SOME APPARENT ANOMALIES OF POTASSIUM METABOLISM

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The importance of potassium in the body economy has for long been a matter of interest only to the physiologist. Within recent years, however, the recognition of serious potassium depletion in clinical conditions has aroused interest in potassium metabolism in health and disease. Our knowledge of this important cation has been derived from a wide variety of experimental and clinical observations, and the time seems ripe for a brief summary of the more important contributions.

Potassium Deficiency

In 1915 Benedict showed that potassium was lost along with nitrogen in fasting states, and, later, similar observations of potassium loss in diarrhoea (Butler *et al.*, 1933) and in diabetic coma (Atchley *et al.*, 1933) were made. The relationship of potassium to muscle contraction and muscle metabolism has always been of interest. In 1936 Brown and Feldberg showed that potassium liberated acetylcholine at ganglionic synapses. Fenn and Cobb (1936) found that, after indirect stimulation of the muscles of anaesthetized rats, potassium was lost from the muscle cell in exchange for sodium. These changes were reversed after rest, indicating that no irreversible damage had been done to the muscle. Cuthbertson *et al.* (1939) showed that, following operative fracture of the femur in rats, large amounts of potassium were lost in the urine, associated with an increased excretion of nitrogen and phosphorus. They observed that the potassium loss was relatively greater than the nitrogen loss, and seemed to be far greater than could be accounted for by the local changes at the site of injury.

The observations of Mullins *et al.* (1941) on the sodium permeability of the red cell indicated that the older concept of the impermeability of the cell to the cation sodium was not correct. Miller and Darrow (1941) showed that deoxycortone acetate reduced the muscle potassium content of rats and increased the muscle sodium content. This exchange of sodium for potassium in the cell was also demonstrated by Heppel (1939) and Miller and Darrow (1940a) in animals fed on a low-potassium/high-sodium diet. It was later observed in some clinical conditions such as alkalosis (Gamble *et al.*, 1945; Darrow, 1945), and in some types of infantile diarrhoea (Darrow, 1946).

By this time the loss of potassium in clinical conditions, often associated with signs of paralysis, had become recognized. Brown *et al.* (1944) observed a low serum potassium in chronic nephritis, associated with attacks of paralysis. Similar paralysis as a result of diminished extracellular potassium was described by Holler (1946) in treated diabetic coma. Govan and Darrow (1946) reported large losses of potassium in infantile diarrhoea, and observed that treatment with potassium improved the clinical state. In the development of hypokalaemia during the treatment of diabetic acidosis, Greenman *et al.* (1949) suggested that the dilution of extracellular potassium by intravenous infusions, the continued loss of potassium in the urine,

and the migration of potassium from the extracellular to the cellular phase might all contribute to the final clinical picture.

Potassium loss has also been observed after saline infusions (Stewart and Rourke, 1942; Gamble, 1942), after major surgical operations (Blixenkron-Møller, 1949; Wilkinson *et al.*, 1950), in *p*-aminosalicylic acid therapy, using the sodium salt (Cayley, 1950), in the use of ion-exchange resins (Dock and Frank, 1950), in idiopathic steatorrhoea (Lubran and McAllen, 1951), in pyloric stenosis (Hawkins *et al.*, 1951), and in chronic nephritis (Davidsen *et al.*, 1951). It seems probable that the potassium loss in such widely divergent conditions may be due to a few factors common to many clinical states. No matter the cause, the symptoms of hypokalaemia in all these conditions are similar, and are well summarized by Darrow and Pratt (1950): (1) weakness and hypotonia of skeletal muscle, leading finally to paralysis; (2) dyspnoea with gasping respirations; (3) cyanosis, chiefly respiratory in origin; (4) abdominal distension; (5) nausea and vomiting; (6) cardiac enlargement with systolic murmurs; (7) increased pulse pressure with Corrigan pulse; (8) elevated venous pressure with signs of cardiac failure; and (9) electrocardiographic changes.

Many of these signs of potassium deficiency are common to deficiencies of other electrolytes and of water, and are not, therefore, always convincing evidence of potassium lack. This matter is considered later, but it is important to appreciate that the electrocardiographic changes can be of considerable aid in diagnosis. These changes have been studied carefully by Frenkel *et al.* (1947), Nadler *et al.* (1948), and by Tarail (1948), and they have correlated the following changes with progressive deficiencies of potassium in the serum: (1) prolonged Q-T interval; (2) decreased height or inversion of the T wave; (3) rounded and prolonged T wave; (4) depression of the ST segment; and (5) inversion of the P wave, extrasystoles, and heart-block.

Hyperkalaemia

The toxic effects of increments in the extracellular potassium have also been widely studied. Hyperkalaemia is a danger only in renal failure and after the injection or absorption of potassium salts. Miller and Darrow (1940b) observed that the toxic effects of injected potassium salts in experimental conditions are directly related to the increase in concentration of that cation in the serum, and only indirectly to the muscle potassium content. This was confirmed in cats by Crismon *et al.* (1943). Folk *et al.* (1948) confirmed that the serum potassium content accurately reflects the potassium content of the extracellular fluids. The effects of increments in the extracellular potassium were studied by Winkler *et al.* (1938). They showed that, in dogs, the electrocardiographic changes due to the toxic effects of extracellular potassium could be directly correlated with the serum potassium concentrations. Briefly they noted: (1) increased amplitude and reduced duration of the T wave regularly appeared at concentrations of 5-7 mM of potassium per litre; (2) depression of the ST segment at 8-10 mM per litre; and (3) intraventricular block began at concentrations of 10 mM per litre, the P wave disappearing at 9-11 mM per litre, and cardiac arrest ensued at 14-16 mM per litre.

By depleting the muscle potassium, Miller and Darrow (1940a, 1941) were able to show that rats could be made resistant to the toxic effects of injected potassium salts. They concluded that this depletion of cell potassium enabled this cation, when injected in excess, to enter the cell, thereby protecting the extracellular fluid from a lethal rise in concentration.

Normally the kidney prevents toxic increases in the potassium concentration in the extracellular fluid. The excretion of potassium, as indicated by Smith (1951), is complicated. Potassium reabsorption occurs in the proximal tubule, but it has been necessary to postulate tubular excretion in the distal system, and this, though normally slight, is increased in all conditions of increased extracellular potassium. As Smith points out, this is the first instance in which experimental evidence has made it necessary to postulate the simultaneous reabsorption and excretion of any substance by the kidney tubules. Durlacher and Darrow (1942) showed that the life of nephrectomized animals could be prolonged by procedures which had previously depleted the body potassium stores. They concluded that the mechanism of this prolonged survival was therefore due to the delay in the post-operative rise in the serum potassium. These experiments were in agreement with the clinical data already available, indicating that some of the toxic effects in renal insufficiency were due to an increase in the serum potassium concentration (Winternitz *et al.*, 1940; Addis and Lew, 1939).

The purpose of this paper is to attempt some correlation of these various facts about potassium exchanges in clinical conditions and to analyse the means of diagnosis at our disposal.

Clinical States of Potassium Deficiency

Deficiency may be induced by prolonged reduction in intake or by abnormal loss. In many conditions, such as surgical operation, diarrhoea, and pyloric stenosis, both these factors are operative, and hasten the onset of the condition. As has been indicated above, the work of Benedict and later observers has shown that the protein catabolism associated with starvation also increases the loss of potassium from the body.

The loss of body fluids containing potassium may also hasten the onset of potassium deficiency. Gastric juice contains about 16 mEq of potassium per litre as well as hydrochloric acid. The starvation associated with pyloric stenosis, resulting in diminished intake, increased urinary output, and potassium loss by vomiting is a good example of the forces acting to precipitate potassium deficiency. If, in addition, saline infusion is liberally used in treatment it is hardly surprising that symptoms of potassium lack become manifest. Deficient intake, loss by the gastrointestinal tract either as stomach contents or diarrhoea fluid, and excessive loss during starvation can all be readily understood, and measures can be taken to estimate the potassium loss and to employ replacement therapy. It is with the urinary potassium loss that we are particularly concerned here.

Tarail and Elkinton (1949) have shown that, even in deficiency states, the kidney appears to have a limited minimal excretion of potassium. Unlike sodium, therefore, the kidney seems unable to conserve potassium when it is most required. This continued excretion in the urine in a patient already depleted of potassium is an important factor in producing severe deficiency. It has also been shown that a major surgical operation markedly increases the excretion of potassium in the urine (Blixenkrone-Møller, 1949; Wilkinson *et al.*, 1950). These writers have also shown that the phase of increased potassium excretion can be detected earlier than the phase of protein catabolism, and that the potassium loss is greater in proportion than the nitrogen loss. These effects are very similar to the experimental observations of Cuthbertson *et al.* (1939) on trauma in rats.

I have shown that this urinary potassium loss occurs also in the first three days after relatively minor operations such as interval appendicectomy and inguinal herniorrhaphy (MacPhee, 1952). In this series of patients the blood loss was minimal, hydration was adequate, and intravenous saline infusion was not necessary, thereby preventing the potassium loss shown by Gamble (1942)

to result from such treatment. This potassium loss may amount to as much as the equivalent of 10 g. of potassium chloride in the first three post-operative days. As a result of these observations and the associated sodium, chloride, and water retention, the eosinopenia, the increased 17-keto-steroid excretion, and the elevation in blood sugar in these patients, I have suggested that the electrolyte changes are the result of increased adrenocortical activity. It is probable that, provided the adrenal cortex is functioning, these metabolic changes are the natural response of the body to trauma. Such observations are in accord with the well-known hypothesis of Selye (1950), and, as he suggests, may occur in a wide variety of disease conditions and "stresses."

It is too early yet to say whether the increased potassium loss in such conditions as diabetic coma and other acute medical conditions is due to this "stress response" or not. Gamble (1942) has suggested from the work of Darrow that, in conditions of extracellular dehydration (as in infantile diarrhoea), potassium along with water is withdrawn from the cell. Wilkinson *et al.* (1950) suggest some similar mechanism to account for the increased potassium excretion after major surgical procedures. As I have indicated, however, this does not seem to be the operative mechanism in minor surgical trauma, as no appreciable changes were detected in the plasma volume or extracellular fluid space volume, and slight increases were detected in body weight, indicating water retention in the body. Further evidence in favour of the stress mechanism in acute medical conditions has been obtained by Prunty (1949), who observed evidence of increased adrenocortical activity in acute porphyria.

Diagnosis

Although there is no complete agreement on the mechanism leading to urinary loss of potassium in these widely disconnected conditions, the fact that potassium deficiency may supervene is now well recognized. The diagnosis of incipient potassium deficiency, however, remains difficult. The reasons for this have not been made clear. Apart from the electrocardiographic evidence, the signs and symptoms detailed above are often similar to the disease initiating the potassium loss. In addition, sodium chloride and water lack may precipitate cyanosis, abdominal distension, and peripheral circulatory failure, and must be considered as factors in addition to the concomitant potassium deficiency.

Concentrations of potassium in the serum below 3.5 mEq per litre are generally thought to indicate a deficiency of the cation. It is not generally appreciated, however, that the serum potassium concentration may be essentially normal when there is considerable cellular potassium depletion. I have now seen on several occasions electrocardiographic evidence of potassium deficiency associated with a "negative" potassium balance in the presence of a normal extracellular potassium concentration. Danowski *et al.* (1949), in accurate balance experiments, have shown that positive cell balances of potassium were recorded in patients who had normal serum levels of the ion. In the clinical experiments previously noted I have shown that the post-operative serum potassium concentration did not fall below 4.5 mEq per litre in my series, although a large increase had occurred in the urinary excretion of potassium. Frequently, indeed, the serum potassium was observed to rise during this phase. I believe this indicates that potassium is derived from the cells in the post-operative phase as rapidly as, or even more rapidly than, it is excreted by the kidney. This would account for the apparently anomalous findings of potassium deficiency in the presence of a normal or near-normal serum concentration of the ion.

In view of these observations and the experimental records cited above, it may be said that, in the early stages at least, the symptoms of potassium depletion are due to a reduction in the intracellular potassium and not in the serum potassium. It is therefore unwise to wait for biochemical evidence of potassium depletion in the serum before

considering potassium deficiency. Provided renal function is adequate, potassium deficiency must be *expected* in all patients who have undergone major surgical procedures, especially if oral feeding is not possible by the fourth post-operative day; if deficient potassium intake has occurred before operation; if potassium loss is augmented by vomiting, diarrhoea, dehydration, or saline infusion; and if potassium is not supplied at least in maintenance doses. If oral feeding is not possible the potassium loss in the urine, intestinal aspiration, and diarrhoea fluid should be estimated, and the appropriate quantity of potassium supplied.

One further point in regard to potassium deficiency needs to be mentioned. Low concentrations of serum potassium have recently been recorded in association with paralytic ileus. Streeten and Ward-McQuaid (1952) have published observations on this subject, but were unable to prove conclusively that paralytic ileus is always due to serum potassium deficiency. The paralytic ileus which results immediately on the perforation of a peptic ulcer is not associated with a serum potassium deficiency and it seems improbable that this should be the case. (In the absence of other evidence, a reflex "neurogenic" basis must be postulated.) Such a condition, if untreated, is rapidly followed by peripheral circulatory insufficiency due to sodium chloride deficiency which itself increases the ileus (Streeten and Williams, 1952). In the early stages such an ileus will recover rapidly after saline infusion. If, however, the ileus is allowed to persist untreated, the intestinal aspirations and the frequently associated operation may precipitate a potassium deficiency which will increase the tendency to ileus.

The fact that the early stages of potassium deficiency are not necessarily associated with a low level of serum potassium indicates that some method of determining the cellular potassium concentration is required. Electrocardiographic evidence is helpful. In the study of potassium loss after operation associated with normal serum potassium concentration I attempted to measure the erythrocyte potassium concentration (MacPhee, 1952). By estimating the serum potassium and the potassium content of lysed blood, and by utilizing haematocrit readings, the red-cell content can be measured. Although able to detect increases in the erythrocyte sodium immediately after operation, no constant changes were observed in the erythrocyte potassium. Such studies, though pursued in only a small series, seem to indicate that the erythrocyte potassium cannot be satisfactorily used as an index of muscle potassium content.

Treatment of Potassium Deficiency

Potassium deficiency states exist usually with deficiencies of other ions, and the object of treatment is to correct the total ionic imbalance rather than to correct any particular deficit. Any discussion of potassium replacement therapy alone must therefore, of necessity, be brief, and in general terms only.

If an adequate diet containing meat and vegetables can be taken there is little need to supply potassium by other means. If possible it is best to supply any potassium deficit by mouth, thereby allowing absorption as required and preventing a too rapid rise in the extracellular potassium concentration. Serious potassium deficiency, however, usually arises in cases in which oral feeding and therapy are not possible.

Elkinton and Tarail (1950) have estimated that the usual potassium deficiency encountered in the adult may vary from 228 to 936 mEq, roughly about 8–36 g. of potassium. They suggest that, if replacement therapy is to be undertaken by the intravenous route, no more than 20 mEq of potassium per hour in a solution with a maximum strength of 80 mEq per litre should be administered. As an example, a solution containing 4.5 g. of the monohydrogen phosphate (K_2HPO_4) and 1 g. of the dihydrogen phosphate (KH_2PO_4) added to a litre of water supplies 60 mEq of potassium per

litre. In severe deficiency states 250 ml. of this solution may be supplied each hour, provided adequate means of checking the serum potassium concentration are available.

A chloride deficiency in association with the potassium deficiency is often present in pyloric stenosis. In such cases potassium chloride (KCl) provides a suitable means of rectifying the cation and some of the anion deficiency. Each gramme of potassium chloride contains 13.4 mEq of potassium.

If the potassium deficiency is associated with severe sodium depletion, as in prolonged vomiting of intestinal contents, Darrow's solution provides a suitable method of treatment. This "K-lactate" solution contains 4 g. of sodium chloride, 2.7 g. of potassium chloride, and 52 ml. of molar sodium lactate per litre. The solution can be given in a four-hour period, but, as the potassium concentration is about ten times that of the serum, it is safer to prolong the administration over a somewhat longer interval.

It will be readily appreciated that the parenteral therapy outlined above cannot be followed unless renal function is adequate and unless the concentration of potassium in the serum can be rapidly estimated as treatment progresses.

Increased Extracellular Potassium

Unlike the effects of potassium deficiency, the toxic effects of increased body potassium are usually related to the extracellular concentration of the ion. As already indicated, the toxic effects can be correlated directly with the serum potassium concentration. As a result, the curious anomaly of potassium intoxication may occur during the treatment of cellular potassium deficiency. I have seen a case of pyloric stenosis in the late post-operative period complicated by paralytic ileus, and with an initial serum potassium concentration of 3.5 mEq per litre, showing signs of potassium intoxication as a result of too rapid parenteral replacement therapy.

In clinical practice increased concentration of potassium in the serum is encountered mainly in states of renal insufficiency and in oligaemic shock.

Anuria and Severe Oliguria

The experimental work on this subject has already been considered. In spite of the experimental evidence obtained by Durlacher and Darrow (1942), they did not believe that fatal increases in concentration in the extracellular potassium were the cause of death in anuria. In association with Winkler *et al.* (1938) they thought that the symptoms of potassium intoxication were totally different from those of uraemia.

The cause of the increase in extracellular potassium is an interesting problem. An exogenous source can be excluded, because the rise in the serum potassium can be observed when such patients are starved. Elkinton *et al.* (1949) showed that the rise in extracellular concentration was derived mainly from intracellular potassium. It has been assumed that this increase in extracellular potassium in the anuria associated with mismatched transfusion results from haemolysis and the liberation of potassium from the red cells. There are many objections to such a theory. The rise in serum potassium is rarely noticeable in the first day

Chart showing effect of peritoneal dialysis on blood urea and serum potassium concentration in patient with severe oliguria.

or two after the transfusion. The Chart demonstrates this point in such a case, and shows that the rise is progressive in the later stages. The Chart also illustrates the effect of peritoneal dialysis in reducing the blood urea, but not in reducing the serum potassium concentration when a solution such as Ringer's is used as the dialysate. It is also interesting to note that the patient remained clinically well, though suffering from severe oliguria, until the eighth day, when symptoms of uraemia began to appear. At this time the blood urea concentration had been greatly reduced by dialysis, the carbon dioxide combining-power of the plasma had returned to 60 volumes%, and the plasma chlorides had risen to 82 mEq per litre. Though this is not direct evidence of potassium intoxication, the uraemic symptoms were certainly associated with the increase in the serum potassium. When recovery ensued after thirteen days' oliguria, the serum potassium rapidly returned to normal.

In view of the fact that the rise in extracellular potassium in such states is a progressive one, I believe that increased adrenocortical activity may be the cause of the potassium withdrawal from the cells. The "stress" origin of such a cell depletion would be in line with the mobilization of potassium from the cells after trauma, operation, and other tissue injuries. There is as yet, however, no real proof of this mechanism. The gradual rise in the serum potassium could be explained in other ways. For example, after crush injuries much potassium may be liberated from the damaged muscle. Potassium may also be derived from the cells during the protein catabolism of starvation. The mechanism therefore remains in doubt.

Treatment

Kolff (1950) has shown that *subnormal* serum potassium concentrations may actually be produced in uraemia in patients on a Borst diet (high carbohydrate, low protein). Fenn (1939) showed that potassium is deposited in the liver along with glycogen. Experimental evidence suggests therefore that after injections of carbohydrate a movement of potassium from the extracellular to the intracellular spaces takes place. This may be a part of the merit of a treatment such as that of Bull *et al.* (1949), in which a high carbohydrate intake is advocated.

If the extracellular potassium concentration has already reached toxic levels before adequate treatment is begun, some form of dialysis may be necessary. Intestinal dialysis as described by Black and Stanbury (1948) is a most suitable method of reducing the extracellular potassium concentration in such cases. Peritoneal dialysis is cumbersome, and may be dangerous.

Summary

Potassium deficiency may occur as a result of deprivation of the ion, by excessive loss though vomiting, by diarrhoea, or in the urine.

The loss is accentuated by saline infusion, operation, injury, and perhaps by other stress conditions.

The symptoms of potassium deficiency may occur when the serum potassium concentration is still within the normal range. The symptoms are therefore due to cellular potassium depletion.

The erythrocyte potassium concentration is not an index of the muscle-cell potassium content.

Symptoms of potassium intoxication are directly related to the extracellular potassium concentration, and not to the cell potassium content.

ADDENDUM.—In the recovering phase of renal cortical necrosis when diuresis ensues, it has always been our experience that excess potassium is rapidly cleared from the extracellular fluid. In a recent case, however, I have observed a potassium and non-protein nitrogen retention after the onset of diuresis. In this case the urine continued to approximate to a glomerular filtrate for several days. On

theoretical grounds it was believed that, in the presence of a satisfactory urinary output, the excess potassium and nitrogen would be cleared by giving cortisone. This was done, and a dramatic fall in the serum potassium and non-protein nitrogen was observed. If the urine volume had not been sufficient, however, it would have been dangerous to use cortisone.

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"Egg white is the most alkaline natural fluid known, having a pH of about 9.5; this high alkalinity confers on it a definite bactericidal character, which is enhanced by the presence of certain proteins, such as lysozyme, a known antibiotic. The pH of yolk is about 7, and the whole egg therefore should act as an electric cell or battery because of the difference in acidity between the yolk and the white. The yolk, having an excess of positive hydrogen ions over the white, as it is more acid, ought to be at a positive potential relative to the white and should correspond to the positive pole of a cell. This difference in electric potentials within an egg can be demonstrated directly with the aid of a sensitive galvanometer. . . . The potential difference between yolk and white varies considerably from egg to egg and with the age of the egg; it is about 1/10 of a millivolt."—From a lecture given by D. P. Riley, D.Phil., at the Royal Institution on November 7, 1952.