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Potassium metabolism in relation to acid base balance

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POTASSIUM METABOLISM
IN RELATION TO ACID BASE BALANCE

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Potassium Metabolism In Relation to Acid-Base Balance

I. INTRODUCTION

The significance of changes in intracellular composition associated with disturbances in the acid-base balance of extracellular fluid has only recently been recognized. Potassium, the principal intracellular cation, is dynamically involved in the ionic interplay between extracellular fluid and the intracellular compartment. This paper is a review of current concepts, and their experimental formulation, of the role of potassium metabolism in the phenomena of acid-base balance.

II. CHANGES IN INTRACELLULAR COMPOSITION IN ALKALOSIS AND ACIDOSIS

Until recently, disturbances in acid base balance were considered largely in terms of their manifestations in extracellular fluid. Gamble,[1] in 1925, described the elevation in serum bicarbonate which he observed following experimental pyloric obstruction in dogs as an "automatic consequence" of chloride depletion. Changes in intracellular composition were not measured.

Wilson[2] in 1940 reported electrolyte balance studies in a patient who had Cushing's disease associated with alkalosis and a lew plasma potassium concentration. The plasma electrolyte pattern in this patient had returned to normal following simultaneous administration of potassium chloride and ammonium chloride, and was subsequently maintained with potassium chloride alone. The quantity of potassium retained during the balance period was far greater than the amount required to account for the relatively small increment in serum potassium observed. It was inferred that this patient had had an intracellular potassium deficit.

Darrow[3] subsequently demonstrated loss of muscle

potassium and increase in muscle sodium concentration in rats receiving injections of des oxycorticosterone acetate. This change was observed even though the diet contained "adequate" quantities of potassium.

In 1946 Darrow[4] subjected rats to experimental pyloric obstruction producing alkalosis with chloride depletion. The intracellular sodium concentration in these animals was found to be increased and the intracellular potassium decreased. The decrease in muscle potassium apparently occurred in spite of abundant supply of potassium in the diet. He concluded that alkalosis is associated with loss of muscle potassium and replacement by sodium.

Darrow, Schwartz, Ianucci and Coville[5] reported results of depletion of sodium, potassium, and chloride in groups of rats, using adrenalectomized rats as controls. They found that following renal adjustment in the presence of such deficits there is a correlation between the serum bicarbonate concentration and intracellular ionic composition. In particular, changes in serum bicarbonate concentration varied directly with the calculated intracellular sodium concentration and inversely with muscle potassium. Therefore, in alkalosis, one would expect to see increased intracellular sodium and decreased intracellular potassium. In

acidosis the reverse of this relationship would be expected. From these experiments it was concluded that sodium, potassium and bicarbonate are interdependent, their concentrations in the cell and in extracellular fluid being related in a "predictable" way following renal adjustment in the presence of a deficit of one of them.

In order to determine whether respiratory disturbances in acid base balance would have effects on muscle composition similar to the effects of metabolic acidosis and alkalosis, Cooke, Coughlin and Segar[6] subjected rats to environments containing 10-15% carbon dioxide for 14-21 days. Analyses of muscle revealed potassium content at the upper limit of normal along with minor decreases in sodium content. These changes parallel those associated with metabolic acidosis even though the serum bicarbonate was elevated. It was concluded that the pH of extracellular fluid, rather than the bicarbonate content, was the determinant of the changes in composition of cells.

III. QUANTITATIVE RELATIONSHIPS

Muntwyler and Griffin[7] reported analyses of plasma and muscle of rats during potassium depletion showing that replacement of potassium lost from cells by sodium is less than complete. In fact, the ratio of potassium lost to sodium gained approximated 1.5. There was, however, evidence that after an initial rapid loss of potassium from cells, there follows a slower rate of loss which tends to be compensated for by an equivalent gain of sodium.

Miller and Darrow[8] had previously noted this quantitative difference in the reciprocal relationship between intracellular sodium and potassium concentrations. According to their calculations, for each two mM's of potassium leaving cells, one mM of sodium entered.

IV. ALTERATIONS IN RENAL FUNCTION IN POTASSIUM DEFICIENCY

A case of severe alkalosis following prolonged gastric suction was reported by Kennedy[9] in 1949. Determinations of red cell composition revealed low intracellular potassium and high intracellular sodium. The plasma potassium was consistently low and it was therefore concluded the patient had a "total body" deficit of potassium. In spite of the alkalosis the patient excreted a definitely acid urine. This phenomenon had been observed before in potassium deficiency with alkalosis.

Darrow, in his experiments showing the relationship of serum bicarbonate to muscle composition,[5] had pointed out that the development of alkalosis in potassium deficieney involves some alteration in renal function in that it represents a failure on the part of the kidney to compensate for a change in extracellular composition.

V. TUBULAR SECRETION OF POTASSIUM AND ION EXCHANGE MECHANISMS IN THE KIDNEY

A number of experiments have been performed in which the quantity of potassium excreted in the urine is compared with the quantity of potassium filtered during a given clearance period. Berliner[10] reported ratios of excreted potassium to filtered potassium as high as 1.9 in more than 300 clearance periods in normal dogs. Also, ratios ranging from 1.05-1.3 in seventeen clearance periods in normal human subjects were found. These ratios greater than unity are considered as evidence that potassium is secreted by the renal tubule.

Pitts[11] in 1945 had postulated an ion exchange mechanism to account for the tubular acidification of urine. He suggested either a direct exchange of sodium and hydrogen ions across the tubule cell membrane, or an indirect process involving addition of hydrochloric acid or carbonic acid to tubular urine and subsequent reabsorption of sodium from the tubules as the chloride or bicarbonate. Berliner[10] proposed a similar mechanism for the tubular secretion of potassium. To test this hypothesis he infused potassium ferrocyanide into dogs after a "priming" dose

of sodium ferrocyanide. Measurements of the excretion of sodium, potassium, ammonium, ferrocyanide, inorganic sulfate, inorganic phosphate, chloride and bicarbonate during clearance periods (along with plasma potassium and creatinine clearance) revealed the amount of potassium secreted, i.e. the amount excreted in excess of that filtered, exceeded the total of all the anions excreted except for ferrocyanide by 100-300 microequivalents per minute. Since ferrocyanide is excreted "consistently at the level of glomerular filtration", it was assumed that this ion is not secreted or reabsorbed by the tubule cells.

In other words, the secreted potassium appears to be present in excess of anions which might have been secreted with it. It should follow that the potassium secreted replaced some other cation in the filtered urine. Without implicating a specific chemical mechanism, the overall effect of this process is cation exchange. One might expect that the cation removed from tubular urine is sodium although there is no direct evidence to support this assumption.

In order to study the relationship between urine acidification and potassium excretion, Berliner,[12] in 1951 administered 2-acetylamino, 1, 3, 4-thiadiazole 5-sulfonamide (No. 6063) to dogs and measured urine pH, K^+ excretion and filtration, inulin clearance, and

creatinine clearance.

The compound, #6063, had been shown to be a potent inhibition of the enzyme carbonic anhydrase. Carbonic anhydrase was thought to be a component in the mechanism by which hydrogen ions are made available for the ion exchange process in which sodium is reabsorbed inasmuch as Pitts[11] has observed decreased excretion of acid in the urine on inhibition of the enzyme with sulfanilamide. Potassium excretion was found consistently to be increased following administration of No. 6063, in some instances the increase being equal to or greater than the total amount of potassium filtered. The increment was found to be greatest in dogs who were already acidotic, while in dogs made alkalotic by sodium bicarbonate injection, potassium excretion was high before infusion of #6063, and increased relatively little afterwards.

In order to determine whether the increase of potassium excretion observed was due to increased tubular secretion alone or partially to decreased reabsorption, the effects of #6063 in combination with mercurial diuretics (salyggan) were studied. Increases in potassium excretion were minimal following administration of the two drugs, but potassium excretion increased greatly after the effects of the

mercurial were abolished by administration of B.A.L.

This experiment is based on the assumption that inhibition of a transport mechanism by one drug prevents any enhancing effects of another. Because the mercurial inhibited the increased excretion of potassium expected following administration of #6063, it was concluded that the effect of carbonic anhydrase inhibitor in increasing potassium excretion is the result of increased secretion of potassium by the tubules.

The finding of increased potassium excretion, presumably increased tubular secretion of potassium, after inhibiting hydrogen ion secretion suggests "that there is competition between potassium and hydrogen ions for some component of the ion exchange mechanism whereby sodium is reabsorbed in the distal tubules."

Berliner feels that the effect of alkalosis would be similar to the effect of carbonic anhydrase inhibition on renal tubule cells in that there would be a decrease in hydrogen ion concentration and exchange of sodium for potassium would be favored over exchange of sodium for hydrogen, resulting in the potassium loss seen in alkalosis. Similarly, in acidosis, exchange of sodium for hydrogen would be favored and potassium retention would occur. With

primary depletion of body potassium, on the other hand, competition between potassium and hydrogen ions would be in favor of the hydrogen, and a metabolic alkalosis with excretion of an acid urine would result. With increased potassium concentration, hydrogen ion secretion would be suppressed and an alkaline urine along with acidosis because of loss of base would result.

These experiments would seem to indicate, then, that the concentration of potassium in the renal tubule cells, or, more properly, the relation of potassium concentration to hydrogen ion concentration is important in the control of the rate of potassium excretion.

A reciprocal relationship has also been noted between potassium excretion and bicarbonate reabsorption in the kidney.

Fuller, Macleod and Pitts[13] infused potassium as the chloride and also as the bicarbonate into dogs. In order to keep the filtered load of bicarbonate relatively constant they simultaneously infused sodium bicarbonate.

They found that, on administration of the potassium salts, potassium excretion increased while bicarbonate reabsorption decreased. The administration of the carbonic anhydrase inhibitor (No. 6063) also

resulted in decreased bicarbonate reabsorption along with increased potassium excretion. They were not able to demonstrate any additive effect of potassium infusion and carbonic anhydrase inhibition. Along with the increase in potassium excretion in these experiments, there was decreased excretion of hydrogen ions. During these experiments less than half of the potassium administered and about one-third of the bicarbonate could be accounted for in the urine or in extracellular fluid. Although the extracellular fluid volume was not measured, they assumed that this discrepancy was accounted for by interchange between extracellular fluid and cells. If the renal tubule cells gained potassium by this mechanism one might expect increased secretion of potassium along with decreased secretion of hydrogen ions. In general, these results are compatible with the idea that potassium and hydrogen compete for secretion by the renal tubule cells.

VI. EXTRARENAL MECHANISMS

In order to evaluate the mechanism proposed by Berliner, Cooke[14] constructed experiments comparing renal excretion with the ionic composition of muscle and serum of rats during recovery from alkalosis associated with potassium deficiency. Two groups of rats were rendered alkalotic with injections of disoxcorticoteron acetate in addition to a diet deficient in potassium and containing sodium in excess of chloride. One group received injections of potassium chloride, while the other, the control, received equivalent amounts of chloride in the form of isotonic sodium chloride injections. The group receiving potassium excreted urine of higher titrable acidity and increasingly lower pH and bicarbonate content than the group receiving sodium. Moreover, the experimental group demonstrated increased excretion of sodium following injection of potassium, whereas in the control group, excretion of sodium approximated the amount administered. Excretion of potassium did not increase at all in the control group but did increase after administration of 12 mM/Kg of potassium and reached the level of the amount administered after 24 mM/Kg had been given to the experimental group. Serum analyses revealed complete correction of alkalosis

in the group receiving potassium, but the serum bicarbonate remained essentially unchanged in the control group. Cumulative balance studies of sodium, potassium, and chloride revealed retention of approximately 20.2 mM of potassium and 10.8 mM of sodium per kilogram of body weight in the group receiving potassium. There was insignificant retention of sodium and small loss of potassium in the control group. The group receiving potassium excreted chloride in excess of the sum of sodium plus potassium.

Analysis of muscle at the end of the control period before injection of potassium or sodium revealed increased sodium content approximating two-thirds of a decrease in potassium content as described previously. The muscle composition in the group receiving potassium gradually returned to normal during the experiment.

From these findings, the authors concluded that the correction of alkalosis must have resulted from an interchange of ions between extracellular fluid and muscle cells, because the effects of the kidney alone as inferred from the excretions measured, would not have corrected the extracellular alkalosis. Considering the excretions, in particular the fact that more chloride was excreted than the sum of both

sodium and potassium, they concluded that the animals had a "deficit of fixed cation in excess of a deficit of fixed anion." In development of alkalosis, the increase in intracellular sodium is about equal to two-thirds of the decrease in intracellular potassium. Therefore, during recovery following potassium administration, three potassium ions must enter the cell for every two sodium ions which leave it. In order to preserve electrical neutrality, some other cation within the cell must exchange for potassium.

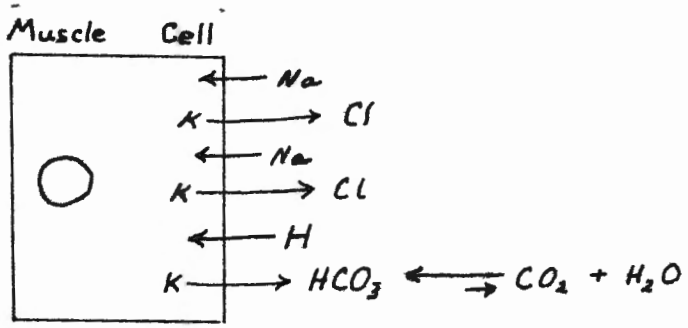
Cotlove et al[15] subjected dogs to electrolyte depletion in the presence of acidosis and alkalosis and found no evidence that magnesium or calcium might account for the discrepancy between the balance of sodium and potassium.

By exclusion, then, Cooke concluded that hydrogen ions within the cell are exchanged for potassium in extracellular fluid. This addition of hydrogen to extracellular fluid leads to formation of carbonic acid eliminated as CO_2 through the lungs with resultant reduction in extracellular bicarbonate. The theoretical quantitative reduction in extracellular bicarbonate as calculated from changes in intracellular composition would be much greater than that actually observed. The authors account for the

discrepancy by pointing out that there is renal compensation for that load of hydrogen ions transferred from cells as evinced by the urine of high titrable acidity, low pH and bicarbonate content.

The authors reason that during development of alkalosis with potassium deficiency, the reverse of the above changes must take place. That is, three potassium ions from cells are exchanged for two sodium from extracellular fluid along with one hydrogen ion which is derived from dissociation of extracellular carbonic acid. The ultimate effect is the same as if potassium bicarbonate were added to extracellular fluid.

DIAGRAM



Cell Transfer

Producing Alkalosis

in Potassium deficiency (From Cooke).[14]

Utilizing the data reported above, and those of other experimenters, Cooke and Segar[15] attempted to formulate a theory which would explain the inter-

dependence of extracellular fluid and muscle composition. They assumed that the ion exchange systems discussed above represent an equilibrium reaction, and therefore, a change in concentration of the reactants on one side of the reaction would shift the equilibrium point so that there would be a corresponding change in concentration of the reactants on the other side. In this case the transport of sodium or hydrogen ions out of the cell in exchange for potassium which is transported inward would be dependent on their concentrations on either side of the cell membrane. It is necessary to assume that intracellular sodium enters the cell by passive diffusion and that potassium leaves the cell by the same process. Intracellular hydrogen is present as a product of cell metabolism. Passive diffusion depends simply on the gradient in concentration across the membrane, and this gradient would be altered relatively little by changes in extracellular potassium concentration or intracellular sodium concentration. Therefore, the process of passive diffusion of sodium and potassium would remain relatively constant. On the other hand, since the extracellular concentrations of potassium and hydrogen ions are small relative to their intra-

cellular concentrations, the equilibrium point in their transport is altered relatively more by a slight change in their extracellular concentration than a similar absolute change in their intracellular concentrations.

In metabolic alkalosis, then, with decrease in extracellular hydrogen ion concentration, the equilibrium point in the exchange of intracellular hydrogen for extracellular potassium is shifted and more hydrogen is transported out of cells. (This may account for the fact that administration of bicarbonate does not produce a quantitative rise in serum bicarbonate.) At the same time, the exchange of intracellular potassium is believed to be reduced because of competition between sodium and hydrogen for exchange with potassium. If the exchange of sodium for potassium is of greater magnitude than the exchange of hydrogen for potassium, (as is indicated by the fact that in potassium deficiency the increase in intracellular sodium is about 2/3 the increase in intracellular potassium), then less potassium will be transported into the cell and less sodium transported out. The ultimate result would be increased intracellular sodium and decreased intracellular potassium.

In metabolic acidosis, with increased extra-

cellular hydrogen ion concentration, the equilibrium point in the exchange of intracellular hydrogen for extracellular potassium would be shifted so that the reaction would be decelerated; therefore the exchange of intracellular sodium for extracellular potassium would be accelerated, and the result would be decreased intracellular sodium and slightly increased intracellular potassium.

In respiratory acidosis and alkalosis, the changes in equilibrium would again depend on the concentration of hydrogen ions in extracellular fluid but the measured changes are of lesser magnitude than with the corresponding metabolic disturbances. The authors believe that, because all membranes are permeable in carbon dioxide, the intracellular hydrogen ion concentration varies directly with the extracellular concentration when carbon dioxide is retained or lost because of respiratory disturbances.

The mechanism pertaining to primary potassium deficiency has already been described.[14] Here, the exchange of both intracellular hydrogen and intracellular sodium for extracellular potassim would decrease. Therefore, intracellular sodium rises and intracellular potassium decreases. Alkalosis should develop because of diminished transfer of hydrogen

out of the cell. The hypochloremia which develops is explained as follows: for each hydrogen ion which is retained within the cell because of diminished transport one fixed cation, i.e. potassium, in excess of fixed anion is added to extracellular fluid. This load of fixed cation in excess of fixed anion is excreted by the kidney along with chloride.

VII. THE NATURE OF THE ALTERATION IN RENAL FUNCTION IN POTASSIUM DEFICIENCY

Some alteration in renal function in potassium deficiency is indicated by the failure of the kidneys to conserve chloride and to compensate for the load of fixed cation in excess of fixed anion. Otherwise one would expect the kidney to excrete the bicarbonate which is, in effect, added to extracellular fluid by transport of hydrogen into cells in exchange for potassium. This failure in renal regulation of extracellular composition might be explained, as Berliner[12] had suggested by changes in the renal tubule cells similar to those described for muscle cells in potassium deficiency. With increased hydrogen ion and sodium ion concentrations along with decreased potassium concentration in the tubule cells, there might be interference with the reabsorption of anion.

In order to determine whether or not such changes are present in renal tubule cells in potassium deficiency, Darrow, Cooke and Caville[13] undertook analyses of serum, muscle and kidneys of rats subjected to potassium deficiency. The analyses of serum and muscle revealed the changes expected in potassium deficiency alkalosis; those of kidney revealed statistically significant increase in chloride and increase in

phosphorous. The latter was the only change referable to kidney cells themselves since the method of analysis includes both cells and extracellular fluid. The change in chloride showed a significant direct correlations with the serum chloride. Changes in kidney cells analogous to those of muscle were not demonstrated. The method of analysis would probably not detect such changes if they occurred in a small number of tubule cells; but, there is no support for this explanation of the failure of the kidneys to restore extracellular composition in potassium deficiency.

Cooke and Segar et al[18] reported a remarkable series of experiments in 1954 which helps to clarify the relationship between alkalosis and potassium deficiency. In one experiment designed to study the effects of potassium intake on the metabolic response to loads of sodium bicarbonate it was found that, in the absence of potassium deficiency, alkalosis did not develop in rats in spite of daily intake of sodium bicarbonate greater than 10-30 mM/kg. Moreover, alkalosis did not develop in more than 12% of a group of animals receiving large loads of fixed cation (sodium) in excess of fixed anion (chloride) provided potassium intake exceeded 0.4 mEq/kg per day. In some groups of animals on low chloride intake alkalosis

developed when the potassium intake was at a level which had been demonstrated to prevent alkalosis with higher chloride intakes. However, increased potassium intake prevented alkalosis in the presence of low chloride intake. The authors concluded that potassium intake may prevent alkalosis partly by its influence on chloride conservation.

Since the electrolyte intake of these animals was regulated over a period of 14-21 days during which time the bicarbonate intake exceeded the potassium intake by fifteen to thirty times, it was concluded that the potassium excreted could not have exceeded 3-7 per cent of the total bicarbonate and organic anion excreted.

In a second experiments, the response of alkalotic potassium deficient rate to acute loads of sodium bicarbonate was studied and compared with the response of normal animals to a similar load. The normal animals showed only slight decrease in serum potassium and slight increase in pH; the serum bicarbonate was 25 mEq/L and chloride was 99 mEq/L. The potassium deficient animals, who had a mild hypochloremic alkalosis before loading with sodium bicarbonate, developed severe alkalosis in which the mean pH of

serum was 7.70, serum bicarbonate 42 mEq/L, and chloride 78 mEq/L. Muscle analyses in the normal animals showed significant decreases in muscle potassium and increases in muscle sodium after loading with sodium bicarbonate. The potassium deficient animals had markedly decreased muscle potassium and increased muscle sodium before loading with sodium bicarbonate. But, unlike the normal animals, there was no appreciable change in muscle composition after loading.

Analyses of urinary excretions during the loading period showed that the normal animals excreted about 90% of the water and about 45% of the bicarbonate administered. They excreted an amount of cation about equal to the amount administered (i.e. 15-16 mEq/Kg of body weight). About one-third of the cation excreted was potassium and the rest was sodium.

In contrast, the potassium deficient rats excreted only about 30% of the water and 15% of the bicarbonate administered. The cation excretion equalled 6 mEq/kg of body weight of which 99% was sodium. In spite of the low serum chloride before loading, these animals excreted about four and one-half times as much chloride as the normal animals.

Because the normal animals had excreted a large quantity of potassium following loading with bicarbonate

and because this quantity of potassium approximately equalled the calculated decrease in total muscle potassium, it was concluded that part of the muscle potassium constituted a reserve of cation which is available for rapid excretion. The authors believe that this potassium, which had previously been termed the "labile potassium of muscle" by Miller and Barrow,[8] is the "first line of defense against alkalosis". Since cation excretion is facilitated by the exchange of intracellular potassium for extracellular sodium yielding a large quantity of potassium for rapid excretion, a rise in serum bicarbonate is prevented. Also, this mechanism may prevent a fall in serum potassium during bicarbonate loading and thus help to preserve the composition of renal tubular cells. These mechanisms did not operate in the deficient animals who had lost their "labile potassium".

Alteration in renal tubule cell function in potassium deficient animals is indicated by the marked increase in chloride excretion, probably the result of diminished reabsorption. The authors point out the similarity in the extracellular electrolyte patterns in respiratory acidosis and potassium deficiency alkalosis. Because of the increased carbon dioxide tension in respiratory acidosis there is intracellular

acidosis. Increase in muscle cell acid had been demonstrated in potassium deficiency.[4] It was therefore suggested that increased acidity of renal tubular cells might account for disturbance in the ratio in which sodium and chloride are reabsorbed from the tubules in potassium deficiency.

A third requirement involved administration of potassium bicarbonate to rats with potassium deficiency and alkalosis. A gradual correction of hypochloremic alkalosis was observed along with rise in muscle potassium to low normal levels and a fall in intracellular potassium. Sodium excretion increased until 12 mM/Kg of potassium bicarbonate had been given, and then began to decrease. Water excretion increased along with a 10% loss in body weight. Potassium excretion was low for the first two days of the experiment and then gradually increased to the level of potassium administered. Ammonia excretion progressively decreased, but the pH and titratable acidity were relatively unchanged during the experiment. Balance studies showed that there was more potassium retained than there was sodium lost, and body chloride remained relatively constant. The sum of sodium, potassium and ammonium ions excreted was greater than the sum of chloride, bicarbonate and phosphates. This discrepancy was accounted for by an

increase in excretion of organic anion, part of which was identified as citrate.

These results were compared with the previous experiments[4] in which potassium chloride was used to correct potassium deficiency alkalosis. In that case, correction does not appear to depend on the kidney primarily. But, when potassium bicarbonate is used, three potassium ions are exchanged for two sodium and one hydrogen ion from cells. This would lead to an increase in sodium bicarbonate in extracellular fluid unless the kidneys excrete sodium. Therefore, the kidneys are involved in the correction of potassium deficiency alkalosis with potassium bicarbonate.

The authors suggested that the correction of hypochloremia was most likely the result of reduction in extracellular fluid volume, since there was no evidence for a transfer of chloride from cells. There was, in support of this concept, a variable loss of weight during the experiment, although transfer of water from extracellular space to cells may also have occurred.

In the authors' view, these experiments demonstrate that the ultimate determinants of acid base balance in the body are the relations of the principal fixed cations, sodium and potassium, to the principal fixed anion, chloride. Thus, the correction of potassium

deficiency alkalosis with potassium bicarbonate involved a loss of sodium in excess of chloride from extracellular fluid, and an overall retention of fixed cation in excess of fixed anion indicating that the alkalosis had been associated with a deficit of fixed cation.

Furthermore, these experiments have indicated that potassium deficiency may alter the ratio at which sodium and chloride are reabsorbed from the renal tubule cells; and they indicate that the volume of extracellular fluid as well as its ionic composition may be altered in potassium deficiency.

Black and Milne[19] had found evidence of expanded extracellular volume in potassium deficiency in their experiments in human subjects. They based their conclusions on the assumption that chloride does not shift from extracellular to intracellular compartments in short experiments and that changes in extracellular fluid volume will be reflected by the cumulative balances of chloride, sodium, potassium and water. They observed positive balances of sodium and chloride during depletion. Cooles et al suggested that this increase in extracellular fluid volume might be accounted for by alteration in the ratio of sodium and chloride reabsorbed by the tubules with retention of sodium and water.

The finding of increased organic anion excretion during administration of potassium bicarbonate to potassium deficient rats has suggested to Cooke *et al* that organic anion may be secreted by the renal tubule cells in exchange for chloride from the glomerular filtrate. Thus, a mechanism has been proposed by which chloride is conserved by the kidney in defense against alkalosis which is similar to the renal defense against acidosis in which sodium is conserved by exchange for ammonium ion.

VIII. SUMMARY

The experimental results of a number of investigators have revealed a correlation between changes in the pH and bicarbonate concentration in extracellular fluid and the ionic composition of cells. In particular, extracellular pH varies directly with intracellular sodium and inversely with intracellular potassium. It has been pointed out that the development of potassium deficiency in metabolic alkalosis implies some alteration deficiency in renal function as does the failure of the kidney to compensate for the changes in extracellular composition in primary potassium deficiency, allowing alkalosis to develop. The finding that inhibition of the enzyme by which hydrogen ions are added to tubular urine leads to increased excretion of potassium has suggested a possible explanation for this phenomenon. That is, hydrogen and potassium appear to compete for some part of the ion exchange mechanism by which these ions are excreted, and deficiency of one would favor excretion of the other.

Further experiments have demonstrated correction of alkalosis associated with potassium deficiency which involved interchange of ions between extracellular fluid and intracellular fluid outside of the kidney. It is inferred that the reverse of these changes takes

place in the development of potassium deficiency alkalosis. Specifically, three potassium ions from cells are exchanged for two sodium and one hydrogen ion from extracellular fluid. The result is the same as if potassium bicarbonate were added to extracellular fluid. It has been suggested that this interchange of ions between the extracellular and intracellular compartments is an equilibrium reaction and therefore conforms to the "law of mass action".

Alteration in the composition of renal tubule cells similar to those described for muscle cells in potassium deficiency would possibly explain the failure of the kidneys to compensate for the load of fixed cation in excess of fixed anion imposed by the above mechanism. Such changes have not been demonstrated.

Further work by Cooke et al[18] has suggested that potassium deficiency may alter the ratio at which sodium and chloride are reabsorbed by the renal tubules. This alteration may explain the persistence of alkalosis in potassium deficiency. Evidence is presented which would indicate that organic anion secreted by the renal tubules may participate in the mechanism by which potassium maintains the normal ratio of sodium to chloride in the reabsorbate.

IX. CONCLUSION

One concept which has been accented by the experiments reviewed in this paper is that, in the presence of an intact respiratory apparatus, the ultimate determinants of acid-base equilibrium in the body are the balances of the principal fixed cations in relation to the principal fixed anions. Cooke and his associates[14] have demonstrated that animals having alkalosis with potassium deficiency have a deficit of fixed cation in excess of fixed anions. To account for this observation they have suggested that of three potassium ions leaving the cell, one is exchanged for a hydrogen ion from extracellular fluid and the remainder are exchanged for sodium.

Black and Milne[19] have contested this quantitative relationship suggesting that a smaller number of hydrogen ions entering the cell would lower pH enough to alter the valence of intracellular anions such that electrical neutrality would be maintained in the presence of fewer cations. But, Cooke points out hydrogen ions entering the cell would combine with anions to form poorly dissociated acids altering "base-binding capacity" without decreasing the number of cations entering the cell. It would seem that the latter is the more correct interpretation.

A rather elaborate, noumenal explanation of acid-base equilibria in terms of the Law of Mass Action has been proposed by Cooke and Segar.[16] While much of this is lacking in experimental verification, it is worth considering as a "working hypothesis". Nevertheless, ionic interchanges between extracellular fluid and intracellular fluid do not explain the persistence of alkalosis in potassium deficiency, i.e. the failure of the kidney to compensate for the load of fixed cation in excess of fixed anion.

An attractive hypothesis was suggested by the demonstration of increased potassium excretion during inhibition of carbonic anhydrase with diamox (No. 6063). As Berliner[12] proposed, a competition between potassium and hydrogen ions for exchange with sodium in the renal tubules would seem to explain the development of alkalosis in potassium deficiency as well as the loss of potassium in alkalosis. Further evidence in support of such a competitive relationship has been offered by Fuller et al.[13]

While one cannot deny that potassium and hydrogen may compete for exchange with sodium, it may be doubted that such a mechanism explains the phenomena observed. Berliner's proposal requires the assumption that changes in the renal tubule cells parallel to those observed

in muscle cells occur in potassium deficiency and alkalosis. Darrow et al[12] did not demonstrate such changes in their analysis of kidney composition in rats with alkalosis and potassium deficiency. However, as has been stated before, the analysis of the organ as a whole would not be sensitive enough to detect such changes if they were confined to a fraction of the tubule cells themselves.

More sensitive, although rather indirect, are the findings of Cooke et al[18] in their long term experiments delineating the effects of potassium intake on the metabolic response to bicarbonate loading. While neither renal excretion of potassium, nor tubule cell composition, were measured in these experiments, the overall balance of what was taken in and what remained in the animals as inferred from analysis of muscle and serum, indicated that potassium excretion had been relatively slight as compared with bicarbonate and organic anion excretion. The authors considered this as evidence that the substitution of potassium in place of hydrogen in the tubule cell was of little quantitative significance.

The fact remains that there does appear to be some alteration in renal function in potassium deficiency. The experiments reported by Cooke et al[14, 18]

suggested that potassium deficiency may alter the ratio at which sodium and chloride are reabsorbed by the tubule cells leading to hypochloremic alkalosis. The authors pointed out the similarity between potassium deficiency alkalosis and respiratory acidosis in that the ratio of sodium to chloride reabsorbed is altered in both. There is an intracellular acidosis in respiratory acidosis. In potassium deficiency the acidity of muscle cells is increased.[14] Possibly, then, the pH of the renal tubule cells may control the ratio at which sodium and chloride are reabsorbed.

This hypothesis also lacks experimental verification, and does not indicate the mechanism involved. The finding of increased excretion of organic anion during recovery from potassium deficiency alkalosis with administration of potassium bicarbonate is extremely provocative. As the authors point out, the exact nature of this organic anion is now known and further work will be necessary to determine whether it actually comes from the renal tubule cells themselves. Nevertheless, it is plausible to consider that excretion of organic anions in the presence of adequate potassium content may be a mechanism by which chloride is conserved in the renal defense against alkalosis.

Cooke[18] drew attention to a variability in

response to a given dose of sodium bicarbonate between normal animals and those suffering from potassium deficiency. He points out that the administration of bicarbonate solutions to patients according to empiracle formulae in the absence of any indication of intracellular composition is grossly inaccurate. It is suggested that cautious administration of small amounts of these solutions and observation of the effects on serum composition would be more accurate and certainly safer.

No attempt has been made to discuss clinical conditions such as diabetic acidosis in which potassium metabolism is altered by specific metabolic defects. Rather, this paper is a review of the basic role of potassium in the mechanisms of acide-base balance.

Note: The writer is indebted to Dr. Herbert P. Jacobi for his guidance and assistance in the preparation of this paper.

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