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The Treatment of Renal Diseases

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Abstract
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Broadly speaking, the kidneys are responsible for maintaining the stability of the body fluids. If acute destruction of renal tissue occurs the body fluids are acutely altered, whereas in chronic renal destruction the disturbance is slowly progressive. The acute upset of normal physiology accompanying rapid destruction is the syndrome known as acute renal failure, and the progressive physiological imbalance known as chronic renal failure is the result of chronic tissue destruction.

This leads me to the first and most important point I wish to make. Therapy in renal disease must be two-fold. Firstly, it must deal with the pathological process causing renal destruction. Secondly, it must correct the disordered physiology which the renal disease has created. Whereas the pathological processes are legion, they lead to only two types of physiological upsets—acute or chronic renal failure.

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THE TREATMENT OF RENAL DISEASES

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Based on a Dissertation read before the Royal Medical Society on Friday, 8th December, 1961.

All the well-known processes of pathology—acute and chronic inflammation, immune reactions, degenerative changes, etc.—may be found in the kidney, and the forms of therapy required to reverse them are equally diverse. All these processes, however, lead to one thing, destruction of renal tissue. This destruction may be rapid and severe, followed by regeneration in many cases, or a slow but progressive destruction with fibrous overgrowth.

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This leads me to the first and most important point I wish to make. Therapy in renal disease must be two-fold. Firstly, it must deal with the pathological process causing renal destruction. Secondly, it must correct the disordered physiology which the renal disease has created. Whereas the pathological processes are legion, they lead to only two types of physiological upsets—acute or chronic renal failure.

In renal failure of either type management consists of either augmenting or completely taking over the functions the kidney normally performs in homeostasis. These functions fall into four groups.

First, the EXCRETION of non-volatile end-products of metabolism. These pass into the glomerular filtrate and are either not reabsorbed or only partially reabsorbed by the tubules. Second, the maintenance of WATER BALANCE. The tubules allow only sufficient water to be reabsorbed from the filtered fluid to provide normal tonicity. Thirdly, ELECTROLYTE BALANCE. Normally the dietary intake provides an excess of Na, K and Cl. Na Cl is filtered and only the

right amount is reabsorbed. The appropriate amount of K is secreted by the tubular cells. These activities are under the control of the adrenal cortical hormones.

Lastly, ACID-BASE BALANCE. Bodily metabolism leads to the production of mainly acid end-products. These are buffered in the blood, mainly by the HCO_3 ion. Exhalation of the resulting CO_2 provides a rapid stabilisation of the pH. However, although the pH is corrected, the blood HCO_3—that is the alkali reserve—is depleted.

The function of the kidney in acid-base balance is, in fact, to maintain the normal plasma HCO_3 level, by producing one HCO_3 ion for every H^+ ion excreted.

CAUSES OF ACUTE RENAL FAILURE

HYPOVOLAEMIC SHOCK commonly arises from loss of blood, and renal complications are especially common after obstetrical haemorrhage. Loss of plasma after burning, and of fluid and electrolytes as in diabetic coma can also lead to renal damage. The renal failure is thought to be due to ischaemia of the kidneys, following intense vasoconstriction in an attempt to maintain the systemic blood pressure. The renal medulla has a poorer blood supply than the cortex, and hence prolonged shock leads first to acute tubular necrosis. If the state of shock persists for an extreme length of time, cortical damage ensues and irreversible renal cortical necrosis occurs. The treatment of a shocked patient found to be anuric therefore consists of immediate vigorous resuscitation with the appropriate fluid. In many cases recovery of the blood pressure will be followed by resumption of urine flow. If oliguria persists, acute tubular necrosis must be assumed to have taken place, and the resultant acute renal failure must be managed along the lines I shall indicate later. Spontaneous regeneration of the tubules leads to resumption of urine flow some ten to twenty days later. If anuria persists much beyond this time, renal cortical

TABLE 1

Causes of Acute Renal Failure

Mechanism	Condition	Treatment
Renal Ischaemia	HYPOVOLAEMIA	Volume Expansion
Acute tubular necrosis	SEPTICAEMIA	Chemotherapy
Renal cortical necrosis	HEPATO-RENAL SYNDROME	Chemotherapy
Direct tubular damage	CRUSH SYNDROME	None
	INCOMPATIBLE TRANSFUSION	None
Acute tubular necrosis	RENAL POISONS	None
	NECROTISING PAPILLITIS ..	Chemotherapy
Diminished filtration	GLOMERULONEPHRITIS	None
	DIFFUSE ANGIITIS	Steroids
Back pressure	OBSTRUCTION	Surgery
	INFECTION	

necrosis must be assumed to have taken place, and the prognosis is hopeless.

SEPTICAEMIA often leads to acute renal failure, and here again the mechanism is thought to involve ischaemia. Bacterial toxins have been shown experimentally to depress renal blood flow. The HEPATO-RENAL SYNDROME is an interesting rarity in which a severely jaundiced patient goes into super-imposed renal failure. This is now thought to be due to an E. coli septicaemia complicating the initial cholangitis. The treatment for both these conditions is clearly appropriate chemotherapy.

In the CRUSH SYNDROME renal failure occurs when the circulation is restored to a region which has had its blood supply occluded for many hours, as after a fall of rock in the mines. Renal damage is caused by the action of toxins liberated from the injured tissue. The same applies after INCOMPATIBLE BLOOD TRANSFUSION. These two conditions are therefore grouped with the RENAL POISONS, and really have no specific treatment.

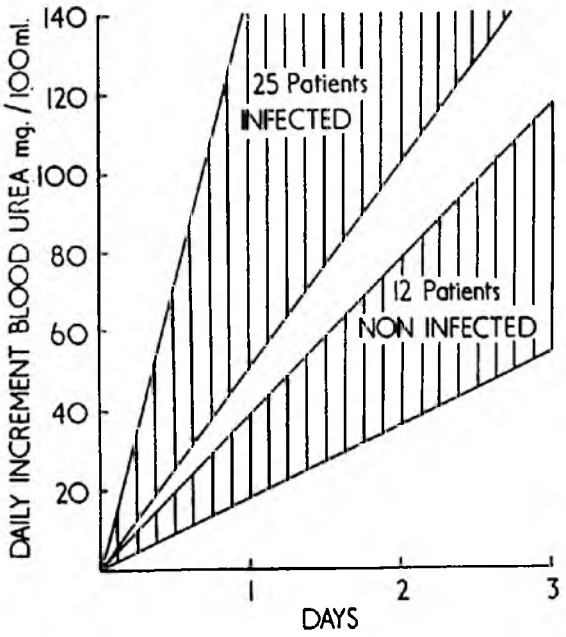

Fig. 1.—The influence of severe infection on the course of acute renal failure. The daily increment of blood urea was calculated for each patient over a period of 3 days.

(Robson, J. S. (1961). Symposium. Some Aspects of Renal Disease. Royal College of Physicians, Edinburgh.)

By NECROTIZING PAPILLITIS I mean very virulent forms of pyelonephritis which can cause acute renal failure by direct tubular damage. Treatment again is appropriate chemotherapy.

The next two conditions cause acute renal failure at the glomerulus by diminishing filtration. Acute GLOMERULONEPHRITIS has no specific treatment. By DIFFUSE ANGIITIS I refer to collagen diseases such as polyarteritis nodosa, which can at least be made to remit (in certain cases) by the exhibition of steroids.

Finally, OBSTRUCTION. In cases of total anuria, obstruction is nearly always the cause, whether from prostatism, stricture, pressure from a tumour, and so on. There should never be any hesitation in carrying out cystoscopy and retrograde pyelography in these cases, and surgery may be life-saving.

Across the bottom I have written INFECTION, in large letters. In an infection,

with accompanying pyrexia, tissue catabolism is greatly increased. The excretory load on the kidney is therefore increased, and a kidney which is well able to cope with normal conditions may be unable to excrete this additional load. Although output is normal the urine is of low specific gravity. Thus acute renal failure can exist even when quite large urine volumes are being excreted in an infected patient. Infection should always be remembered both as a primary cause of renal failure and as an exacerbating factor in failure from any other cause.

These, then, are some of the pathologies leading to acute destruction of renal tissue and the rapid development of oliguria or anuria. The renal destruction can rarely be altered by specific therapy, but in time spontaneous regeneration of the renal tubules frequently takes place. But during the anuric interval the well-known picture of acute renal failure appears. The absence of renal function leads to a rising blood urea and progressive derangement of the internal environment. This acute renal failure can rapidly kill the patient, but if the failure itself is treated, survival can frequently be prolonged until the new renal tissue becomes functional.

THE TREATMENT OF ACUTE RENAL FAILURE

As outlined, the kidney performs four functions, and each is impaired or abolished in renal failure.

The EXCRETION OF NITROGENOUS END-PRODUCTS virtually ceases, and therefore the production of these must be cut to a minimum. Protein is excluded from the diet. Secondly, a high caloric intake is given in the form of carbohydrate. This reduces endogenous production of urea to a minimum, as protein catabolism to provide energy is rendered unnecessary. The calories are supplied as dextrose, lactose or glucose.

The so-called anabolic steroids have been used to oppose protein catabolism. The initial promising results, however, were obtained in patients with renal

TABLE 2

Treatment of Acute Renal Failure

Failing function :	**Therapeutic measures:**
Excretion	No protein High caloric intake
Water balance	Fluid balance chart Clinical assessment Weighing
Electrolyte balance	Prevent NaCl depletion Prevent K+ intoxication
Acid-base balance	Administration of alkali

failure after post-partum haemorrhage, and the effect may be a specific one on the involuting uterus. It has also been found that while these drugs check the rise in blood urea, other end-products such as creatinine continue to accumulate and clinical deterioration occurs. There is probably no place for these drugs in the treatment of renal failure at present.

Secondly, WATER BALANCE. The anuric patient cannot excrete excess water, and unless fluid intake is restricted he rapidly becomes water intoxicated. The insensible water loss through the lungs and skin totals about 500 ml/day, and water administration must therefore be restricted to 500 ml plus the volume of fluid lost during the previous day, by vomiting or diarrhoea as

well as in the urine. If the patient is fevered, an extra ration must be given to replace the volume lost in the sweat.

Successful control of the state of hydration rests on three measures. Accurate fluid balance charts must be kept. The usual slap-dash affair is worse than useless. The exact quantity of all fluids given must be accurately recorded, and any loss by vomiting, diarrhoea or as urine carefully measured. The correct amount of water for a uraemic patient can only be prescribed on the basis of the previous day's fluid balance.

Secondly, the patient's state of hydration must be assessed clinically each day. A trace of sacral oedema or a few basal crepitations are warning signs of overhydration.

Thirdly, daily weighings are most helpful in indicating gain or loss of total body water.

The amount of water which can be allowed as a vehicle governs the number of calories which can be given. If 50% glucose is used an adequate caloric intake is ensured by any volume over 500 ml. At first this may be given by mouth or intragastric drip, but when the B.U.N. reaches about 100 mg % the incidence of vomiting makes intravenous administration essential. Venous thrombosis can be very troublesome, and some authorities use only 20% glucose intravenously. The passage of a plastic cannula into a large vein, frequent change of vein, and heparinisation of the infusion fluid all minimise this problem.

Thirdly, ELECTROLYTE BALANCE. The normal kidney controls this by excreting an appropriate amount of the dietary intake, which is normally excessive. As this excretion cannot occur in anuric patients, no sodium chloride should be given as a rule. Some salt is lost in the sweat and scanty urine, however, and if vomiting occurs salt loss may be serious. The salt lost in this way should be estimated, and a suitable amount of the water ration given as normal saline to correct this. The sodium depletion would otherwise lead to a fall in circulatory volume and further deterioration in renal function would ensue. Nevertheless, very slight overtransfusion with saline easily tips over these patients into pulmonary oedema, and salt replacement should be undertaken with caution.

With potassium the problem is a different one, for cellular catabolism leads to a steady release of the ion into the blood stream. The blood level therefore rises in the course of renal failure, and if there has been much cellular damage, this rise is very rapid. This is most marked in crush injuries and haemolysis, where cellular breakdown is extensive. Unlike sodium and chloride, high potassium levels are very dangerous, and ventricular fibrillation due to hyperkalaemia is a common terminal event in uraemia. It is important to prevent a high potassium level, as once this is established it is very difficult to lower. Potassium is rigorously excluded from the diet—fruit juice is quite a potent source. Cellular breakdown with potassium liberation is minimised by the high caloric diet already discussed. Depletion of sodium chloride must be corrected, as any diminution of circulating blood volume would allow liberated potassium to cause a correspondingly greater rise in blood potassium con-

centration. Finally, acidosis must be controlled, as it is thought that some of the excess hydrogen ions in acidotic states enter the cells in exchange for potassium ions, thus again causing a high blood potassium level.

If haemolysis or extensive soft tissue injury has occurred, however, the blood potassium will reach dangerous levels despite these precautions. Two emergency measures may be life-saving in these circumstances. A 50% glucose drip with 20 units of soluble insulin added to every 100 ml has been found to promote the passage of some potassium back into the cells. Unfortunately this requires the concomitant administration of quite large volumes of water, which may be dangerous. The alternative is the use of an ion exchange resin such as Resonium A, either by mouth or as a retention enema. These non-absorbable resins are saturated with sodium, and in the gut lose some of this sodium in exchange for an equivalent amount of potassium, which thus leaves the body per rectum. 30 g. of Resonium A may lower the blood potassium level by 1 m. eq/litre, and can be repeated thrice daily.

The final feature of acute renal failure is ACIDOSIS, as the anuric kidney is unable to excrete hydrogen ions, and the damaged tubules cannot manufacture bicarbonate. I have already mentioned the dangers of potassium intoxication which are intensified by acidosis. The bicarbonate level must be monitored, and if it falls seriously an appropriate amount of the daily water ration should be given as 1/6 molar lactate.

These measures constitute the basic regime in acute renal failure. The general medical care of these patients must maintain a very high standard, and extensive laboratory facilities are required. The blood chemistry must be analysed at least once every day. These patients rapidly become profoundly anaemic due to toxic depression of the bone marrow, and transfusion of packed cells may be required. The most important general measure, however, as I mentioned earlier, is the prevention of infection. This is important firstly because these patients are particularly susceptible, and secondly because if infection occurs the build-up of renal failure is much more rapid. Nursing in isolation is the ideal plan, but where this is not possible strict hygiene and the use of antiseptic creams, etc. can be rigorously enforced. If an infection does arise, antibiotics must be used with the greatest precision. No antibiotic must be used without the sensitivity of the organism being known. To make this possible routine daily cultures of blood, urine and sputum, should always be carried out. If this is done, by the time an infection becomes apparent clinically, the infecting organism is known and its sensitivity is being determined. The circumstances in which an antibiotic must be used "blind" therefore never arise.

Infection is the crucial factor in acute renal failure. If it is prevented, the patient can usually be tided over until urine flow is resumed by the conservative measures I have outlined. If infection occurs, renal failure progresses rapidly to a fatal stage despite these measures. Fig. 1 shows the rate of rise of BUN in infected patients compared with a non-infected group. It is in the treatment of this infected group that the so-called "artificial kidney" plays a principal part.

THE ARTIFICIAL KIDNEY

In the artificial kidney the patient's blood is led through a coil in which it is separated by a semi-permeable dialysis membrane from a bath containing

the plasma electrolytes in their normal concentrations. The patient's blood is thus allowed to equilibrate by simple diffusion with normal ionic concentrations. Blood urea and potassium levels are rapidly lowered, whilst bicarbonate ion passes from the bath into the blood to restore the alkali reserve. After some 4 to 6 hours of circulation through this coil, the blood chemistry will have been radically improved. The normal solution in the bath will of course have been altered, and must be changed at least once during dialysis.

Certain fixed biochemical criteria have been established as indications for dialysis. Thus if the blood urea level exceeds 350 mg % dialysis should be undertaken. This level is reached in a very few days in severely infected cases. A blood potassium level higher than 7-5 m. eq./litre (usually associated with soft tissue injury or haemolysis) or a bicarbonate level below 14 m. eq./l, calls for immediate dialysis.

Apart from these three fixed criteria, dialysis is undertaken if signs of undue clinical deterioration occur, such as mental confusion or the onset of twitching. Dialysis is also undertaken early in severely infected cases when it is obvious from the outset that conservative measures will be inadequate.

The only contra-indication to use of the kidney lies in the necessity for anticoagulants. In certain patients this is obviously a risk, but as dialysis is a life-saving procedure this risk must be taken. It must also be admitted that in using extra-corporeal dialysis we are interfering with physiological mechanisms which are far from being fully understood, and many unexplained sudden deaths occur shortly after the blood chemistry has been rendered apparently normal. These deaths occur, however, in patients who were extremely ill before dialysis, and thus they perhaps constitute an argument for using dialysis early rather than for not using it at all.

It should be remembered that the anuric phase of acute tubular necrosis is followed by a diuretic phase. During diuresis the patient can become dehydrated, and due to delay in the recovery of tubular reabsorptive powers serious urine loss of sodium, chloride and potassium can occur. Indeed, before treatment of renal failure became effective, over 25% of the deaths occurred not in the oliguric phase but during the subsequent diuresis. A plentiful water intake must therefore be ensured. Salt losses can be estimated by monitoring the serum electrolytes and also by measuring the quantities of the various ions lost in the urine. Supplements of these ions may be required until normal renal concentrating power is regained.

CAUSES OF CHRONIC RENAL FAILURE

In acute renal failure specific treatment is rarely able to influence the causative pathology. The important procedure is to treat the physiological dislocation and maintain the patient until spontaneous recovery of renal function takes place. Chronic renal failure however is caused by progressive fibrosis of the kidney, and no regeneration of renal tissue takes place. The most important step in chronic failure is therefore to determine the underlying cause of the condition and attempt to arrest the pathological process.

Table 3 shows a few of the more common causes of chronic renal failure. The order looks haphazard because I have placed the conditions which can be treated with most success at the top of the list. A chronic obstruction to the urinary tract as from prostatism can usually be eradicated. Chronic pyelonephritis is particularly liable to linger on, progressively destroying renal tissue, in the pre-

sence of obstruction. Removal of the obstruction followed by isolation of the organism and appropriate intensive chemotherapy may arrest this process. Tuberculous infection may also be eradicated. Hydronephrosis will regress after removal of the obstruction. The renal lesions in hyperparathyroidism, diabetes, and even amyloid disease may regress with treatment of the underlying condition. Control of the blood pressure will arrest the progressive renal sclerosis which accompanies hypertension. Treatment for polyarteritis, D.L.E., the

TABLE 3

Some Causes of Chronic Renal Failure	
Chronic urinary tract obstruction Chronic renal infection, inc. T. B. Hydronephrosis Hyperparathyroidism	Amenable to treatment
Diabetes Amyloid disease Hypertensive vascular disease	Partial recovery possible
Diffuse angiitis, D.L.E., etc. The leukaemias Chronic nephritis Polycystic disease	Palliative therapy only
Associated with the Nephrotic Syndrome	
Type II nephritis Chronic glomerulonephritis Diabetes	Amyloid disease Thrombosis of the renal veins

leukaemias and so on can only delay the inevitable fatal outcome. When these potentially treatable conditions have been ruled out, we are left with a hard core of cases due to chronic nephritis and polycystic disease which are not amenable to treatment.

Other treatable factors affect the course of C.R.F. I make no apology for returning once again to infection. Any systemic infection places an additional strain on the kidneys and intensifies the degree of renal failure. If the infection is eradicated, failure will become less marked, and the patient may continue tolerably well for a further indefinite period. All the causes of acute renal failure are particularly liable to occur in the course of chronic failure, and again if the acute phase is energetically treated the patient may regain reasonable health.

THE NEPHROTIC SYNDROME

I have grouped certain causes of chronic renal failure separately because they are often associated with the clinical picture known as the nephrotic syndrome. The hallmark of this syndrome is massive proteinuria, with marked lowering of the plasma proteins and consequent gross oedema. It can occur when the kidneys are involved by any of these processes, but conversely any of them may progress to chronic renal failure without ever presenting a nephrotic picture. Often the proteinuria will regress spontaneously, and the oedema clears. Whilst recovery may be permanent, most cases present again some years later with chronic failure. Indeed, some cases go on to extensive renal fibrosis with renal failure whilst proteinuria and oedema still persist.

In children the nephrotic syndrome is nearly always due to type II nephritis. That is, its onset is insidious, and no underlying cause such as diabetes exists.

The histology of the kidney presents a typical appearance. There is now good evidence that steroid therapy is of benefit in these cases. Arneil in Glasgow reviewed his patients at a date two years after the onset of the disease. Previous to the use of steroids only 62% of his patients survived this period. Using prednisolone the two year survival rate is 91%. Regression of proteinuria is quicker and more of the patients are symptom-free after two years. There is some evidence that under steroids the electron-microscopic appearances of the kidney sometimes return completely to normal. Although steroids have proved far from completely successful their use is thus a real therapeutic advance.

TABLE 4

Treatment of Chronic Renal Failure

Failing function :	**Therapeutic measures:**
Excretion	Low protein, high caloric intake Generous water intake
Water balance	Generous water intake
Electrolyte balance	Prevent NaCl depletion Prevent K+ intoxication (Prevent Ca ++ depletion)
Acid-base balance	Administration of alkali

In the adult presenting with the nephrotic syndrome one of the other causative factors, such as diabetic nephropathy is commonly found, and treatment is aimed at the basic disease. Even with diagnosis by renal biopsy, however, a certain number of so-called idiopathic cases do present, in which no specific abnormality is found, and which may be benefited by steroids.

THE TREATMENT OF CHRONIC RENAL FAILURE

As in acute failure, all the functions of the kidney are impaired. The ability to concentrate and dilute the urine is lost, and large volumes of urine isotonic with plasma are excreted. Excretion of urea is impaired and as in acute failure a low protein, high caloric diet is essential. Anorexia is common, but the disease may run on for several years and it is essential to insist on a good diet being taken. Vitamin supplements are commonly prescribed.

If the tonicity of the urine is constant it follows that the greater the volume of urine passed, the greater the excretion of waste products. A generous water intake should therefore be ensured to promote excretion. An intake of from 2 - 3 litres is also required to preserve water balance, since polyuria is a constant feature.

It is a common misapprehension that salt should be restricted in renal failure. There is no indication for salt restriction in the absence of oedema or cardiovascular disease. These patients become salt depelted, both through renal wasting and by vomiting and diarrhoea. Indeed a supplement of 5 G/day of sodium chloride should be given. Much of the malaise associated with chronic renal failure is in fact due to chronic dehydration from salt depletion and failure to replace the large urinary water loss.

Some rare types of chronic failure do lead to potassium wasting. Usually, however, levels tend to be high, and potassium intoxication is a danger. The

prevention of this is on the lines suggested in discussing acute failure. The calcium loss does not usually require treatment.

Lastly, pH balance. The mechanism through which the acidosis occurs in chronic failure is a complex one. The end result, however, is a depletion of the alkali reserve, and oral supplements of sodium bicarbonate are therefore the correct treatment.

The regime which I have merely outlined is suited to most cases of chronic renal failure, but the nephrotic group with gross oedema present a different problem. In the presence of massive proteinuria a high protein, high caloric diet is indicated. There is no call for water restriction, but sodium intake should be restricted to less than 1 gm/day. Where the use of steroids is not applicable, long term treatment with chlorothiazide and potassium chloride supplement should be instituted and continued for as long as the drug remains effective.

I have already stressed the dangers of infection, and the likelihood of acute episodes disrupting the normal chronic course. A third hazard is cardiovascular disease. The great majority of these patients develop hypertension, followed by cardiac failure which complicates the terminal stages of the disease. Anaemia is quite intractable, and in general the haemoglobin is kept at about 40% by periodic transfusions of packed cells. Diarrhoea, vomiting, muscular twitching, mental changes and convulsions all require symptomatic treatment in the terminal stages.

Chronic renal failure always progresses to a stage where despite treatment the blood urea is high and rising, the potassium level is dangerously high and the alkali reserve dangerously low. At this stage the artificial kidney can be used, but its benefits are short-lived. The grafting of permanent plastic cannulae into the forearm vessels is being developed, through which the patient can be periodically "plugged in" to the artificial kidney. One questions, however, whether it is justifiable to prolong a life, which is an increasing burden to the patient, in this way. The main function of the kidney in chronic failure is in the treatment of acute episodes when the patient still possesses sufficient renal tissue to continue a useful life afterwards. The future cure of chronic renal disease may perhaps come by a break-through in the field of kidney transplantation.

In all the renal diseases, the many pathologies interfere with a single physiological unit. My hope has been that the physiology of the kidney would provide a unifying backcloth against which it would be profitable to survey the whole range of its diseases.

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