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.

REFERENCES


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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element: less than $0.1\%$ of the dry matter of the feed. This reabsorption of Na results in the faecal juice becoming hypotonic compared with blood plasma, and may restrict the reabsorption of K, since K concentrations in the fluid of the colon and rectum contents increase to a level approximately seven times greater than in blood plasma. Since the normal diet of the cow is high in K and low in Na, it is appropriate that faecal losses of Na are minimal whereas faecal losses of K are of no great concern. K deficit of alimentary origin in any species is very rare (Rowinski, 1960). In considering urinary losses of these elements, it is misleading to regard the kidney solely as an excretory organ. In a nutritionist's balance sheet the urinary excretion of electrolytes may sometimes be regarded as a regrettable feature, incidental to the necessary elimination of nitrogenous waste of one sort or another. The kidney, however, is a regulatory rather than an excretory organ, and the urinary excretion of K and Na should, if possible, be regarded in relation to this regulatory function so far as we understand it.

Urinary losses of K and Na in fact vary widely, since excretion of these elements must be adjusted to balance their intake against utilization over a very wide range of varying metabolic requirement. In this paper I propose to show that, though the urinary excretion of K and Na by the cow does, in general, reflect the dietary intake, wide variations in the urinary losses of these elements occur in response to a wide variety of physiological influences.

Qualitative and quantitative considerations

The normal diet of cattle, compared with that of man and the dog, is high in K and low in Na content. Spector (1956) quotes figures for daily urinary output which reflect these differences in dietary composition. In comparing K and Na concentrations in human and bovine urine, Anderson & Pickering (1962a) found a mean molar ratio, K : Na, of $0.43$ (SD $0.21$; range $0.12-0.87$) in human urine, and of $5.3$ (SD $4.75$; range $1.65-20.8$) in bovine urine. These differences in urinary composition arise during the renal processes of filtration, reabsorption and secretion so that the excretion of some fraction of the filtered quantity is sufficient to balance the daily intake.

Pitts (1963) gives figures for the quantitative aspects of filtration, reabsorption and excretion of Na and K by the kidney of man (Table 1). These figures assume a value for the glomerular filtration rate of $125\text{ ml/min}$. The quantity of each ion filtered per day is the product of the glomerular filtration rate (in l./day), the plasma concentration (in m-equiv./l.) and a Donnan factor for univalent cations of $0.95$.

The figures for the cow, shown in Table 1, have been calculated from values obtained in sixty-six control clearance periods carried out at the outset of thirty-three experiments, which involved various subsequent procedures, in investigations of bovine renal function at the Veterinary School in Glasgow. Urine was collected continuously under epidural anaesthesia, by means of a self-retaining urethral catheter as described by Anderson & Pickering (1961). The glomerular filtration rate (mean value $936\text{ ml/min}$) was measured as the plasma clearance of inulin by constant-infusion techniques described by Anderson & Pickering (1962a, 1964).
Table 1. Quantitative aspects of filtration, reabsorption and excretion of sodium and potassium in man and cow

<table>
<thead>
<tr>
<th>Cation</th>
<th>Plasma concentration (m-equiv./l.)</th>
<th>Glomerular filtration rate (l./24 h)</th>
<th>Quantity filtered (m-equiv./24 h)</th>
<th>Quantity excreted (m-equiv./24 h)</th>
<th>Quantity reabsorbed (m-equiv./24 h)</th>
<th>% reabsorbed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>140</td>
<td>180</td>
<td>23 940</td>
<td>103</td>
<td>23 837</td>
<td>99.6</td>
</tr>
<tr>
<td>Potassium</td>
<td>4</td>
<td>180</td>
<td>684</td>
<td>51</td>
<td>633</td>
<td>92.6</td>
</tr>
</tbody>
</table>

Man

<table>
<thead>
<tr>
<th>Sodium</th>
<th>140</th>
<th>1348</th>
<th>179 284</th>
<th>2287</th>
<th>176 997</th>
<th>98.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>4</td>
<td>1348</td>
<td>5 122</td>
<td>2651</td>
<td>2 471</td>
<td>48.2</td>
</tr>
</tbody>
</table>

Cow

Figures for man are from Pitts (1963) and those in parentheses have been calculated from the mean values for daily excretions in the cow quoted by Spector (1956).

These figures for 24 h excretions are considerably higher than the mean values quoted by Spector (1956) and may indicate a larger dietary turnover of Na and K in the animals studied. The calculated values for daily excretions should be accepted with some reservation, however, since a falling rate of excretion of Na and K in successive clearance periods has been shown to occur in cattle (Knudsen, 1960), a finding which was attributed to the stress associated with the experimental procedures. The seven animals used in the study now described, however, were fully accustomed to the experimental room. They stood quietly, frequently ruminated, and showed no excitement or distress during the procedures used. If the mean values for daily excretion of Na and K that are quoted by Spector are used in the calculations, they do not alter the main point illustrated, namely, that only a tiny fraction of the Na which is filtered at the glomeruli is allowed to escape in the urine. In more familiar units, the renal tubules of the cow reabsorb about 23 lb Na (expressed as NaCl) per day—nearly thirteen times the Na content of the extracellular fluid.

Table 1 also shows that, in man, less than 10% of the filtered load of K is excreted, whereas approximately 50% of the filtered load is excreted by the cow—a consequence of the greater dietary turnover of K in this species. The mechanism of excretion of K, however, is more complex than these figures imply. There is good evidence that essentially all the K filtered in the mammalian kidney is reabsorbed in the proximal segments of the renal tubules, and that the K which appears in the urine is the result of secretion by distal portions of the nephrons (Black & Emery, 1957). Moreover, this secretion of K by renal tubular cells is believed to be by an ion-exchange mechanism involving concomitant reabsorption of Na from the tubular urine (Davidson, Levinsky & Berliner, 1958).

This ion-exchange mechanism suggests a reciprocal relationship between the urinary losses of K and Na, which is appropriate for the simple theoretical requirements of nutritional balance in the cow; but if K excretion in urine is dependent on
tubular secretion it seems possible that the cow will have a proportionately smaller
capacity for increasing urinary losses of K than will man and the dog, which have
lower normal rates of K excretion. This possibility is discussed below.

Renal responses to K loading

Slow intravenous infusion of potassium chloride in the cow causes some rise in
plasma concentrations of K, but no progressive rise with continuing infusion; and
K excretion in the urine rises rapidly to equal the rate of administration (Vogel,
1959; Anderson & Pickering, 1962a). This contrasts with the finding that the dog,
during K loading, shows a progressive rise of plasma K concentrations and an
increase in the urinary excretion of K which is less than the rate of infusion. The
responses resemble those of the cow, however, if K salts are added to the diet of the
dog for 2 weeks before the intravenous infusion, a procedure said to lead to the
development of the state of K tolerance (Berliner, Kennedy & Hilton, 1950). The
ability to tolerate intravenous loading with K seems to result from adaptation to a
high dietary intake of this element, and to involve an enhanced excretory capacity
rather than tolerance of high K levels in plasma. Thus the normally large turnover
of K in the cow is associated with a large excretory reserve capacity.

Nevertheless, de Groot (1962) points out that a sudden increase in the K intake,
as may occur when the cow starts to graze lush spring grass, not only increases
serum K concentrations for a few days, but may also increase the K content of the
cells. The cow, however, is able to promote very high rates of excretion of K to
restore K balance so that the hyperkalaemia is slight and transitory, and is not
recognized per se as a metabolic disorder attributable to excessive use of nitrogenous
or potash fertilizers.

Factors influencing Na excretion by the kidney

The physiological importance of Na, so far as it is known, derives from its
relationship to other electrolytes and its osmotic effects in aqueous solution. Its
importance in the maintenance of the osmotic pressure of the extracellular fluid is
emphasized by the fact that Na and its attendant anions are largely responsible for
the contribution of approximately 280 m-osm/kg made by serum electrolytes to the
total serum osmolality of approximately 290 m-osm/kg (Fuisz, 1963). Na balance
may therefore be considered from the viewpoint of osmotic homeostasis, provided
that, in addition to Na losses, variations in the excretion of water are also taken into
account.

Verney (1947) defined a sensitive neurohumoral mechanism, capable of monitoring
minute alterations of the tonicity of extracellular fluid, which, by controlled release
of antidiuretic hormone, increased or decreased urinary water losses under widely
varying surfeits and deficits of water intake. More recent work has shown that
alterations in the volume of the extracellular fluid can also influence the release of
antidiuretic hormone, and that reduction of the volume of extracellular fluid can
supersede tonicity in control of the release of the hormone (Leaf & Mamby, 1952).
For example, in salt depletion experiments with man, the initial 500 m-equiv.
negative Na balance was accompanied by a diuresis which eliminated an isotonically equivalent volume of water so that plasma tonicity was maintained constant whilst body-weight decreased by 3–4 kg. When the Na deficit exceeded 500 m-equiv., release of antidiuretic hormone greatly reduced the loss of water in the urine, an occurrence marked by sudden curtailment of the decline in body-weight and the onset of a rapidly progressive hyponatraemia due to relative overhydration of previously depleted Na stores. Under these circumstances some function of body volume displaces tonicity as the major factor controlling the release of antidiuretic hormone. These findings illustrate how kidney function can delay recognition of Na deficiency since hyponatraemia is not manifest until negative Na balance has persisted for some time.

In the absence of renal or cardiovascular disease, and of endocrine disturbances such as adrenocortical insufficiency, Na depletion is the result of a dietary intake of Na inadequate for metabolic requirements. Normal kidney function does not appear in these circumstances to entail an obligatory excretion of Na since, when Na intake is severely limited, reabsorption by the renal tubules can reduce the Na concentration of the final urine essentially to zero (Pitts, 1963). It is tempting to suggest, therefore, that, if a urine sample from an animal contains any Na at all, the diet of the animal may be presumed to be adequate in Na content. This application of the known ability of the mammalian kidney to conserve Na does not take account, however, of many factors which can affect kidney function, and give rise to transient increases in Na excretion which might prove misleading. For example, emotional disturbance of the animal, caused by sampling, may well give rise to a diuresis and an increased excretion of Na. Miles & De Wardener (1953) describe an emotional diuresis with increased salt excretion in women which occurred on bladder catheterization, or resulted from apprehension of a surgical procedure. Anderson (1961) has described a similar phenomenon in cattle, in which a marked transient diuresis was seen in response to the painful stimulus of brachial arterial puncture, and, after repeated experiments on the same animal, a similar response was also seen during the preliminary procedure of clipping, swabbing and anaesthetizing the site for puncture. These observations support the findings of Knudsen (1960) in experiments on cows, that the rate of excretion of Na declined in successive clearance periods, the high initial rates of excretion being attributed to the initial excitement associated with introduction to the experimental room and the disturbance of urethral catheterization.

Feeding is another simple factor which may produce transient alterations in the rate of Na excretion. Stacy & Brook (1964) report that pen-fed sheep show acute reduction in the rate of urine flow and in the rate of excretion of Na and K when given their daily feed. The authors suggest that the response is a reflection of the sudden shift of extracellular fluid into the gut at the onset of feeding.

It is clear that, in studies of electrolyte balance, the rate of excretion in urine is difficult to measure without recourse to facilities that permit the collection of urine over long periods, in circumstances affording minimum disturbance to the experimental subjects. If such facilities are available, the Na status of an animal may be
inferred by application of the experimental findings for the sheep reviewed by Wright (1962). Thus an intake of Na in excess of requirements is indicated by the excretion of significant amounts of Na in the urine, whereas an inadequate intake elicits conservation of Na by the kidney and also by the salivary glands. When the balance of intake against requirement is nicely poised, Na excretion by the kidney is virtually zero with no inversion of the normal ratio of the concentrations of Na and K in the parotid saliva, such as appears when the animal suffers from Na depletion.

The effects of renal regulation of acid–base balance on Na and K excretion

The importance of the bicarbonate–carbonic acid buffer system in stabilizing the reaction of the body fluids does not derive from the fact that it is an especially effective chemical buffer at normal blood pH, since its pK is too far removed from this pH value. Rather it derives from the fact that the concentrations of the two components of this buffer system are regulated and stabilized by very effective physiological mechanisms. The carbonic acid concentration, a function of the carbon dioxide tension, is regulated by the respiratory system, and the bicarbonate concentration is regulated by the kidneys. In considering the renal processes which regulate the bicarbonate ion concentration of the extracellular fluid, it is apparent that the ultimate composition of the urine is the result of some compromise between the requirements of acid–base equilibrium and of K balance.

The processes involved in the urinary excretion of bicarbonate have been the subject of extensive study in man and the dog, and are clearly described by Pitts (1963). The excretion of bicarbonate in bovine urine is believed to involve similar mechanisms (Anderson & Pickering, 1962b) but it should be noted that, unlike the urine normally produced by man and the dog, bovine urine is alkaline in reaction and contains high concentrations of bicarbonate. The bulk of the bicarbonate present in the glomerular filtrate is believed to be reabsorbed in the proximal part of the renal tubule as a result of a process in which hydrogen ions move from the renal tubule cells into the tubular urine in exchange for Na ions which are reabsorbed. The hydrogen ions then associate with bicarbonate in the tubular urine to form carbonic acid which decomposes into carbon dioxide and water. The carbon dioxide diffuses into tubule cells where it undergoes rehydration to form carbonic acid, a reaction which is catalysed by carbonic anhydrase. Subsequent dissociation provides the hydrogen ions, which are exchanged for Na ions across the luminal membrane, and bicarbonate ions, which accompany the reabsorbed Na into the peritubular fluid. Thus the concept is of bicarbonate being reabsorbed indirectly by conversion, within the tubular urine, into carbon dioxide.

Pitts (1963) estimates that some 90% of the filtered bicarbonate must be reabsorbed in the proximal tubule, but because of concurrent reduction in the volume of the fluid, concludes that the gradient against which reabsorption occurs is not great, being approximately 2 : 1 or 3 : 1. In the distal regions of the nephron, in man and the dog, most of the acidification of the urine takes place, and a mechanism is believed to operate in the collecting ducts which is specialized to reabsorb the re-
mainder of the filtered bicarbonate against a high concentration gradient. The fluid entering the collecting ducts contains Na ions and bicarbonate ions, the latter in reduced concentration. Active reabsorption of Na ions in this region can reduce the Na concentration of the final urine almost to zero, as is seen when Na intake is severely limited, and Na is reabsorbed as part of an ion-exchange mechanism which pumps either hydrogen ions or K ions from the cells of the collecting duct into the urine to replace the reabsorbed Na. In man and the dog, normally, the secretion of hydrogen ions in this process is sufficient to reduce the bicarbonate concentration of the urine to zero by operation of the indirect reabsorptive process described for the proximal tubule. In the cow, however, bicarbonate reabsorption is not complete and bicarbonate constitutes one of the major anions in the final urine (Anderson & Pickering, 1962b). Nevertheless, Na reabsorption is well maintained so that Na concentrations in the final urine of this species may still be reduced almost to zero.

Hydrogen ions and K ions (in the cells of the distal portions of the nephron) are believed to compete for secretion in exchange for reabsorbed Na (Berliner, Kennedy & Orloff, 1951), and in the bovine kidney, K appears to take a greater share of the secretory mechanism than it normally does in the kidney of the dog and of man. Displacement of hydrogen ions by K in this luminal exchange mechanism explains the well-known effect that oral administration of potassium chloride increases the excretion of bicarbonate, and intravenous infusion of K salts in the dog has been shown to reduce the rate of tubular reabsorption of bicarbonate (Fuller, MacLeod & Pitts, 1955). In the cow the large dietary intake of K may thus account for the normally alkaline reaction of bovine urine, and for its high concentration of K and bicarbonate. Loading with K salts in the dog results in hyperkalaemic metabolic acidosis as a consequence of the reduction in urinary acidification. That the cow normally does not suffer from a permanent hyperkalaemic metabolic acidosis seems to be the result of a fortunate coincidence—that in the herbivorous diet, the large amounts of K are part of an excess of inorganic cations which necessitates the excretion of an alkaline urine in order to avoid metabolic alkalosis.

The operation of these renal mechanisms in the cow, therefore, enables Na excretion to be minimal whilst maintaining a high level of K excretion in a urine of alkaline reaction. To impose increased requirements for the excretion of fixed acid, by feeding with silage treated with mineral acids, for example, may well disturb the nice balance normally achieved by the renal processes. Increased secretion of hydrogen ions by the renal tubules is limited by the large turnover of dietary K, and metabolic acidosis has been reported in cattle in these circumstances (Lepard, Pagé, Maynard, Rasmussen & Savage, 1940). One may predict with confidence that such a practice would also disturb K balance because K excretion would be reduced as a result of increased competition from hydrogen ions for the shared excretory mechanism.

Conclusions

The rate of excretion of K and Na in the urine can vary widely but, in general, it is clear that the kidney plays an important part in Na and K balance by adjusting
urinary losses of these elements according to variations in their intake. Detailed knowledge of the processes regulating electrolyte excretion, however, is fragmentary at best. From clearance techniques what goes on between the two ends of the renal tubule is purely inferential. Micropuncture studies are providing welcome direct evidence from amphibia and small laboratory mammals, but such studies are limited in scope because technical difficulties and the conditions of study are perforce such as to modify appreciably renal function. It may well be that the main difficulty lies in uncontrolled, unmeasured and probably often unrecognized variables. This difficulty will be familiar to anyone who has attempted to explain the apparent vagaries of Na excretion under presumably constant conditions. In balance studies, therefore, urinary losses of Na and K should be measured over relatively long periods so that acute alterations in the rates of excretion are seen in true perspective.

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