Papers and Originals

Control of Sodium Reabsorption*

H. E. de WARDENER,† M.D., F.R.C.P.

British Medical Journal, 1969, **3**, 611–616

Dr. Oliver was a general practitioner, who with Professor Schafer demonstrated the presence of adrenaline in the adrenal gland. They had both been taught physiology by Professor Sharpey at University College. Sharpey was a remarkable person. Though he was appointed to the Chair of Anatomy he took it on himself to be the first in this country to give a systematized course of lectures and demonstrations on physiology. He was greatly admired by those he taught, for, in addition to Dr. Oliver's wish to commemorate him by instituting this lecture, Professor Schafer added Sharpey's name to his own many years after Sharpey's death. It is a great honour to be asked to give a lecture in memory of such a person. I am particularly moved that in so doing I am following in the footsteps of Schafer's grandson, Peter Sharpey-Schafer, who gave this lecture in 1961 and in whose department I once worked.

By the end of this lecture the kidneys of each one of us will have filtered and reabsorbed rather more than 1,000 mEq of sodium. Or, in other words, about 6 litres of physiological saline. Whereas less than 1% of this amount, about 6 to 8 mEq, will be excreted in the urine. My purpose is to try to give an account of the present state of knowledge of those mechanisms involved in this massive reabsorption of sodium.

Movement of Sodium and Water

The first stage of sodium and water reabsorption, and by far the most important, occurs in the proximal tubule, where about two-thirds of the filtered sodium and water are reabsorbed. In the proximal tubule the tubular fluid remains isosmotic to plasma, and normally no gradient for sodium is established across the proximal tubular epithelium.[56 120 130 132] Nevertheless, in certain experimental conditions it can be shown that sodium reabsorption can occur against a steep electrochemical gradient, which provides direct proof that sodium is actively pumped out of the proximal tubule.[16 51 52 53 62 104 125 126 129] Additional evidence that sodium transport is an active process comes from the finding of a linear relationship between renal oxygen consumption and sodium reabsorption, so that about 20 to 30 mEq of sodium are reabsorbed per mole of oxygen.[31 48 65 68 70 113 114]

In normal circumstances, therefore, the osmolality of the fluid in the proximal tubule is the same as that of the plasma. Thus it is not immediately obvious what makes water follow the sodium and move from the lumen of the proximal tubule to the peritubular capillary; and, of course, if it is prevented from doing so sodium reabsorption eventually ceases. The following hypothesis to explain the movement of water has been put forward by Curran and MacIntosh[25] and Diamond and his colleagues.[32 33 34] It is a theory which is based on the ultrastructural finding that the tubule cells are associated with two groups of long narrow channels. One group consists of channels between the cells (the intercellular channels), and the other of channels within the cells.

Fig. 1 is an electron microscopy photograph of an intercellular channel between two proximal tubule cells. The brush border is in the top left-hand corner. The intercellular channel can be seen extending diagonally upward from right to left. The important thing to notice is that the channel is blocked

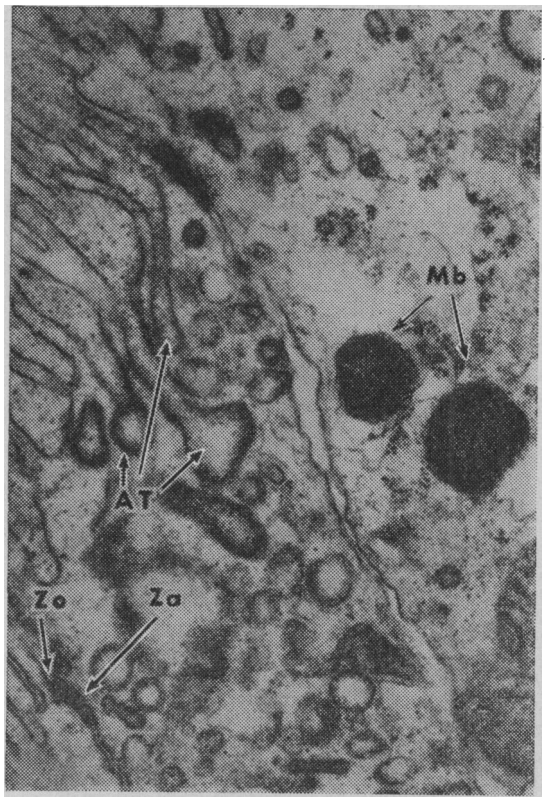

FIG. 1.—Intercellular channel between two proximal tubule cells. The brush border is on the left. The channel runs diagonally upwards from right to left and can be seen to be blocked by a black "plug" just beneath the brush border. (Tisher, Bulger, and Trump, *Laboratory Investigation*, 1966, **15**, 1357.)

at the luminal end, the obstruction appearing as a solid black area.[115] The other end of the channel, which is not shown, opens directly into the interstitial space on the basal or capillary side of the cell. The other group of long narrow channels consists of deep infoldings at the base of the cell. These can be seen in Fig. 2, which shows the basal side of a proximal

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† Professor of Medicine, Charing Cross Hospital Medical School, Fulham Hospital, London W.6.

tubule. The basal infoldings can be seen extending upwards between the mitochondria. Each infolding has an open end which opens directly on to the basement membrane (marked B) while the other end finishes blindly within the cell. Lining the intercellular channels and basal infoldings there is a layer of adenosine triphosphatase, an enzyme which is closely connected with sodium transport.[64 116] Fig. 3 illustrates these anatomical arrangements diagrammatically.

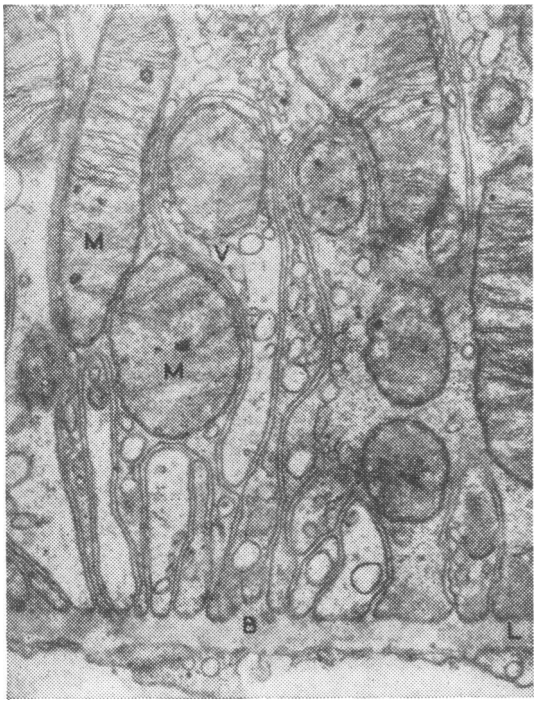

FIG. 2.—Basal infoldings in proximal tubule cell running upwards from the basement membrane (B); some invest the mitochondria (M). (Rhodin, in *Diseases of the Kidney*, edited by M. B. Strauss and L. G. Welt, p. 1. London, Churchill, 1963.)

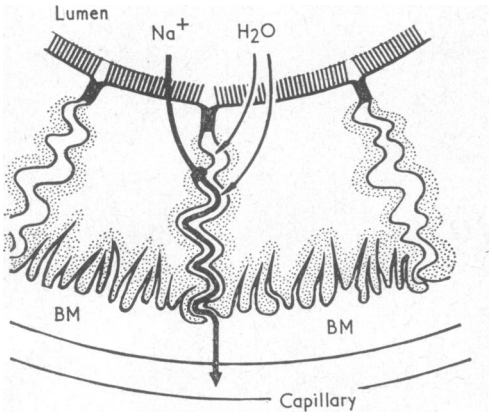

FIG. 3.—Schema of sodium and water reabsorption through the intercellular channels in the proximal tubule. On the luminal side the brush border and the "tight junctions" of the intercellular channels. The basal infoldings on the capillary side of the cell are shown opening on to the basement membrane (BM). The shaded area is the site of adenosine triphosphatase.

Diamond's[32] hypothesis is that sodium is actively transported from the inside of the cell into the intercellular channels and basal infoldings. This makes the fluid within them hypertonic. Water consequently flows across the walls of the channels down the osmotic gradient and into their lumen so that the sodium and the water in the channels are then swept towards their open end at the base of the cell towards the capillary. In this way there is a continuous movement of sodium and water, from the tubule lumen to the interstitial space in contact with the peritubular venous capillaries, through the intercellular channels and basal infoldings. Or, in other words, an isotonic solution passes from one isotonic solution in the tubule lumen to another isotonic solution in the interstitial space via a standing osmotic gradient built up deep in the intercellular channels and basal infoldings.

The bulk of the sodium and water reabsorption occurs in the proximal tubule. Therefore the amount of sodium that is reabsorbed in the ascending limb of the loop of Henle, the distal tubule, and the collecting duct per unit length of tubule is a great deal less than in the proximal tubule. And as this part of the nephron can sustain large concentration gradients for sodium, the path that sodium and water take across the wall need not be the same as that proposed for the proximal tubule. Nevertheless, it is probable that sodium and water do travel along the same paths. There is certainly some objective evidence that in the collecting ducts water travels along the intercellular channels.[49]

Micropuncture Techniques

Before discussing some of the mechanisms which control the rate of tubular sodium reabsorption I should like to describe briefly some of the techniques with which they have been studied. The ones which are least familiar, but which have been the most revealing, are those which involve the use of micropipettes inserted into the tubule lumen. Originally the place in the tubule into which the micropipette was placed had to be determined, after the experiment, by microdissection and isolation of the individual nephron, which was a laborious business.[120]

Lissamine Green

The subsequent use of lissamine green dye, however, simplified localization considerably.[109 110] The dye is introduced into the renal artery, it is filtered at the glomerulus, and it travels down the tubule lumen so that it is possible first to identify the proximal tubules and then, after an interval, the distal tubule. The surface of the kidney is viewed through a dissecting microscope. After the injection of lissamine green the surface of the kidney becomes green as the dye travels through the capillaries. The dye in the vessels passes quickly but that which has been filtered is then seen moving along in the proximal tubules towards the loops of Henle. When all the dye in the proximal tubules has been pushed into the loops it disappears from the surface of the kidney. It takes a remarkably long time to reappear in the distal tubules. What is most striking is the irregular strung-out way in which the distal tubules reappear and how few there are. This demonstrates that some nephrons are longer than others, and particularly that distal tubules tend not to come up to the surface of the kidney.

Flee-flow Micropuncture

Several micropipette techniques are used to study tubular function. The first is to obtain a sample of fluid with a micropipette from the tubule lumen during what is known as free-flow conditions. That is, the fluid that is collected has been filtered from the glomerulus. The osmolality, electrolyte, and inulin concentration of the fluid are then measured. As inulin is not reabsorbed its rise in concentration as it travels down the tubule is a measure of the water that has been removed from the lumen. But, as was mentioned earlier, in the proximal tubule water leaves the lumen only because of sodium reabsorption. Therefore in the proximal tubule the

inulin concentration is a measure of sodium reabsorption. Clearly the inulin concentration will be greater the further the fluid has travelled down the tubule. For this reason it is important to know from which part of the proximal tubule the fluid has been removed. If the experiment consists in studying the effect on sodium reabsorption of a particular stimulus it is important that the fluid which is removed before and after the stimulus should come from the same place. The most convenient way to do this is to repuncture the same nephron in the same place before and after the stimulus. This is known as the re-collection technique.[35] On the other hand, instead of taking a sample of fluid it is possible to collect all the fluid that is being delivered at the point where the micropipette has been inserted and thus to calculate the glomerular filtration rate of that nephron.[10 58]

Microperfusion

The lissamine green technique not only makes it possible to distinguish the proximal from the distal tubules but also makes it possible to identify the course of a single nephron. To do this a micropipette is introduced into a proximal tubule near its glomerulus and lissamine green is injected into the lumen. The course of the whole of the proximal tubule is seen, and then the distal tubule which belongs to that proximal tubule is clearly identified. With this information it is then possible to study the function of a tubule in situ while it is perfused by known solutions at a control rate.[22 82 99] The proximal tubule can be studied by introducing a solution at the beginning of the tubule with one micropipette and withdrawing the solution with another micropipette at a point further down the same tubule (Fig. 4). While the loop of Henle or distal tubule can be studied by introducing a solution at the end of the proximal tubule and removing it either at the beginning or at the end of the distal tubule (Fig. 5). An extension of this technique has been Burg and Orloff's[15] remarkable technical feat of isolating a 1-mm. length of tubule, inserting micropipettes into each end, and perfusing it in vitro in a warm saline bath (Fig. 6). Technically the most difficult problem was to get the piece of tubule to stay on the end of the micropipette securely enough to enable it to be perfused.

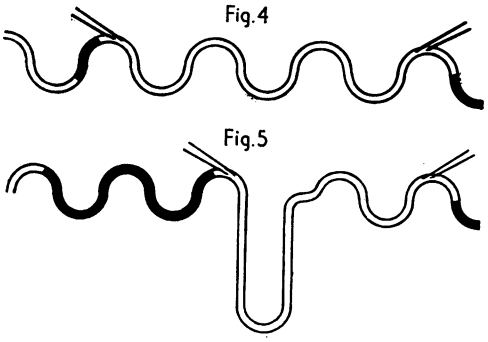

FIG. 4.—Arrangement for perfusing proximal tubules in vivo. The lumen is blocked with oil near each micropipette. (By kind permission of T. Morgan.)

FIG. 5.—Arrangement for perfusing the loop of Henle and distal tubule in vivo. The lumen is blocked with oil near each micropipette. (By kind permission of T. Morgan.)

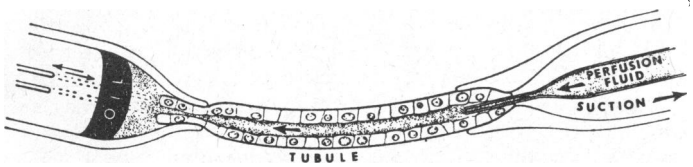

FIG. 6.—Arrangement for perfusing kidney tubules in vitro. (Burg and Orloff, *Journal of Clinical Investigation*, 1968, **47**, 2016.)

Split Oil-drop

The last technique is one that has been used almost exclusively to study salt-and-water reabsorption.[50] It is illustrated in Fig. 7. In this technique a double-barrelled micropipette is introduced into the lumen of the tubule. One barrel contains oil and the other usually contains saline. A drop of oil is first injected into the tubule lumen (line 1 in Fig. 7) and then the oil drop is split by the introduction of the saline into its centre (line 2 in Fig. 7). Now the oil is allowed to

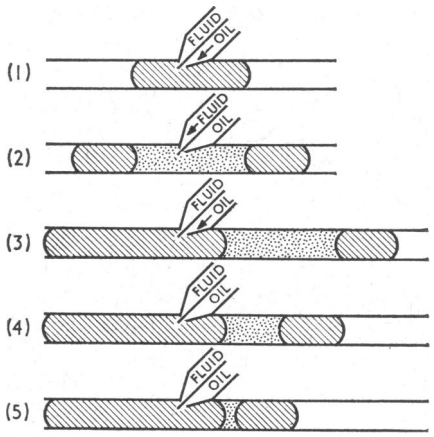

FIG. 7.—Technique of "split oil-drop" of Gertz. A double-barrelled micropipette injects oil into the lumen of the tubule, which is then split by a droplet of aqueous solution such as saline (steps 1 and 2). More oil is then added to move the fluid droplet away from the puncture site (step 3). The rate at which the fluid droplet becomes smaller is then photographed (steps 4 and 5), and is an index of the rate at which sodium is reabsorbed. (Giebisch and Windhager, *American Journal of Medicine*, 1964, **36**, p. 647.)

move down the nephron so that the saline drop is away from the tip of the micropipette, and instead the tip lies in the oil again (line 3 in Fig. 7); this is to make certain that no saline leaks out of the hole made by the micropipette in the wall of the tubule. The rate at which the drop of saline is reabsorbed is then photographed (lines 4 and 5, Fig. 7). First the drop shrinks rapidly, but then as the surface area of the drop in contact with the tubule shrinks so the drop shrinks more and more slowly. The time taken for the drop to shrink to half its size is the unit of measurement, and is known as the reabsorptive half-time of the split oil-drop. It is normally about 9 seconds. This is a good technique with which to distinguish the tubule wall's capacity in vivo to reabsorb sodium, independently of any simultaneous changes which might be taking place in the amount of sodium delivered into the tubule by glomerular filtration. Its main disadvantage is that it is vulnerable to subjective bias.

These micropuncture techniques have established that urinary sodium excretion is almost entirely dependent on changes in tubular reabsorption and not on glomerular filtration rate. And that tubular reabsorption is controlled by certain physiological factors which probably act on the basal side of the cell and by hormones, some of which are yet to be identified.

Effect of Filtration Rate on Sodium Excretion

It has been appreciated for some time that rapid changes in glomerular filtration rate and therefore the amount of sodium delivered into the tubule by the glomerulus are much less closely related to sodium excretion than might be expected if glomerular filtration rate were an important factor in the

control of sodium excretion.[3 7 8 9 24 30 61 71 77 101 102 106 111 112 128] It is therefore not surprising that micropuncture studies under free-flow conditions have shown that this discrepancy is due to rapid compensatory changes in sodium reabsorption that take place all along the nephron whenever there is a change in glomerular filtration rate, and that quantitatively the most important of these compensatory changes takes place in the proximal tubule.[35 69 94]

The nature of these changes has been the subject of many speculations. Recent experiments by Wiederholt, Hierholzer, Windhager, and Giebisch,[127] Burg and Orloff,[15] and Morgan and Berliner,[83] have considerably cleared the air. Morgan and Berliner[83] perfused a proximal tubule in situ and showed that under these conditions absolute sodium reabsorption remains the same over a wide range of perfusion. In other words, when the delivery of sodium into the tubule is controlled by a micropipette and a pump no compensatory mechanism can be detected. Burg and Orloff[15] obtained the same results on the isolated in-vitro proximal tubule. In contrast, Morgan and Berliner[83] found that when they perfused the loop of Henle and the distal tubule some compensatory changes could be discerned.

It appears, therefore, that in the proximal tubule there is a discrepancy between the findings when the tubule is being perfused by its own glomerulus (free-flow studies), when changes in filtered sodium are accompanied by a compensatory change in sodium reabsorption by the tubule; whereas when it is perfused with a micropipette changes in the rate at which sodium is delivered into the tubule do not induce any change in sodium reabsorption. This suggests that the proximal tubule has no intrinsic capacity to adjust to changes in filtration, and the compensatory change that occurs during free-flow studies is due to the accompanying changes in the peritubular environment, the environmental changes having been induced by the procedure or mechanism which caused the change in filtration rate. On the other hand, the loop of Henle and distal tubule do appear to have the capacity to change sodium reabsorption, whether the rate of delivery of sodium is altered by a change in filtration or during microperfusion. Morgan (personal communication) has proposed that this may be due to changes in back diffusion from the loop of Henle into the hypertonic environment of the renal papillae.

In brief, the relative constancy of the urinary sodium excretion in face of large changes in glomerular filtration rate is due to parallel changes in sodium reabsorption in the proximal tubule, the loop of Henle, and the distal tubule. And throughout the nephron the adjustment appears to be due to the nature of the peritubular environment.

Plasma Protein Concentration

I would now like to focus on the sort of environmental changes which might cause a change in sodium reabsorption, particularly around the proximal tubule where the bulk of sodium is reabsorbed. Theoretically, a change in glomerular filtration rate may entail a simultaneous change in filtration fraction or a change in the peritubular capillary hydrostatic pressure. The filtration fraction is that proportion of the plasma flowing through the glomerulus which is filtered into the tubule. A rise in this fraction causes a rise in the plasma protein concentration in the blood flowing out of the glomerulus into the peritubular venous capillary network. And it is intuitively acceptable that changes in plasma protein concentration in the blood circulating around the tubules could have an effect on the rate of sodium reabsorption. It has, however, been extraordinarily difficult to devise experiments to obtain evidence on this point. The main difficulty has been that changing the plasma protein concentration of the blood will usually cause a change in the packed cell volume and the blood volume, and it is then usually impossible to distinguish whether the resultant change in urinary sodium excretion is due to a change in plasma protein concentration, packed cell volume, or blood volume.

Micropuncture studies should be able to avoid all these hazards, and the first investigations were quite clear-cut. Surprisingly they seemed to show that plasma protein osmotic pressure had no effect on sodium reabsorption. In these experiments the split oil-droplet technique was used. Solutions of albumin were placed into the lumen of the proximal tubule. It was found that 5% albumin solutions were absorbed and disappeared at the same rate as solutions of isotonic saline.[44 54 63] It was concluded from these experiments that protein osmotic pressure gradients across the wall of the tubule had no effect on sodium reabsorption. And this was in agreement with the finding that the proximal tubule wall has such a low permeability to water that the plasma protein osmotic pressure across the wall cannot account for the reabsorption of more than 1% of the glomerular filtration.[118]

In contrast to this evidence, which is not disputed, there is now an overwhelming amount of evidence that when the protein osmotic gradient across the tubule wall is changed by altering the concentration of the plasma protein on the outer side of the tubule the expected change in sodium reabsorption does take place. For instance, Lewy and Windhager[74] have recently performed some excellent experiments in which they measured tubular reabsorption with the split oil-drop technique in rats in which spontaneous fluctuations in filtration fraction were occurring. Changes in filtration fraction, you will remember, must cause changes in plasma protein concentration. Lewy and Windhager[74] found a significant correlation between filtration fraction and the reabsorptive half-time (Fig. 8). In other words, the higher the filtration fraction the shorter the reabsorptive half-time, or the higher the plasma protein concentration the quicker the rate of sodium reabsorption.

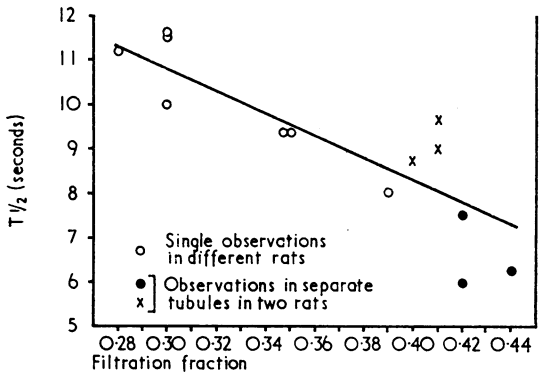

FIG. 8.—Effect of spontaneous fluctuations in filtration fraction on reabsorptive half-time ($T\frac{1}{2}$) of the split oil-drop in the proximal tubule of a control anaesthetized rat. Sodium reabsorption is greater—that is, the reabsorptive half-time is shorter—the higher the filtration fraction. (Windhager, Lewy, and Spitzer, *Nephron*, 1969, **6**, 247.)

Windhager, Lewy, and Spitzer[131] followed up these results by infusing hyperoncotic dextran into the peritubular venous capillaries directly with a micropipette (Fig. 9). One pipette perfused the capillary while another either sampled tubular fluid during free flow or placed a split oil-drop into the lumen. It was found that sodium and water reabsorption were again inversely related to the plasma protein osmotic pressure in the peritubular capillaries.

It would appear, therefore, that the plasma protein osmotic pressure of the blood in the peritubular capillaries certainly has a direct effect on tubular reabsorption and urinary excretion of sodium. The lack of effect on sodium reabsorption of placing albumin within the lumen of the tubule, and the low permeability of the tubule wall to water suggests that this effect is not produced by changes in protein osmotic gradients

across the wall. It seems rather that changes in plasma protein concentration affect sodium reabsorption by producing some change in the basal side of the cell. I would like to discuss the possible nature of this change a little later.

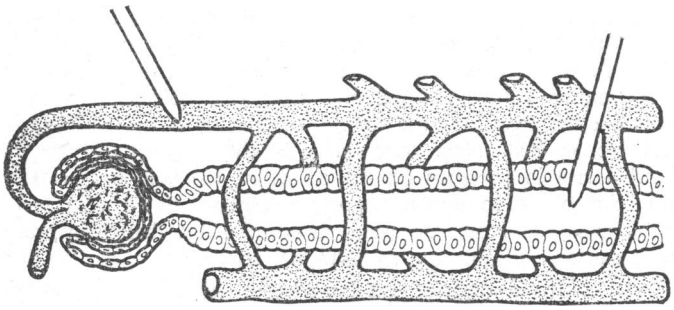

FIG. 9.—Schematic drawing showing technique of peritubular capillary perfusion and simultaneous micropuncture of a proximal tubule receiving its vascular supply from the perfused capillaries. (Windhager, Lewy, and Spitzer, *Nephron*, 1969, **6**, 247.)

Hydrostatic Pressure

Now I want to discuss the second of the changes which I suggested earlier might take place in the environment of the tubule which may affect sodium transport. That is, the hydrostatic pressure surrounding the tubule, which presumably is related to the peritubular capillary pressure.

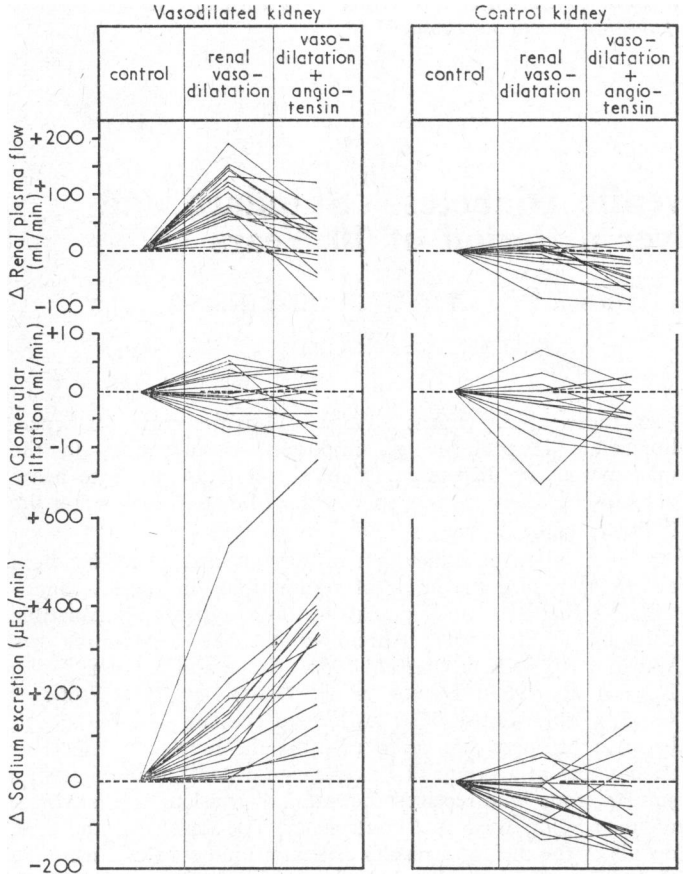

FIG. 10.—Effect of raising the arterial pressure on urinary sodium excretion in the vasodilated and control kidney of a dog. Renal vasodilatation produced by unilateral infusion of acetylcholine into the renal artery. Rise in systemic arterial pressure caused by intravenous infusion of angiotensin. Urinary sodium excretion rises in the vasodilated kidney but does not change in the control kidney. (Earley and Friedler, *Journal of Clinical Investigation*, 1966, **45**, 542.)

It has been known for years that in acute experiments the renal artery perfusion pressure and renal venous pressure have profound effects on sodium excretion. Cushny in 1917[26] stated that "no other gland is known to respond so readily to changes in the blood pressure." But on the whole it was thought that this was due to the changes in filtration rate with which such changes in pressure were usually associated.

Earley and his co-workers[28 37 38 39 40 41 42 43 80] were among the first to devise experiments which showed that the effect of arterial pressure on sodium excretion was mainly due to its effect on sodium reabsorption, and not to changes in filtration rate. One of their most convincing experiments began by inducing unilateral renal vasodilatation in the dog by renal arterial infusions of acetylcholine or bradykinin. This manœuvre produced the expected large increase in renal blood flow in the infused kidney, but though there was no great change in glomerular filtration rate there was a brisk rise in sodium excretion. At this point either angiotensin or noradrenaline was given intravenously to raise the systemic arterial pressure to both kidneys. The rise in arterial pressure produced a further substantial rise in sodium excretion from the vasodilated kidney, though the renal blood flow fell and the filtration rate showed no significant change. The sodium excretion from the other control kidney which was not vasodilated had much the same changes in renal blood flow and filtration rate but had no change in urinary sodium excretion. These results are illustrated in Fig. 10.

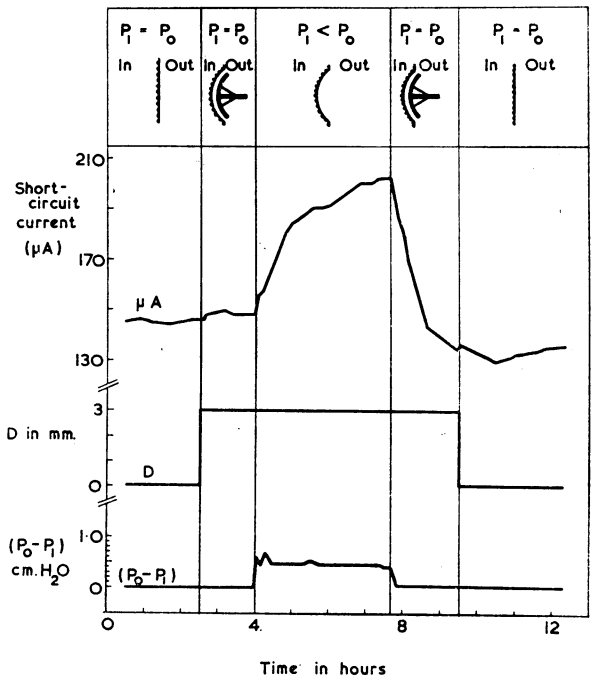

FIG. 11.—Effect of a hydrostatic pressure gradient on sodium transport across the frog skin. An index of sodium transport is obtained by measuring the short-circuit current (μA) across the skin. The skin was made to bulge inwards, firstly, by pushing it mechanically in the absence of a pressure gradient, and, secondly, by means of a constant hydrostatic pressure gradient. P_0 and P_1 are the pressures in mm H_2O outside and inside surfaces of the skin respectively; D is the displacement in mm. of the centre of the membrane from the midline. (Nutbourne, *Journal of Physiology*, 1968, **195**, 1.)

Earley and Friedler[42] concluded that the natriuretic effect of increasing the arterial pressure in the vasodilated kidney was not associated with a change in filtration rate or renal blood flow. They suggested that the rise in urinary sodium excretion was therefore due probably to a transmission of the increased perfusion pressure, to some distal portion of the renal vasculature (because of the vasodilatation); and that it was this rise in pressure which in some way decreased tubular sodium reabsorption. The effect of hydrostatic pressure on

sodium reabsorption has since been demonstrated more directly by Koch, Aynedjian, and Bank,[67] who studied the effect of acute hypertension on sodium reabsorption in the proximal tubule of the rat. Sodium reabsorption from the proximal tubule was measured by the split oil-droplet technique. They found that a rise in arterial pressure caused a decrease in reabsorptive half-time in the proximal tubule and therefore a diminution in sodium reabsorption.

It is not known how a change in peritubular venous capillary pressure can alter sodium reabsorption. Earley, Martino, and Friedler[43] were the first to propose that the change in sodium reabsorption which accompanies a change in peritubular capillary pressure may be due to a change in the interstitial volume between the cell and the peritubular capillary wall. Nutbourne,[88] who was the first to demonstrate that a hydrostatic pressure gradient can alter active sodium transport of a sodium-transporting membrane in vitro, suggested that this effect might be due to a distortion of the intercellular channels, for the change in sodium transport was far greater than could be accounted for by the pressure gradient. Nutbourne's experiments were performed on the frog skin. She designed an apparatus in which the pressures on each side of the frog skin could be controlled to within 0·5 mm. H_2O. She found that if the skin was made to bulge by a pressure gradient across the skin there was a marked effect on sodium transport, whereas if the same amount of bulging was produced by mechanical means there was no change in sodium transport. One of the most remarkable findings was that pressure gradients of less than 5 mm. H_2O had the greatest effect. And more recently the phenomenon has been confirmed with pressure gradients of only 0·5 mm. H_2O.[88a] Nutbourne[88] concluded that increasing surface area did not influence sodium transport, whereas small hydrostatic gradients had a pronounced effect (Fig. 11).

The relevance of Nutbourne's findings to sodium reabsorption in the nephron are indirect, to say the least. On the other hand, they do provide the only in-vitro evidence that pressure per se can influence sodium transport across a sodium-transporting membrane. There are some similarities in the metabolic nature of the sodium pump in the proximal tubule and the frogskin. Anatomically also there are some fundamental similarities. The cells of the frog skin epidermis, like those in the proximal tubule, are each surrounded by intercellular spaces which open freely on the inner dermal side of the epidermis but are blocked at the outer layer of the epidermis.[45 46 47 119] And a rise in pressure on the inside of the skin against the direction of net sodium transport corresponds to a rise in peritubular capillary pressure ; and in both such a change in pressure causes a diminution in sodium transport.

The evidence suggests that the effect of hydrostatic pressures and plasma protein osmotic pressures may produce their effect on sodium reabsorption by a final common path which acts on the basal side of the cell. Perhaps both alter the volume of the interstitial space, and it is this which controls sodium reabsorption.[43] For instance, a rise in peritubular capillary pressure or a fall in plasma protein osmotic pressure may each increase the size of the interstitial space. Such an increase may dilate the basal infoldings or distort the intercellular channels in such a way that the efficiency of both the channels and the basal infoldings is diminished.

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[*The conclusion of this lecture, with a list of references, will be published in our next issue.*]

Control of Hyperlipidaemia in Juvenile Diabetes. Standard and Corn-oil Diets Compared Over a Period of 10 Years

G. W. CHANCE,* M.B., M.R.C.P., D.C.H. ; E. C. ALBUTT,† B.SC., F.I.M.L.T. ; S. M. EDKINS,‡ A.I.M.L.T.

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Summary : The results of the first 10 years of a prospective study of the effect of corn-oil and standard diets given to diabetic children since diagnosis suggest that the corn-oil diets currently available in Britain are not acceptable to most diabetic children and adolescents. Attempts to administer such diets may result in hyperpre-beta-lipoproteinaemia. In most diabetic children normal serum lipid levels can be maintained with adequate diabetic control and a standard diabetic diet.

Introduction

Hyperlipidaemia is common in diabetic children at the time of diagnosis (Chance *et al.*, 1969) and in diabetic adults during periods of inadequate control (Strisower *et al.*, 1958 ; Schrade *et al.*, 1963). It is now recognized that hyperlipidaemia is associated with atherosclerosis (Albrink *et al.*, 1961 ; Kannel *et al.*, 1964 ; Hatch *et al.*, 1966), and that in diabetic persons atheromatous lesions tend to appear at an earlier age and progress more rapidly (Kinsell, 1955). Thus prevention of hyperlipidaemia is probably an important consideration in the management of diabetes, particularly in children, since many of them are likely to develop vascular disease in early adult life (White, 1960).

Consumption of a diet rich in polyunsaturated fat has been shown to reduce the levels of serum lipids in healthy volunteers, in diabetics, and in patients with hypercholesterolaemia (Shapiro *et al.*, 1957 ; Ahrens *et al.*, 1957 ; Malmros and Wigand, 1957 ; Kinsell *et al.*, 1959 ; Stone and Connor, 1963 ; Keys *et al.*, 1965 ; Dayton *et al.*, 1968). In 1958 Professor O. H. Wolff,[1] Dr. J. K. Lloyd,[1] and the late Mr. H. B. Salt began a prospective trial to examine the long-term effects of such a diet in a group of newly diagnosed diabetic children, a similar group who received the standard regulated carbohydrate regimen being used as "controls." The design of the trial, details of the diet, and results of serum lipid studies during the first five years have already been described (Salt *et al.*, 1960 ; Lloyd and Jukes, 1961 ; Lloyd *et al.*, 1962 ; Lloyd, 1966). During this period the initial objects of the trial—namely, to determine whether such a diet was practicable for children on

* Senior Lecturer and Honorary Consultant Paediatrician.
† Senior Research Associate.
‡ Senior Technician.
Institute of Child Health and the Children's Hospital, Birmingham 16.

[1] Present address: Institute of Child Health, University of London, London.