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STRUCTURAL AND FUNCTIONAL ADAPTATION IN RENAL FAILURE*

BY

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[WITH SPECIAL PLATE]

I am very conscious of the honour, and the responsibility, of being asked to take part in a series of lectures which began in 1581 during the reign of another Queen Elizabeth, a series in which William Harvey himself participated. Richard Bright gave these lectures in 1837, but unfortunately they do not seem to have been published, and we are ignorant even of his title, though we may make a shrewd guess as to his subject. Reginald Southey chose Bright's disease for his discourse in 1881, and Rose Bradford was Lumleian Lecturer in 1920, but did not choose to speak on renal disease—which, as I think, is a pity, for some of his original work on the kidney is still of such importance that I shall in due course quote from it, more than half a century after its publication. Croonian Lecturers of this College also, from time to time, have chosen the kidney as their theme.

Adaptive Processes

My own title is "Structural and Functional Adaptation in Chronic Renal Failure," and I shall reserve the right to interpret very freely my self-imposed terms of reference. The study of human disease reveals frequent evidence of the wonderful adaptations which take place in the body in response to pathological situations. A good example is the increased cardiac output which regularly occurs in chronic anaemia (Sharpey-Schafer, 1944). Its purpose is surely to maintain an adequate oxygen supply in spite of a greatly diminished oxygen-carrying power. Sometimes these adaptive processes seem to be a consequence of extreme conditions acting on already existing and well-recognized physiological mechanisms; for instance, the hyperpnoea of acidosis. Perhaps they are really all of this nature. Sometimes it appears to be no more than a lucky accident that the disorder sets in motion a process tending towards its own neutralization. Sometimes the adaptation seems to be specially developed to meet an existing situation.

The raised blood urea in renal disease is a simple example of an adaptation. Urea is excreted by glomerular filtration, and therefore must increase in the blood as destruction of renal tissue leads to diminution of filtration rate. As it does so it automatically reaches a point where the increased height of the blood urea ensures its own excretion. Suppose that you have two funnels—a large and a small one. The large one filters at the rate of 100 ml. per minute and is filtering a solu-

tion of urea containing 30 mg. per 100 ml. Obviously 30 mg. of urea per minute appears in the filtrate. The smaller funnel filters at only 30 ml. per minute, but contains a stronger solution of urea—namely, 100 mg. per 100 ml. Obviously 30 mg. of urea per minute is filtered also by this funnel. You may look upon this as a greatly over-simplified example of what happens in renal failure, the larger funnel representing the normal kidney and the smaller funnel the kidney of chronic renal disease filtering a solution of much higher urea content.

I shall return later to the question of urea excretion in more detail, but I have chosen it as a very simple and self-evident example of an adaptation; so simple, in fact, that we may doubt the justification of calling it an adaptation at all. It may be purely fortuitous that urea retention leads to more efficient urea excretion. But in the more complicated adaptive processes of the body—for instance, the increased cardiac output of anaemia to which I have already referred—it is difficult to doubt that there is a purpose in the phenomenon. If we recognize a purpose then we are speaking teleologically, and that is still thought to be a sin by many physiologists and biologists, so I would like to say a word or two about it. Teleology is explanation by reference to the realization of some purpose or end, contrasted with explanation by efficient causes only. Now adaptation, in our present sense of the term, is making something suitable to or for a purpose (I have consulted recognized authorities for my definitions). Thus it is quite impossible to consider phenomena as adaptive in nature without admitting that they have purpose, and impossible to discuss their purpose without resorting to teleology.

In many of the body's adaptive processes (unlike the simple example of the blood urea) we may see the purpose before knowing or discovering the mechanism by which it is mediated or even the stimulus which sets it in motion, and here the process of teleological thinking, if not misused, can be a valuable aid to hypothesis.

The weakness of teleology is that it never takes us beyond the stage of hypothesis, and as Sir Thomas Lewis (1925) said: "Hypothesis has its right place—it forms a working basis; but it is an acknowledged makeshift, and as a final expression of opinion it is an open confession either of failure or at best of purpose unaccomplished." I fear that these lectures will contain several examples of purpose unaccomplished.

*The first of two Lumleian Lectures delivered before the Royal College of Physicians of London on April 1 and 3, 1952.

Before going further I had better define renal failure, for it is entirely of renal failure that I shall be speaking. It is the function of the kidney to preserve the composition of the extracellular fluid, and when the kidney fails in that function disturbances in the chemical structure of the body fluid occur. The most ready evidence of renal failure is the increase in the urea content of the blood or plasma, so the term uraemia is equally appropriate, though less satisfactory, for it concentrates attention on but one not very important aspect of the subject. Functional tests may detect a state of renal insufficiency before renal failure has actually occurred. I shall not deal with the oedematous syndromes of renal disease or with the acute renal failure which occurs in tubular necrosis and sometimes in acute nephritis, nor shall I discuss the extrarenal causes of uraemia unless these are referred to for purposes of argument or illustration.

Chronic renal failure has many causes, the commonest of which are nephritis in its terminal stage, chronic pyelonephritis, and the malignant phase of essential hypertension (Platt and Davson, 1950). Their common structural basis is a diminution in the number of functioning nephrons.

Structural Adaptation

The most obvious adaptive or compensatory process in renal disease is a structural one. It is well known that in cases of unilateral renal disease in man the sound kidney becomes hypertrophied, and functional studies after nephrectomy have frequently shown that the renal blood flow and glomerular filtration rate of the remaining kidney may reach about 80% of that of the two normal organs (Weiss and Chasis, 1943; Welsh, Wellen, Taylor, and Rosenthal, 1944; Hogeman, 1948).

In animals, unilateral nephrectomy generally results in hypertrophy of the remaining kidney to about 75% of the original weight of the two kidneys (Addis, 1948).

Renal hypertrophy after unilateral nephrectomy seems to be dependent upon the integrity of the anterior pituitary and probably upon its growth hormone, for it does not take place in hypophysectomized animals (Winternitz and Waters, 1940; White, Heinbecker, and Rolf, 1941), whereas the administration of anterior-lobe extract causes renal hypertrophy even in castrated animals (Selye, Stone, Nielsen, and Leblond, 1945) where the action of pituitary gonadotrophic hormone on testosterone production can be excluded.

Renal hypertrophy can be produced in young animals by a high-protein diet (Addis, MacKay, and MacKay, 1926), but not to the same extent by the administration of urea (MacKay, MacKay, and Addis, 1931; Baxter and Cotzias, 1949).

In experiments which Platt, Roscoe, and Smith (1952) have been making on rats, more than half of one kidney is removed at a first operation and the remaining whole kidney is removed about ten days later (Fig. A). The initial weight of the remaining renal remnant is calculated from the weight of kidney removed and the weight of kidney per unit of body weight in normal control rats. In 18 experiments the

FIG. A.—Removal of renal tissue in experimental renal failure. Only a small portion of the left kidney remains.

calculated gain in weight of the remaining piece of kidney varied considerably, but was over 100% in four cases, with a mean gain of 66%. This hypertrophy had taken place in about two to three weeks after the second operation. Fig. 1a (Special Plate) shows the

normal histology of the rat kidney and Fig. 1b the histology of the remaining fragment. The striking change is one of tubular hypertrophy, most obvious in the proximal tubules and the loops of Henle, and this is due largely to cellular hyperplasia, mitoses being frequently observed. The tubular lumen is often dilated (Figs. 2a and 2b). The glomeruli are also enlarged and altered in shape.

In some parts of the kidney, however, especially where a replacement fibrosis of non-functioning tubules has taken place, the tubules are much dilated and show a low form of atypical epithelium. Often this seems to occur in tubules which have previously hypertrophied. I am indebted to Dr. Smith for the photomicrographs. Similar observations have of course been made by other workers (Addis, 1948). Not only do the nephrons enlarge but the work done by each nephron increases. Using endogenous creatinine clearance as an index of glomerular filtration, we find that the filtration rate per unit weight of renal tissue has increased by an average of over 40% in 18 observations. In many cases the glomeruli appear to be filtering at more than one and a half times their normal rate. The increased function must really be even greater than it seems because the weight of the renal remnant must include a good number of non-functioning nephrons which have been cut across in the course of the operation, a certain amount of scar tissue, and all the pelvic and hilar tissue which is preserved at the operation.

All the structural changes in the rat kidneys can be found in terminal human renal disease, although in these fatal cases regressive and fibrous changes are more evident than hypertrophy. Fig. 3a shows hypertrophied tubules in a case of chronic pyelonephritis, and Fig. 3b shows tubular dilatation in another part of the same kidney. Similar changes occur in unilateral renal disease, and have been seen in a kidney removed from a hypertensive patient in

FIG. B.—(a) Normal human nephron, (b) hypertrophied human nephron from chronic glomerulonephritis. (From J. Oliver (1950), by kind permission of Dr. Oliver and the publishers of the *Journal of Urology*.)

whom the abnormal kidney did not visibly excrete diodrast although the opposite kidney was functioning well in this respect.

These appearances of chronic renal disease would strongly suggest that, whereas most of the renal tissue may be destroyed, the functioning remnant is hypertrophied and may be working at an increased rate.

The beautiful morphological studies of Jean Oliver (1950), in which whole nephrons are separated by microdissection, have shown that the hypertrophy and hyperplasia in nephrons from human chronic renal disease occur chiefly in the glomerulus and proximal tubule, which latter is increased both in thickness and in length and to such an extent that its volume may be 20 times that of a normal proximal tubule. I have Dr. Oliver's permission to reproduce Fig. B from one of his papers. Oliver also shows that, while some tubules undergo this hyperplasia, others, as we have seen, are atrophied. Some show the peculiar anomaly of a hypertrophied tubule unattached to a glomerulus.

That the hyperplastic tubules actually have increased function Oliver (1944-5 and 1950) has also shown by the intravital injection of trypan blue in dogs suffering from chronic canine Bright's disease. The nephrons absorb and store the dye in a normal manner but in greatly increased amount.

I shall several times refer back to these studies of structure in chronic renal disease when considering renal function, for it is most important that functional studies should take them into account, and I would emphasize particularly the contrast between a low glomerular filtration rate due to conditions imposed upon a kidney of normal size, as in heart failure, and a low glomerular filtration rate due to loss of nephrons. In the first instance the rate of filtration per glomerulus is low, and in the second instance, as in our rats, it is high. The total effective renal function is reduced owing to loss of tissue, but the work of each remaining unit is increased. Workers in the field of applied renal physiology have frequently overlooked this essential distinction, and at the risk of overemphasis I will illustrate it by a simile from industry. The total production or output of a factory may fall for one of two reasons. The team of workers may become slack or may not have enough to do, like the nephrons in heart failure; or the team may have been seriously depleted in numbers owing to illness, the few remaining workers actually putting in overtime in an unsuccessful attempt to compensate for the absence of their fellows. The latter is the state of affairs in experimental renal failure, as our obliging rats have clearly demonstrated, and there is good reason to believe that it is the state of affairs also in chronic renal failure in the human subject. If we only study the total production of the factory, without regard to the output per man, or in the case of the kidney the overall function without regard to structure, we fail to distinguish between these two causes of inadequacy, and, since the behaviour of the tubule cells is in a large measure dependent upon the rate at which glomerular filtrate is reaching them, the distinction is of primary importance in the interpretation of the phenomena of renal disease.

Functional Adaptation: Isosthenuria

One of the constant signs of renal failure is the inability of the kidney to produce a concentrated urine, and it is well known that the specific gravity of the urine becomes relatively fixed at about 1010, which is approximately that of the blood plasma minus its proteins. Studies of osmotic pressure or "osmolality" as determined by the freezing-point of the urine again show a similarity to the osmolality of blood plasma. Osmolality depends upon the number of molecules and ions in solution, whereas specific gravity depends upon their weight. Osmolality is really the relevant factor in the present discussion, but, so long as the urine contains only its normal constituents and is free from abnormally heavy molecules such as those of glucose, diodrast, or inulin, specific gravity and freezing-point will give approximately equivalent information.

The phenomenon of isosthenuria—a urine of constant strength—was known to Koranyi as long ago as 1908 (see Volhard, 1931). It is still usually ascribed to tubular insufficiency—a concept which I presume means that the tubule cells are so damaged by disease that they are no longer able to perform the osmotic work required to provide a highly concentrated urine. That this supposition may be erroneous must be clear to anyone familiar with the experiments described by Rose Bradford in 1899, in which he showed that dogs, after removal of three-quarters of their renal tissue, also showed loss of concentrating power. His actual words are as follows: "The fragment of kidney left is quite able to excrete amounts of urea far larger than those usually excreted, as shown by giving the animals considerable quantities of an exclusively meat diet. A concentrated urine, however, is not passed, the increased output of urea being effected by an enormous increase in the amount of the urine." Obviously the remaining renal tubules of these animals have not been subject to any disease process likely to interfere with their ability to produce a hypertonic urine.

In 1939 Hayman *et al.* repeated these experiments and confirmed that after the removal of renal tissue in dogs loss of concentrating power occurred; and they made the further interesting observation that the urinary specific gravity could be increased again by artificially raising the plasma colloids or by reducing the blood pressure, procedures which would, of course, lower the glomerular filtration rate. Other observers, including ourselves, have shown that loss of renal tissue results in loss of concentrating power, and that this may occur independently of the development of hypertension—an observation which applies also to human renal failure, as any clinical observer of renal and hypertensive disease must know.

In a recent paper (1951) I have suggested that the loss of concentrating power is due to osmotic diuresis, and I would like now to examine this hypothesis somewhat more closely. When an osmotically active substance such as glucose or urea appears in the glomerular filtrate in excess it is excreted in dilute solution with a large quantity of water.

McCance (1945) showed, and Rapoport and his co-workers (1949a, 1949b) have since confirmed, that in normal subjects deprived of water the volume of urine passed can be enormously increased by producing an osmotic diuresis, and is in fact determined by the load of osmotically active substances requiring excretion. The interesting fact emerges that if a substance such as urea is ingested in considerable quantity in a state of dehydration the urine becomes less concentrated, not more, and in the fully developed state of osmotic diuresis the urine has an osmolality which approaches or is equal to that of the plasma minus its proteins (Frey and Frey, 1950).

In order to put this to a personal test and to convince myself that a high blood urea reduced the urinary specific gravity, I have made some observations on myself. Under certain standard conditions the morning urine on seven occasions has had a specific gravity ranging from 1026 to 1032. If during the evening I ingest 30 g. of urea with the same amount of fluid as before, which means that I retire to bed with a blood urea of 80-90 mg. per 100 ml., the morning urine has a specific gravity of only 1016-1018. Thus it is quite clear that, in renal failure where the blood urea is high, the kidney must be acting continually under the conditions of an osmotic diuresis, and it is merely adapting itself in a physiological manner to this circumstance in producing a urine of low and fixed concentration.

The phenomenon of osmotic diuresis may be explained in one of two ways. There may be a limit to the amount of osmotic work which the tubule can perform, and to excrete urinary solutes in large quantity it is more economical of work to do so in dilute solution (Hervey, McCance, and Tayler, 1946; Rapoport, West, and Brodsky, 1949b). Homer Smith (1951), on the other hand, ascribes the diuresis to the fact that the excess of solutes interferes with the

reabsorption of water in the proximal tubule, and so the distal tubule is presented with more water than it can absorb.

Thus the isosthenuria of advanced renal failure is easily explained, and the nocturnal polyuria is no doubt also chiefly a consequence of the osmotic diuresis. But if the theory is to have universal application it must explain two further circumstances. The first is that diminution in concentrating power may occur in renal insufficiency before significant elevation of the plasma urea has taken place; and the second is that it may occur in the urine of the diseased kidney only, in cases of unilateral disease (Volhard, 1931; Platt, unpublished data), when the opposite kidney is quite capable of maintaining a normal plasma composition and no condition of osmotic diuresis would at first sight appear to exist.

Returning to the experiments of Rapoport and his co-workers, we remember that in the normal human subject deprived of water the volume of urine and its concentration depend upon the load of solutes requiring excretion. Now it is easy enough to speak in such terms of the intact kidney, but when we apply these findings to renal failure we must think in terms of nephrons rather than kidneys. From our experiments on rats we have seen that when renal substance is reduced the glomeruli enlarge and the infiltration rate per tubule (as estimated by creatinine clearance) is often increased by at least 50%. Thus the load of solutes entering each tubule per minute is greatly increased. Comparison of the structure of the remaining nephrons of the failing human kidney with those of the renal remnant in the rats strongly suggests that the same conditions hold, and, as I have already pointed out, a similar appearance is seen in the diseased kidney when only one organ of a pair is affected. Thus it would seem that in human renal failure the nephrons are acting under increased load even before the stage of nitrogen retention is reached, and should therefore behave as if conditions of osmotic diuresis obtained, producing a urine of low and fixed concentration.

There is another way of looking at this. When we come to discuss the excretion of urea and creatinine we shall see that, in spite of gross reduction of renal tissue in rats or in human disease, the rate of excretion of these substances remains virtually unaltered. There is thus no doubt at all that the solute load being excreted by each nephron is much increased, and this should lead to a condition in which the osmotic work required of each tubule is inconsistent with the production of a highly concentrated urine.

To sum up, then: in the physiological phenomenon known as osmotic diuresis the greater the load of osmotically active solutes requiring excretion the greater is the volume of the urine and the less does its concentration differ from that of plasma. In renal disease the solute load per nephron may be increased either by increasing the osmolarity of the filtrate (for example, by increasing the plasma urea concentration) or by increasing the filtration rate per nephron, or by both conditions acting together. It is maintained that only under such circumstances does isosthenuria occur and that it can therefore be explained as a physiological adaptation to an increased solute load.

I do not intend to dismiss altogether the possibility that damage to tubular cells plays a part. I merely point out that isosthenuria can occur under physiological conditions and in circumstances in which tubular damage is unlikely, and that most of the evidence points, as we shall see, to enhanced tubular activity in renal failure, as the structural appearances might lead us to predict. An exception is almost certainly to be found in acute tubular necrosis and in poisoning of the renal tubules by mercury, uranium, and oxalates. In these conditions (which are not discussed in these lectures) a true tubular failure probably occurs.

The Excretion of Urea and Creatinine

The amount of renal tissue removed from our rats was from 67 to 85%, more being removed in the later experiments than the earlier ones. In eight rats an average of 80%

of their total renal tissue was removed. Before the operation their average creatinine output in 24 hours was 13 mg. After leaving time for recovery from the operation, their creatinine output in 24 hours was 13.3 mg., or 102% of what it had been before.

Compare this achievement of the rats with that of Mrs. B, who had renal failure due to chronic atrophic pyelonephritis. In March, 1947, her blood urea was 178 mg. per 100 ml. and her urea clearance only 9% of the average normal. The blood urea fluctuated a little from time to time, but the lowest figure we ever found was 140. In October, 1948, it was 176 mg. per 100 ml., almost identical with what it had been one year and seven months previously. Clearly she, though like the rats deprived of most of her functioning renal tissue, must have been excreting normal 24-hourly amounts of urea, otherwise her urea retention would have increased.

The most important single factor in securing this amazing adaptation is unquestionably that which I mentioned at the beginning of this lecture—namely, the effect of an increased plasma level of urea (or creatinine). If you filter a stronger solution of urea at a reduced rate the end-result may be the same in terms of urea excretion. The adjustment is, of course, automatic, for when the filtration rate is reduced the plasma urea (or creatinine) rises until its level ensures excretion at a rate corresponding with the rate of formation of urea or creatinine in the body. At that point, if the renal disease does not progress, the blood urea remains stationary. Incidentally, the same considerations answer the question, in case anyone should ask it, why the normal blood urea in the human subject is about 20 to 40 mg. per 100 ml. The reason is that that is the level necessary to ensure the excretion, at normal glomerular filtration rates, of an amount of urea equivalent to that which is being produced in the body by protein metabolism. If we had four kidneys instead of two our blood ureas would be only half as high.

It is interesting to calculate what would happen in a hypothetical case in which the normal urea clearance of 75 ml. per minute was suddenly reduced to 15 ml. per minute, or one-fifth of its former value. The blood urea would rise until it reached five times its normal level, or about 150 mg. instead of 30, after which it would rise no more. Assuming a total body fluid of 50 litres, and that 30 g. of urea is produced daily by protein metabolism the rate at which the blood urea would rise can be calculated and charted (Fig. C).^{*} It will be seen that the blood urea would reach about 100 mg. in two days and nearly 130 mg. in four days. The calculation is not entirely academic in its importance, for it follows that if you have a patient in chronic uraemia whose urea clearance is 20% of normal and whose blood urea is 150 mg., and if by dialysis in some form of artificial kidney you reduced his blood urea to normal, it would rise again to 100 mg. in 48 hours. All this of course follows from a consideration of the clearance formula $\frac{UV}{P}$. This represents the amount of plasma being cleared of its urea (or creatinine) per minute. (The urea clearance is of course lower than the creatinine clearance because some urea is reabsorbed during its passage down

FIG. C.—Calculated rise of blood urea if urea clearance were suddenly reduced from 75 to 15 ml. a minute (see text).

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^{*}I am indebted to Mr. John Allen for the calculation and graph.

the tubule.) U is the concentration of urea (or creatinine) in the urine, P is the concentration in the plasma, and V is the volume of urine in millilitres per minute. UV thus represents the rate of urea excretion which, as we have seen, remains normal in quite advanced cases of renal failure, either natural or experimental. Now, if $\frac{UV}{P}$ is greatly diminished and UV remains normal, clearly P must be much increased, which is exactly what happens.

We have also seen that because of the osmotic diuresis V increases at the expense of U , and the fraction $\frac{U}{P}$, which is related to the osmotic work required to excrete urea or creatinine, is much reduced by a low value for U and a high value for P .

There are, however, three other adaptive processes possibly aiding the excretion of urea or creatinine. The first, which we have already considered, is the increased filtration rate per nephron. The second, which is probably of little significance, is that the slight nocturnal reduction in filtration rate which normally occurs does not take place in renal failure (Brod, 1949).^{*} Thus excretion goes on by day and by night at the same rate. The third adaptation applies to the excretion of urea but not of creatinine. Creatinine is not reabsorbed nor actively excreted by the renal tubule, or not to any significant extent,[†] but urea is reabsorbed, or perhaps we should say it diffuses back into the plasma to the extent of about 30 to 60% at normal rates of urine flow. In other words, the normal urea clearance varies from 40 to 70% of the creatinine clearance. In renal failure reabsorption of urea in the renal tubules is reduced, so that the clearance of urea approaches that of creatinine or inulin (Chasis and Smith, 1938). This may at first sight appear to be an *ad hoc* adaptation or a lucky accident, but in fact it is again explicable as a natural result of an established physiological fact. Möller, McIntosh, and Van Slyke (1929) showed that urea clearance varied with urine flow, and Shannon (1938) has shown that in normal dogs the ratio of urea to creatinine excretion increases with the rate of urine flow, and the same phenomenon has been demonstrated less completely in man (Chasis and Smith, 1938). In chronic renal disease, although total urine flow may not be increased, the rate of flow per tubule is very much greater than normal, as we shall see again in considering water excretion. Thus urea reabsorption will diminish as the rate of urine flow per tubule increases.

To sum up, it may be said that the normal rate of excretion of creatinine and urea is maintained in renal failure even in quite advanced cases, in which probably no more than 10 to 20% of the functioning renal tissue is preserved. This is effected first of all by sustaining a high plasma level of these substances; secondly, by a high rate of filtration per nephron; thirdly, by nocturnal maintenance of maximum possible filtration rate; and, fourthly, by a diminution in the proportion of the urea which the tubules reabsorb.

Conclusion

It may be noted that the *requirements* of urea excretion may be significantly diminished by reducing the protein intake. Pure physiologists mathematically inclined may doubt whether by doing so we are saving the kidney any significant amount of work, since the total osmotic work of the kidney seems to account for only about 1% of its oxygen consumption. "This," as Homer Smith (1951) remarks, "is not to say that the efficiency of the kidney is only 1%; the kidney's efficiency may be very high indeed—it is the thermodynamic approach in terms of final urine that is only 1% efficient." However this may be, clinicians will be more impressed by the fact that in

^{*}Brod's paper deals with acute nephritis, but his illustration on page 323 showing diurnal fluctuations of creatinine clearance gives data for chronic nephritis ("contracted kidneys").

[†]For consideration of the validity of endogenous creatinine clearance as a measure of glomerular filtration rate see Brod and Sirota (1948).

rats whose renal substance was surgically reduced Addis (1948) found that the survival rate was closely related, though in inverse ratio, to their protein intake. I shall continue to recommend a low-protein diet to my renal-failure patients, however competent their adaptive processes. By so doing it would seem that we may increase their survival, and even if we do not achieve that object we may reduce their blood urea. However non-toxic urea may seem to be, anyone who has tried to write the Lumleian Lectures with a blood urea of 80–90 mg. will know from personal experience that it is an impediment to efficiency. But this experiment will be again referred to in its proper place.

(Figs. A and 1–3 are from the paper by Platt *et al.* (1952), by permission of the editor of *Clinical Science*.)

[The second lecture, with a list of references, will appear in our next issue.]

AN OUTBREAK OF ENCEPHALITIS, POSSIBLY DUE TO POLIOMYELITIS VIRUS

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[WITH SPECIAL PLATE]

An outbreak of encephalitis affecting eight young children is described. Somnolence, extrapyramidal type of rigidity and tremor, and spastic paralyses were the dominant features of the illnesses of most of the children, while flaccid paralyses were conspicuously absent. On clinical grounds the cases thus bore little resemblance to poliomyelitis, and this diagnosis was hardly entertained until poliomyelitis virus was found in the stools of two of the cases. Even so, after study of the histology of the brain and spinal cord of the two fatal cases, we have been unable to reach any certain conclusion on the aetiology of the encephalitis.

The eight cases occurred in a period of four weeks in the summer of 1949. All were in children aged 5 or younger. All except one lived in an isolated row of fourteen houses in a rural part of Cambridgeshire; the remaining child, who was the first affected (Case 1), lived two miles away. Dr. Derek Simpson was in medical charge of the families, and gave us invaluable help.

Case 1

A baby boy aged 13 months became fretful and feverish on June 17, 1949. On the third day he was noticed to have difficulty in pulling himself up to stand in his cot. On the fourth day he began to have "attacks" lasting a few minutes and coming on about every three hours; in these attacks he went rigid and opisthotonic, the arms quivered, but consciousness was retained. Between attacks he slept peacefully. He vomited once. On the fifth day his head was noticed to be turned to the left side. On the sixth day head tremor appeared and he was admitted to hospital.

Examination on June 22 showed a well-nourished child, conscious but with a curiously expressionless face. His

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FIG. 1a

FIG. 1b

FIG. 2a

FIG. 2b

FIG. 1.—(a) Normal rat kidney; (b) renal remnant (see text), showing hypertrophy of glomerulus and tubules. (Masson's trichrome. $\times 220$.)

FIG. 2.—(a) Intermediate part of proximal tubule (normal rat); (b) same from renal remnant, showing hypertrophy and dilatation. (Masson's trichrome. $\times 450$.)

FIG. 3.—Human chronic pyelonephritis. (a) Tubules showing hypertrophy and (b) dilatation with flattened atypical epithelium. (Masson's trichrome. $\times 220$.)

FIG. 3a

FIG. 3b

S. MARSHALL AND K. S. MILLINGEN:
CASE OF INFECTIOUS MONONUCLEOSIS

H. J. RICHARDS:
DUPUYTREN'S CONTRACTURE

FIG. 1

FIG. 2

FIG. 3

FIG. 4

FIG. 1

FIG. 2