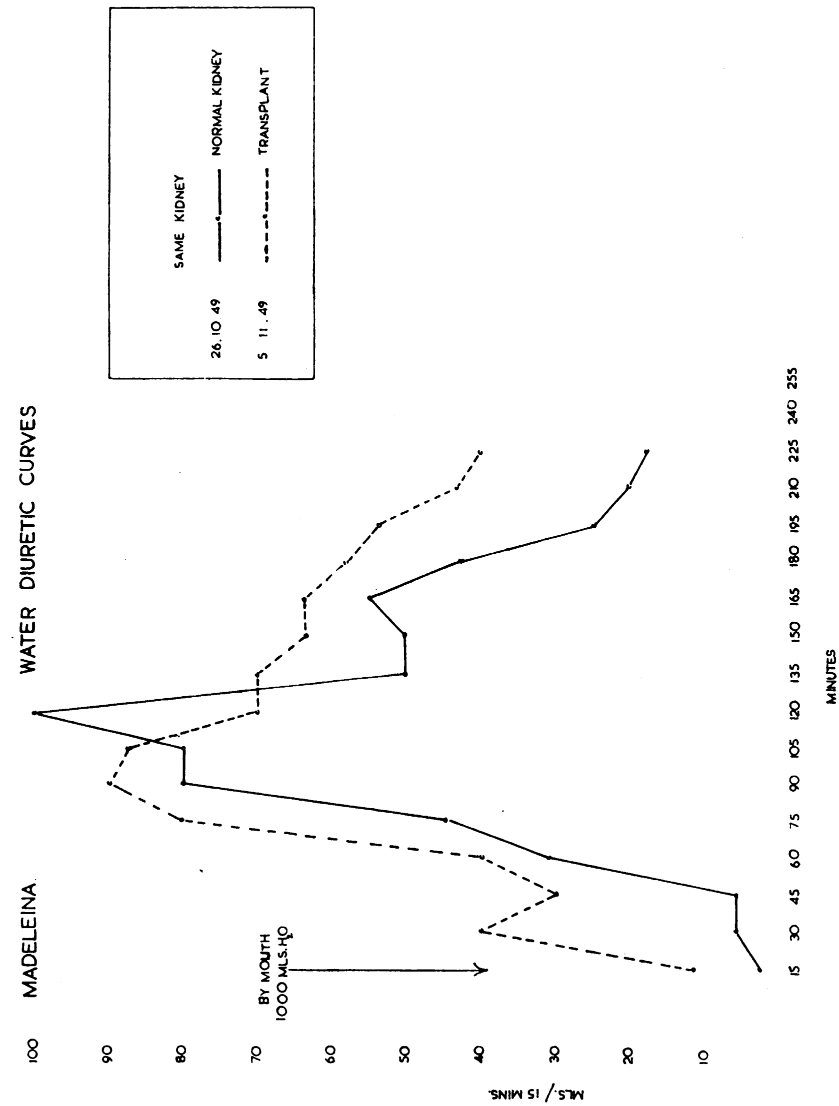

Fig. 15. A water diuretic curve of the same kidney before and after autotransplantation. There is only a small limitation of response to a given load of water by the autotransplanted kidney.

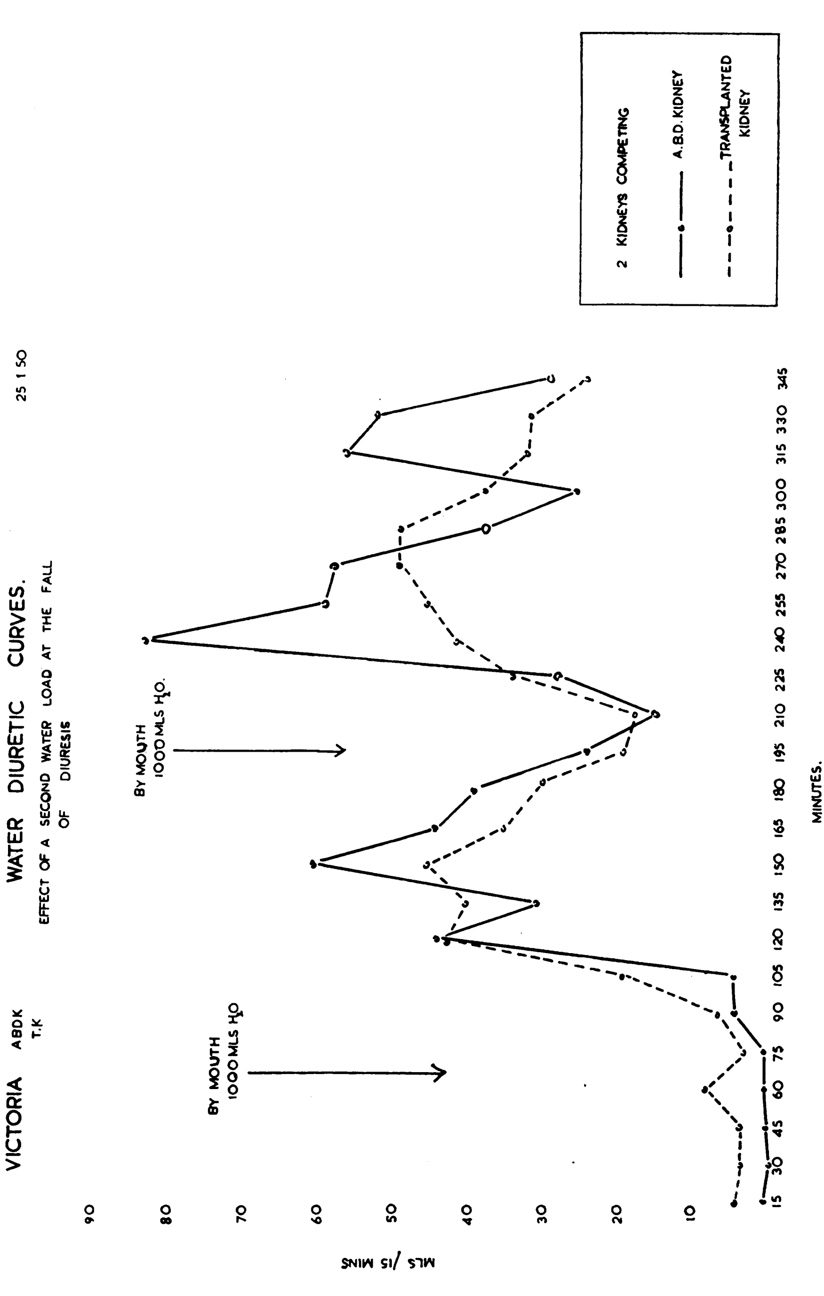

Fig. 16. A diuretic curve of normal and autotransplanted kidneys working together in the same dog. After the second load of water the autotransplant is unable to improve on its previous level of output while the abdominal kidney shows a greater range of response.

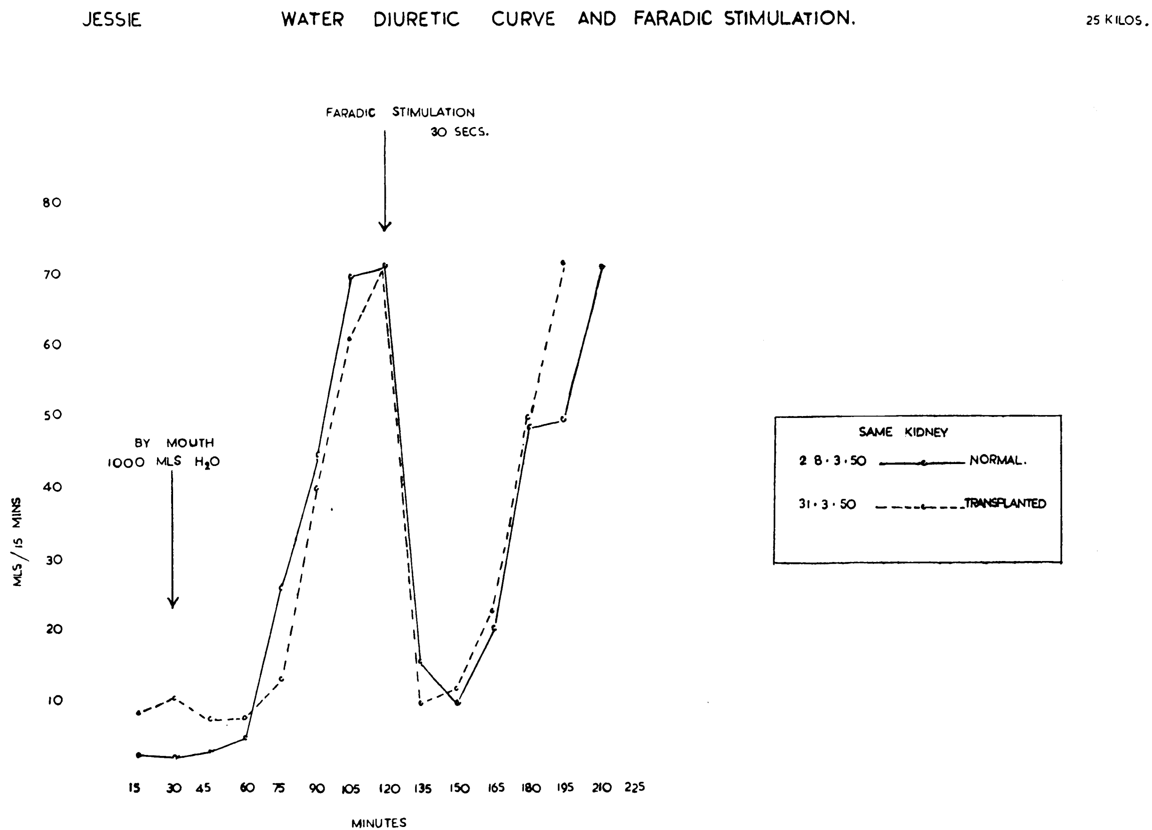

Fig. 17. Emotional inhibition of a water diuresis in the same kidney before and after autotransplantation. As the autotransplanted kidney is a truly denervated kidney, the emotional inhibition cannot be due to any nervous influence.

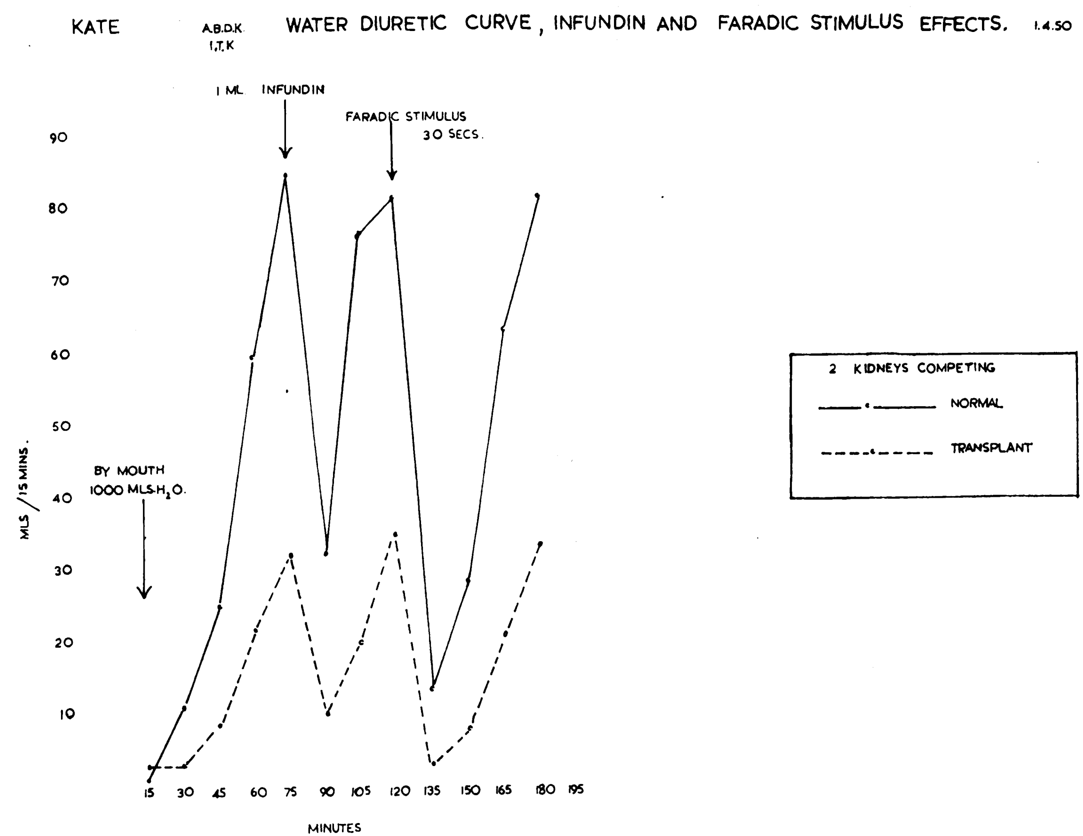

Fig. 18. A diuretic curve of normal and autotransplanted kidneys. The inhibition of the water diuresis brought about by 1 mU of Infundin is almost exactly paralleled by an emotional stress inhibition at a later peak in the curve.

kidney handles electrolytes. Preliminary results will be discussed here.

Fig. 19 indicates the behaviour of the normal and transplanted kidney. During an apparently comparable period there is greater sodium loss from the autotransplanted kidney.

Fig. 20 shows that during an electrolyte depletion experiment, the autotransplant reacts less efficiently to a demand for sodium and chloride retention.

No statement on potassium will be submitted at this stage.

(f) The Investigation into the Nature of the Hyposthenuria and Polyuria

The polyuria and hyposthenuria have no exact clinical parallel. There are various possibilities which can be put forward to explain these phenomena.

ELECTROLYTE EXCRETION OF NORMAL KIDNEY AND LATER AS AN AUTOTRANSPLANT

	DATE	VOLUME Mls. per 24 hrs.	SPECIFIC GRAVITY	CHLORIDES Mgms/ 24 hrs.	Na Mgms/ 24 hrs.	K Mgms/ 24 hrs.
NORMAL	26.2.50	425	1030	609	161·5	710
	27.2.50	550	1030	965	325	1606
	28.2.50	400	1030	760	184	876
	1.3.50	500	1035	630	275	1165
	2.3.50	475	1040	709	219	1701
	3.3.50	430	1042	1385	507	1522
TRANSPLANT	4.3.50	2300	1005	1685	773	966
	5.3.50	985	1020	865	205·8	935·7
	6.3.50	1250	1015	660	112·5	887·5
	8.3.50	1150	1005	1440	310·5	1299·5
	* 10.3.50	1150	1010	Serum 948	350 1694·5	17 1265
	11.3.50	1230	1010	878	805·5	1750
	12.3.50	1500	1010	1230	405	1830
	13.3.50	1650	1010	2940	2607	2164
	14.3.50	1600	1010	1545	880	2052

Average Values : Normal 843 278 1263
Transplant 1380 843 1436

* Blood Urea : 31 mgms. %. Na expressed as Clearance ·055 mls/min
·167 mls/min

Fig. 19. The electrolyte excretion of a normal and later autotransplanted kidney. Besides the polyuria and hyposthenuria there is a greater loss of sodium and chloride from the autotransplanted kidney.

ELECTROLYTE EXCRETION OF NORMAL AND AUTOTRANSPLANTED KIDNEYS AFTER BEING STABILISED FOR TWO DAYS ON ELECTROLYTE-FREE DIET

	Normal Kidney					Transplanted Kidney				
Date	Mls. per 24 hrs.	Chlorides		Na Mgms/ 24 hrs.	K Mgms/ 24 hrs.	Mls. per 24 hrs.	Chlorides		Na Mgms/ 24 hrs.	K Mgms/ 24 hrs.
		Mgms/L	Absolute				Mgms/L	Absolute		
9.6.50	350	154·0	462·0	472	161	200	181·0	360·0	190	96
10.6.50	250	394·0	98·0	142·5	430	300	156·0	467·0	198	231
11.6.50	130	292·0	37·0	40·3	325	350	686·0	240·0	94·5	294
Na expressed as Clearance				·094 mls/min					·038 mls/min	
				·028 mls/min					·039 mls/min	
				·008 mls/min					·019 mls/min	

Fig. 20. An electrolyte depletion experiment shows that, after the third day, the normal kidney starts to retain sodium and chloride as demanded by the body; the autotransplanted kidney is unable to retain these electrolytes as efficiently as the normal. These kidneys were functioning simultaneously in the same animal.

Experimental evidence is against denervation and anoxia, in themselves, as being responsible factors ; in addition, removal of the kidney from the environment of the adrenal gland does not appear to be a significant factor in spite of the effect of unilateral adrenalectomy on homolateral renal function[42 43].

It is possible that as the autotransplanted kidney is a subcutaneous organ it suffers from a reduced temperature environment. An attempt has been made to rule out this factor by wrapping thick pads of cotton wool around the autotransplanted kidney for 12-hour periods. By this method, a temperature of 100.4 F. can be attained inside the cotton wool at a time when the rectal temperature was recorded at 100° F. No change in the polyuria or hyposthenuria was observed.

Verney and Winton found that in the isolated kidney they could produce a polyuria with a low chloride excretion by reducing the intrarenal pressure by 50 per cent.[44 46]. While the autotransplanted kidney may have renal blood flows varying between 50 per cent. and 95 per cent., the characteristic polyuria and hyposthenuria remain constant in all. Thus, reduced intrarenal pressure would not appear to be responsible.

While each individual factor so far discussed does not appear to be responsible for the polyuria and hyposthenuria, it may quite well be that all these factors together may cause the upset in concentrating ability. All that can be stated at the moment is that the behaviour of the autotransplanted kidney does fit in with a fixed minimal distal tubular damage. The mere act of transplantation appears to have been sufficient to upset the mechanism controlling the final delicate elaboration of urine. But, in spite of this minimal tubular damage, an animal can be maintained in a satisfactory state of health by such a functioning autotransplanted kidney alone.

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