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Renal mechanisms of potassium depletion

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In an age in which we are coming to rely more and more upon the results of laboratory investigations as an aid to diagnosis it is perhaps salutary to remember that such investigations are frequently of little value in the diagnosis of potassium depletion. The vast majority of the body K is within the cells, and as a result the

concentration of this ion in the extracellular fluid provides a very poor indication of the state of the body stores. The disparity between the serum K concentration and the body stores of the ion tends to make the diagnosis of K depletion more difficult, and it is now generally appreciated that the most important single factor in making such a diagnosis is a knowledge of those clinical conditions in which abnormal losses of this ion inevitably occur.

When K depletion results from loss of gastro-intestinal secretions the diagnosis is usually obvious, but it is much less obvious when it occurs as a consequence of the loss of excessive K in the urine. Moreover, in such circumstances significant K losses can occur in the absence of signs of sodium and water depletion. As a consequence, none of the elementary features of electrolyte disturbance such as clinically obvious dehydration need be present, and the clinical features of K depletion, being fairly non-specific, are frequently attributed to the underlying disease. It is all the more important, therefore, that the practising clinician should have a clear concept of the factors which are known to increase the excretion of K in the urine.

The average diet provides anything from 30 to 80 m-equiv. K daily and the normal individual who is in K balance excretes a similar quantity of this ion in the urine. In a person with normal renal function this amounts to about 10% of the filtered load of K. In certain circumstances (McCance & Widdowson, 1937; Berliner, Kennedy & Hilton, 1950; Berliner & Kennedy, 1951; Mudge, Foulks & Gilman, 1948; Franglen, McGarry & Spencer, 1953) the amount of K in the urine can be shown to exceed the quantity filtered by the glomeruli, and it is therefore obvious that the renal tubules are capable of secreting K. A great deal of information has accumulated (Berliner, 1960) which suggests that the filtered K is almost entirely reabsorbed in the upper portion of the renal tubule, that which appears in the urine being secreted into the tubular fluid at a more distal point in the nephron.

The only direct information available about the way in which the kidney handles K is derived from animal studies in which micropuncture was performed upon the nephron at different levels and fluid obtained in this way subjected to analysis. Fig. 1 shows the results of such an experiment recently published by Malnic and his colleagues (Malnic, Klose & Giebisch, 1964). Samples of proximal and distal tubular fluid were obtained from the kidneys of rats receiving a diet containing normal amounts of K. These animals were excreting, on the average, 17% of the filtered load of K at the time of the experiments.

The data plotted in Fig. 1 suggest that at a point two-thirds of the way along the proximal tubule about 70% of the K filtered at the glomerulus has been reabsorbed. The pars recta of the proximal tubule is not accessible to micropuncture nor is the first part of the distal tubule, but samples withdrawn from a point one-fifth of the way along the distal tubule show that, on the average, 95% of the filtered K has been reabsorbed by the time the tubular fluid reaches this site in the nephron. Secretion of K into the urine occurs in the distal tubule, and Malnic et al. calculated that in these circumstances about 70% of the urinary K was derived by means of this secretory process. Similar experiments on animals on a low K intake suggest that, when the amount of K in the urine is very small, little or no distal tubular
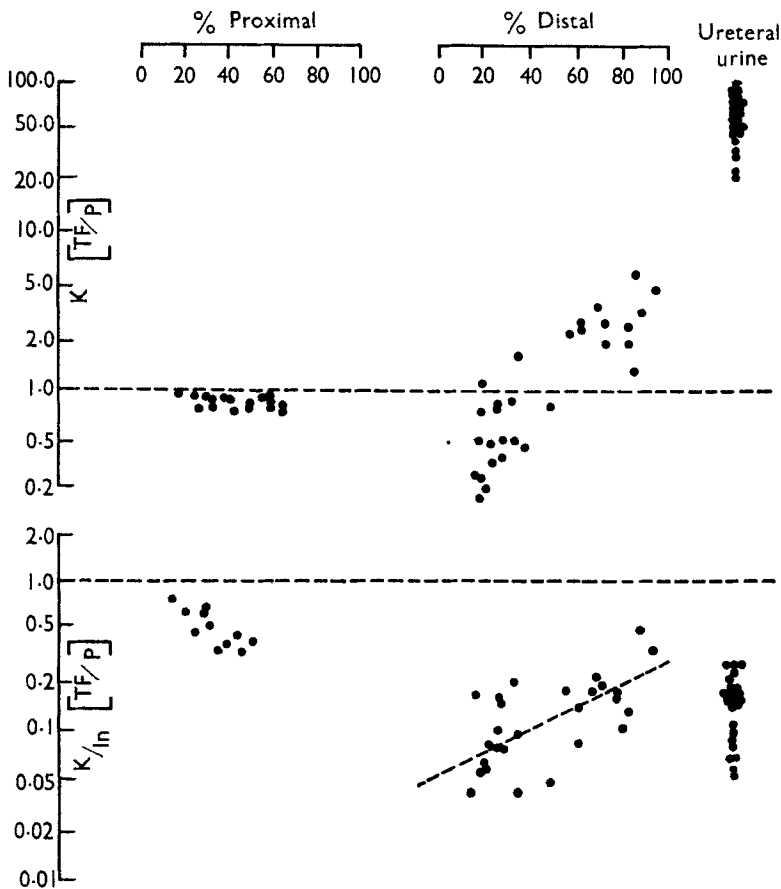
Fig. 1. Micropuncture experiments on rats receiving a normal diet (reproduced from *Amer. J. Physiol.* (Malnic *et al.* 1964), by permission. Upper part, tubular fluid: plasma concentration ratios for potassium as a function of tubular length; lower part, potassium: inulin concentration ratios as a function of tubular length.

secretion of this ion occurs. In animals excreting large amounts of K, the overall pattern is similar to that shown in Fig. 1, the majority of the filtered K being reabsorbed in the proximal tubule and the loop of Henle whereas the K which appears in the urine is secreted into the tubular fluid in the distal tubule.

These studies suggest that the amount of K that appears in the urine depends very largely upon factors which influence the distal secretory system.

Animal experiments (Berliner *et al.* 1950) have shown that the amount of K that appears in the urine cannot be accounted for by secretion of this ion in company with an anion, and it is generally accepted that the urinary K is derived by means of an ion-exchange mechanism whereby the secretion of K into the tubular fluid is coupled to the reabsorption of Na. It is likely therefore that the rate of excretion of K will be influenced by the amount of Na reaching the distal part of the nephron and by the capacity of the cells in this area to reabsorb Na.
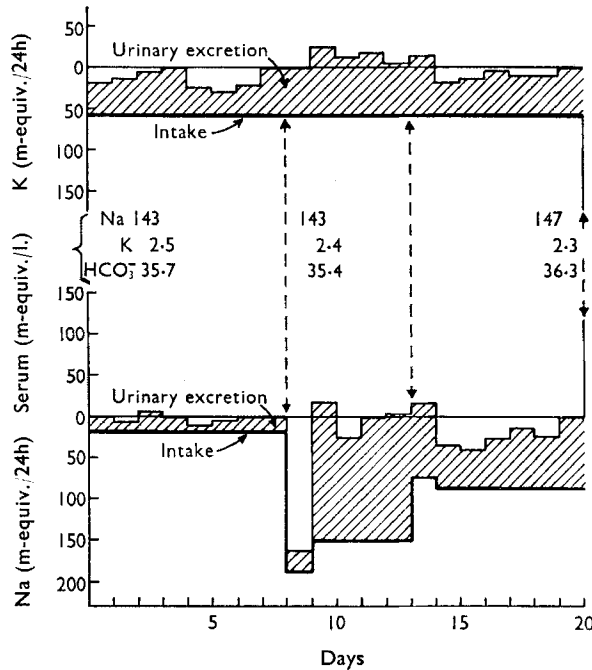
Fig. 2.   Balance of sodium and potassium in a patient with primary aldosteronism (reproduced from
Symposium on Water and Electrolyte Metabolism (Lambie, 1961), by permission).

Fig. 2 shows the effect of changes in the intake of Na upon the excretion of K in
a patient with primary aldosteronism (Lambie, 1961). During the first 8 days the
patient received a constant diet containing average amounts of K but only 12 m-equiv.
Na, and on this régime she was in positive K balance. From the 9th to the 13th day
supplementary sodium chloride was given in order to raise the Na intake to an average
value of 170 m-equiv./day. As one would expect, the result was a fall in urinary
aldosterone; nevertheless during this period her K excretion rose and she went into
negative K balance. Reduction of the Na intake to more normal proportions on the
14th day resulted after 24 h in a fall in the urinary excretion of K and the achievement
of a small positive K balance. It is clear therefore that patients suffering from aldo-
steronism are not necessarily in negative K balance all the time. Moreover, it is
obvious that the urinary excretion of K by such individuals is at least partly governed
by the Na intake, which in turn influences the amount of Na reaching the site of
exchange. These observations can be put to use in the diagnosis of aldosteronism.
This disorder is notoriously difficult to diagnose because measurements of the level
of the hormone in body fluids are frequently unhelpful, and a valuable approach to
the problem is to try to show that the patient cannot conserve K normally when
receiving a diet containing very small amounts of this ion. It is important to ensure
that the intake of Na is high.

Fig. 3 shows the results obtained with five hypertensive patients suspected of
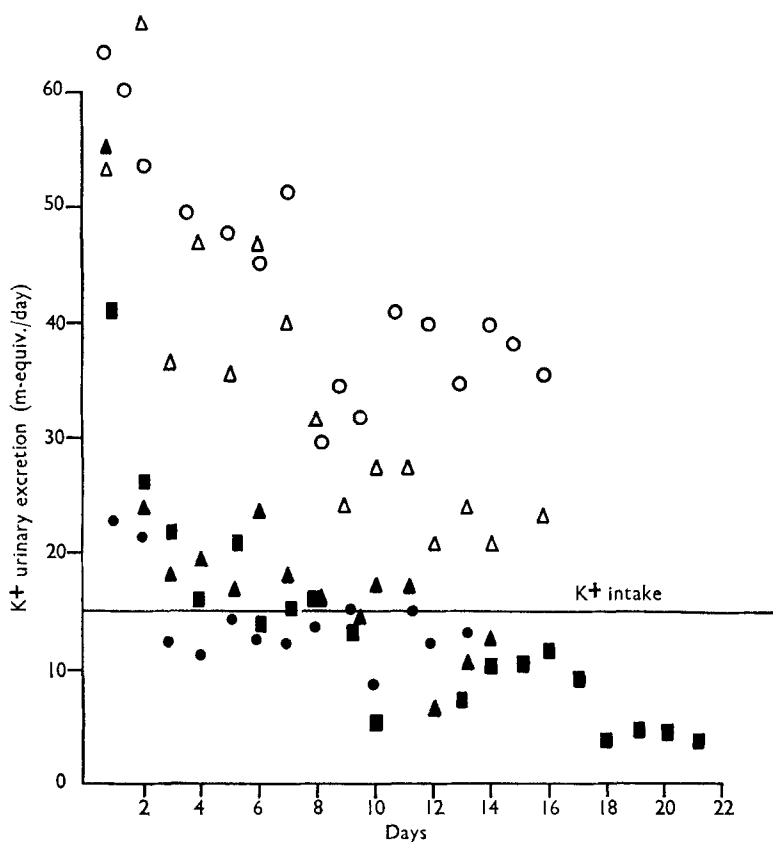aldosteronism who were given a diet containing 15 m-equiv. K/day (Lambie, Doig &

Fig. 3. Urinary excretion of potassium by hypertensive subjects receiving a low-potassium (15 m-equiv./day), high-sodium (200–300 m-equiv./day) diet. O, patient with primary aldosteronism; △, patient with aldosteronism secondary to renal artery stenosis; ●, ▲, ■, patients with essential hypertension.

Robson, 1964, unpublished observations). Their daily intake of Na ranged from 200 m-equiv./day to 300 m-equiv./day. In three cases the amount of K in the urine fell steadily until the urinary output of this ion was less than the dietary intake. This is the normal pattern of K conservation.

The urinary excretion of K by the fourth patient is shown in Fig. 3 by the open triangles. This patient was a woman with renal artery stenosis who was grossly depleted of K, the serum K being 2·4 m-equiv./l. at the beginning of the study. With her, the amount of urinary K fell more slowly, and at the end of 15 days was still greater than the intake despite the fact that the serum K value had fallen to 1·9 m-equiv./l. In this patient, in whom renal conservation of K was deficient, the urinary excretion of aldosterone was increased and the aldosterone production rate was high. The fifth patient, a 15-year-old boy, with moderately severe hypertension and no other evidence of renal impairment, also failed to conserve K. Measurements of the rate of secretion of aldosterone are not yet available, but no other cause for his

hypertension has been found, and it seems probable that his is a case of aldosteronism.*

Another point of practical importance arises from these observations upon the relationship between the intake of Na and the excretion of K. In K-depleted individuals the replenishment of the deficit can be facilitated by the simultaneous restriction of Na intake. This is of particular value in cases of Cushing's syndrome and aldosteronism, in which considerable difficulty is sometimes experienced in replenishing body stores of K before subjecting the patient to surgery.

Animal experiments utilizing the stop–flow technique suggest that the diuretics commonly employed in the treatment of oedematous patients diminish Na reabsorption in the proximal tubule with a resultant increase in the amount of Na which reaches the distal nephron. One might expect, therefore, that other things being equal the administration of such diuretics would be associated with increased K excretion.
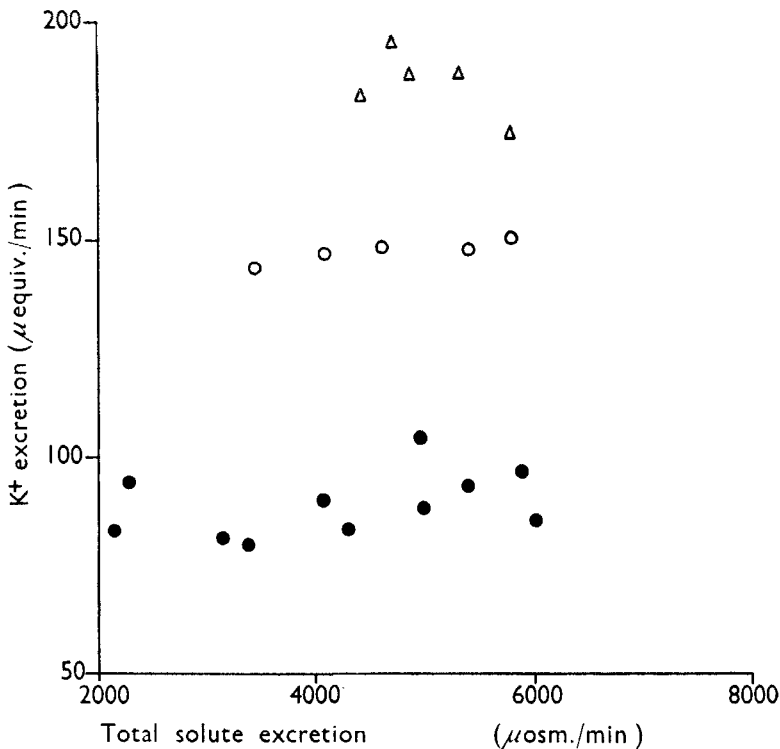

Fig. 4.   Urinary excretion of potassium by subjects during a mannitol diuresis before and after administration of diuretics. ●, results for both subjects during the administration of mannitol; O, results after intravenous injection of 50 mg hydroflumethiazide, the mannitol diuresis being continued throughout this period; △, results after intravenous injection of 100 mg chlorthalidone, the mannitol diuresis being continued throughout this period.

*This patient has since been proved to have primary aldosteronism and has had one adrenal gland removed.

Fig. 4 shows the striking increase in K excretion which results when a normal volunteer receives either hydroflumethiazide or chlorthalidone during the course of a mannitol diuresis.

K excretion is likely to be even further facilitated when there is not only an increased amount of Na reaching the site of exchange but also some factor operating which favours the exchange mechanism.
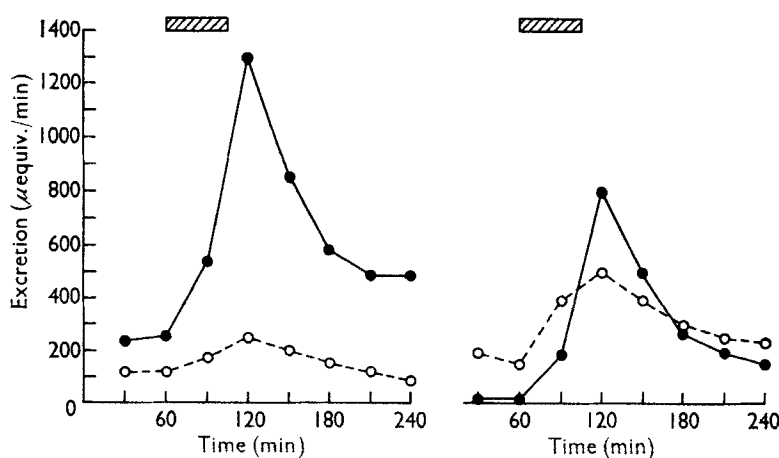

Fig. 5. Urinary excretion of sodium (●——●) and potassium (○- - -○) after the infusion of 1000 ml sodium sulphate solution (190 m-equiv. Na_2SO_4 + 32 m-equiv. $NaHCO_3$) in a normal subject (left) and in a sodium-depleted subject (right). ▨, duration of the infusion. (Adapted from *J. clin. Invest.* (Schwartz *et al.* 1955), by permission).

Fig. 5 shows the results obtained in one of a series of experiments in which a large quantity of Na was presented to the distal part of the nephron by the infusion of Na in company with the poorly reabsorbed anion sulphate. This Na load was given to normal subjects and subjects previously depleted of Na (Schwartz, Jensen & Relman, 1955). In the normal individual most of the administered Na was excreted in the urine although the small but reproduceable increase in K excretion suggests that some of the Na was reabsorbed in exchange for K, and, indeed, the presence of a non-reabsorbable anion is known to enhance K secretion. In the Na-depleted subject a higher proportion of the administered Na appeared to have been exchanged for K, and urine contained more K and less Na. Obviously Na and K exchange had been facilitated by Na depletion. The situation which has been produced in these experiments is similar to that which exists in the oedematous individual who becomes 'resistant' to diuretics. Such patients have an increased capacity for Na reabsorption which may have been exacerbated by rigid salt restriction. The administration of conventional diuretics that interfere with the reabsorption of Na in the proximal tubule results in the delivery of a large amount of this ion to the distal site of exchange where much of it is reabsorbed in exchange for K or hydrion. Consequently the Na diuresis is disappointingly small, and considerable amounts of K may be lost in the

urine. It is therefore logical to give any patient receiving diuretics over a long period of time K supplements.

The increased capacity to reabsorb Na which results from salt depletion and which is seen in oedematous patients may be due in part at least to the increased secretion of adrenocorticoids, and some of the Na retained under the influence of these steroids appears to be reabsorbed in exchange for K, as was shown by Relman & Schwartz (1952). These workers showed that the K depletion induced in normal subjects by the administration of large amounts of DOCA could be prevented by restricting the intake of Na to 14 m-equiv./day.

The ion-exchange mechanism which has been proposed by Berliner (1961) to account for the secretion of K is very similar to that advanced to account for the acidification of the urine (Pitts & Alexander, 1945; Pitts, Lotspeich, Schiess & Ayer, 1948). This latter mechanism consists, fundamentally, of the exchange of a Na ion from the tubular fluid for a hydrogen ion derived in the cell from carbon dioxide and water under the influence of the enzyme carbonic anhydrase. Evidence has accrued which supports the idea that K ions and hydrogen ions can be regarded as 'competing' for Na. The issue is possibly determined by the relative concentration of K and hydrogen ion present in the renal tubular cells.

When the rate of production of hydrogen ions is diminished by the administration of carbonic anhydrase inhibitors, K excretion increases. Fig. 6 shows the increment
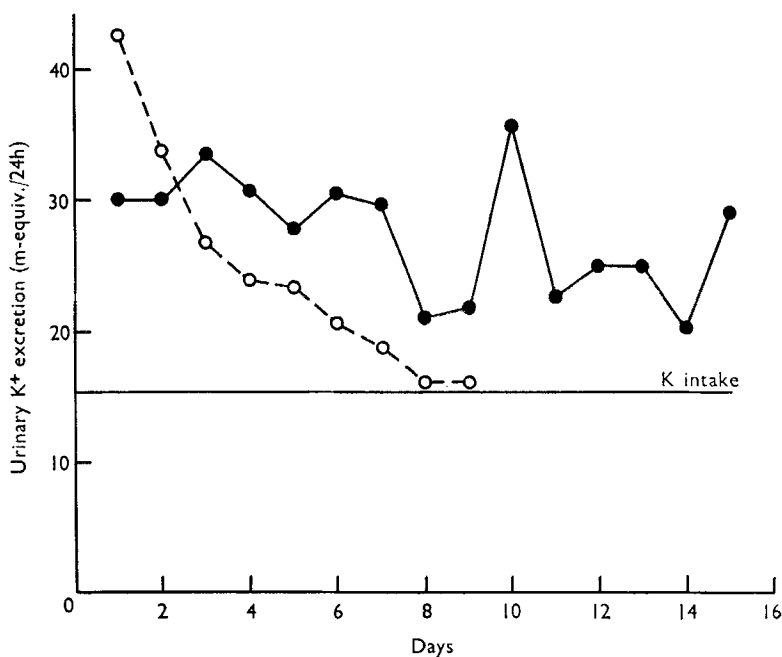

Fig. 6. Comparison of the urinary excretion of potassium on a low-potassium (15 m-equiv./day) intake by a normal subject (O– – –O) and by a patient with acquired renal tubular acidosis due to chronic pyelonephritis (●——●). (From *Symposium on Water and Electrolyte Metabolism* (Lambie, 1961), by permission.)

in urinary K that occurs when acetazolamide and chlorothiazide, both of which inhibit the action of carbonic anhydrase, are given to normal volunteers during the course of a mannitol diuresis.

In clinical conditions in which the capacity to acidify the urine normally is lost, excessive amounts of K may be excreted in the urine. This situation exists in the congenital form of renal tubular acidosis and is also seen in certain patients with chronic pyelonephritis in whom there is an inability to form a normally acid urine. Fig. 7 (Lambie, 1961) shows the results which were obtained when a patient with histologically proven chronic pyelonephritis who was unable to reduce the pH of her urine below 6·1 was given a diet containing 15 m-equiv. K daily. The patient's kidneys were incapable of conserving K normally and she continued to excrete considerable amounts of this ion in her urine despite the presence of a severe degree of K depletion and a serum K value of only 2·7 m-equiv./l.

Any situation in which secretion of hydrogen ions is diminished is liable to be associated with increased K excretion. Diminished hydrogen ion excretion often occurs in the alkalotic subject, whether the alkalosis is of metabolic or respiratory
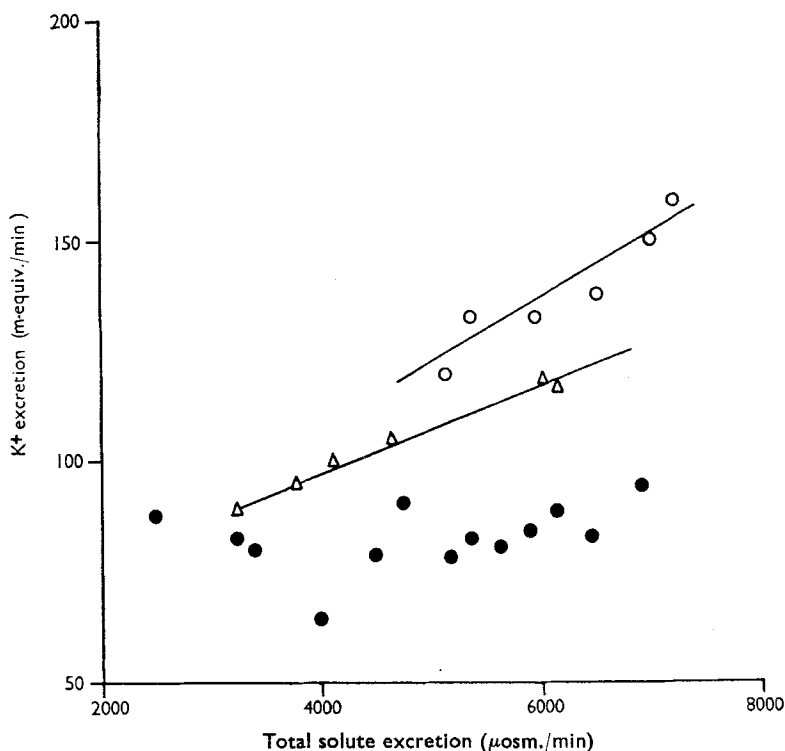

Fig. 7. Urinary excretion of potassium by subjects during a mannitol diuresis before and after administration of diuretics. ●, results for both subjects during the administration of mannitol; ○, results after intravenous injection of 500 mg chlorothiazide, the mannitol diuresis being continued throughout this period; △, results after intravenous injection of 500 mg acetazolamide, the mannitol diuresis being continued throughout this period.

origin, and is associated with a loss of K in the urine. The diminished secretion of hydrogen ions and the increased secretion of K may possibly be due to a reduction of the intracellular hydrogen ion concentration.

Patients with pyloric stenosis not infrequently have a severe degree of K depletion which cannot be accounted for by loss of this ion in vomitus, and it can be shown that such patients excrete considerable amounts of K in the urine despite a low intake of this ion and the presence of a considerable degree of K depletion. Black & Jepson (1954) have suggested that the urinary K loss in these patients is a consequence of increased tissue breakdown and increased secretion of adrenocorticoids, but it may well be that the metabolic alkalosis which results from loss of gastric hydrochloric acid contributes to the loss of K in the urine.

Bearing in mind the factors known to influence the distal tubular mechanism for K secretion, it is possible to analyse the mode of K loss in some common clinical conditions shown in Table 1. The administration of large amounts of Na salts or of diuretics which inhibit proximal tubular reabsorption of Na serves to increase the urinary K and probably does so by increasing the amount of Na delivered to the site of exchange in the distal tubule. The Na-depleted subject or the patient who is suffering from a condition such as congestive cardiac failure or hepatic cirrhosis which is associated with oedema formation may become K-depleted because of increased reabsorption of Na at the site of exchange. This is the likely mechanism of K depletion in patients under the influence of excessive amounts of adrenocorticoids, whether exogenous or endogenous.

Table 1. *Clinical conditions associated with increased potassium excretion*

Clinical condition	Increased amount of Na delivered to distal nephron	Increased reabsorption of Na	Diminished secretion of hydrogen ion
Na loading	+		
Diuretics inhibiting proximal tubular reabsorption Na$^+$	+		
Carbonic anhydrase inhibitors	+		+
Na depletion		+	
Oedematous conditions		+	
Cushing's syndrome		+	
Aldosteronism		+	
Administration of Na$^+$-retaining steroids		+	
Respiratory alkalosis			+
Metabolic alkalosis			+
Renal tubular acidosis			+

The plus sign (+) means that the particular factor is operating in the clinical condition shown in column 1.

The exact relationship that exists between the rate of Na reabsorption and the rate of K secretion remains obscure (Giebisch & Windhager, 1964), but it is possible that increased reabsorption of Na influences K secretion by increasing the electrical potential gradient across the distal tubular epithelium.

Finally, when the secretion of hydrogen ions is diminished, K is lost in the urine. This situation occurs during the administration of diuretics that inhibit the action of carbonic anhydrase and in patients whose kidneys are unable to secrete hydrogen ions against a gradient. It also occurs in patients with respiratory alkalosis due to overventilation and in those with metabolic alkalosis due to loss of gastric hydrochloric acid or administration of soluble alkalis.

Though this analysis undoubtedly oversimplifies the situation, it may possibly be of some value in helping the clinician to understand the pathological physiology of these problems.

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The role of the kidney in sodium and potassium balance in the cow

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I feel honoured to be asked to contribute to this Nutrition Society Symposium but, as a physiologist, I must confess that I am more concerned with biological mechanisms within the animal organism than with the overall relationship of nutritional input to metabolic and excretory output. In considering the role of the kidney in sodium and potassium balance I must, therefore, apologize if the nutritional consequences of the renal mechanisms I hope to describe are largely inferential. Renal physiologists are generally too preoccupied with interesting minutiae to measure the overall balances in which the kidney plays a part, although it is self-evident that renal mechanisms which control the excretion of electrolytes must always be justified in relation to the overall requirements for nutritional balance.

The requirements of the cow for Na and K may be divided into four components: (1) a growth requirement; (2) a lactation requirement; (3) a pregnancy requirement; (4) a 'maintenance' requirement, to meet the losses of these elements in the faeces and urine.

Brouwer (1961) has pointed out that absorption from the large intestine reduces faecal losses of Na so as to enable the cow to subsist on very small amounts of this

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