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Causative factors in intracellular potassium changes

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CAUSATIVE FACTORS IN INTRACELLULAR POTASSIUM CHANGES

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INTRACELLULAR POTASSIUM CHANGES

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I

The role which potassium plays in body physiology has long been known to be an important one. The effects of depletion or over-abundance are immediate and apparent but the mechanisms whereby these effects are produced have remained relatively obscure. This paper represents an attempt to accumulate from the recent leterature the present concepts of the mechanism of potassium depletion from, and restoration to, the intra-cellular fluid.

The pharmacological effects of potassium on the organism have been noted for a long while. Bochefontaine[1] in 1883, injected two grams of a potassium salt in a dog, and noted that death occurred by a "sudden stoppage of the heart". Ringer[2], in A Handbook of Therapeutics, in 1897, stated that the potassium of all potassium salts appeared to be equally poisonous and that prescribing potassium salts in preference to sodium salts should be revised because potassium salts were far more poisonous than the corresponding sodium salt. A. R. Cushny, in 1906, in A Textbook of Pharmacology and Therapeutics stated that potassium has a distinctly poisonous action which is chiefly manifested in depression of the Central Nervous System and the Heart in mammals, the chief symptoms being great muscle weakness and apathy. Respiration becomes rapid and labored---and death is often

preceded by convulsions". The mammalian heart was found to be injured, because the pulse became much slower and weaker, and a sudden drop in blood pressure occurred. When given orally, potassium salts were found to have no effect on the heart because of the rapid excretion in the urine[3]. Sollman[4] in 1906, in his textbook of pharmacology states essentially the same thing, but adds" Potassium is also in part responsible for the toxicity of urine and for uremia". Feltz & Ritter[5] in 1880, in an article concerning experimental uremia found that the amount of potassium salts existing in the blood had an influence in the quantities of urine necessary to cause serious disturbances and death. Intoxications arising from the urine were almost always due alone to the potassium salts which accumulated in the blood. McCallum[6] demonstrated that, although potassium was found throughout renal tissue, it occurred in greatest quantity in the cortical tubules where it varied in amount according to functional activity of the kidney.

Ringer drew attention to the importance of the three ions sodium, potassium and calcium, in maintaining the heart in vitro, and stressed the necessity of maintaining the ions in the same proportions as they exist in the

plasma. Ringer's solution contained the chlorides of sodium, potassium, and calcium, in the following proportions for mammalian experiments:[7]

NaCl	0.9%
KCl	0.03%
$CaCl_2$	0.025%
$NaHCO_3$	0.020%

Locke's solution was very similar, containing:[8]

NaCl	0.92%
KCl	0.024%
$CaCl_2$	0.042%
$NaHCO_3$	0.018%
Glucose	0.1%

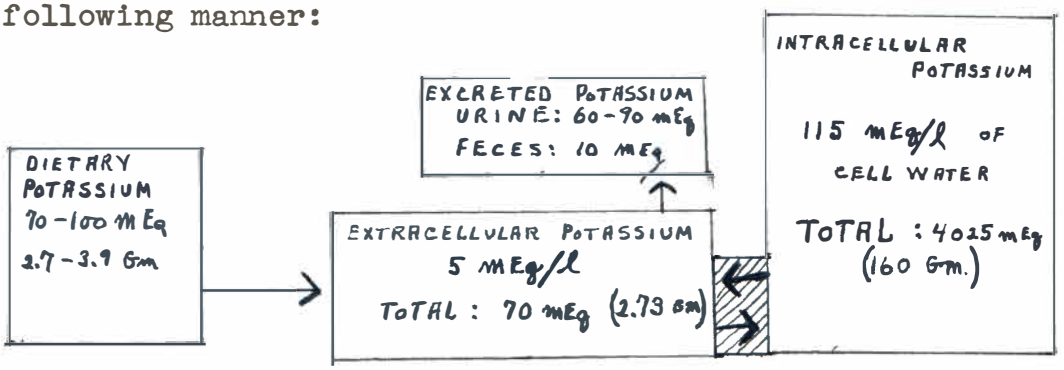
With the advent of improved techniques, our knowledge of the function of potassium has increased consederably. The flame photometer, making it possible to determine accurately the potassium and sodium contents of fluids, both intra- and extra-cellular, has provided the greatest single impetus to the study of potassium that we have developed to date.

II

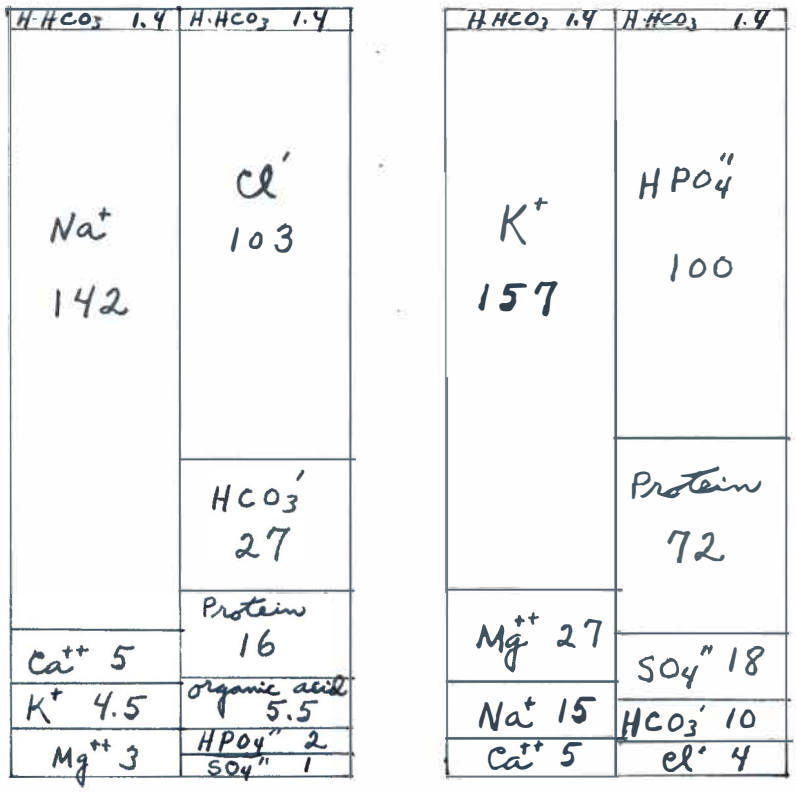
Potassium is found in all body fluids. Its concentration varies, however, there being a much higher concentration in the intracellular fluids than in the interstitial fluid or plasma. Gamble[9] states that the blood plasma level of potassium is approximately 5 mEq./l, while the intracellular level is about 120 mEq/l. Farber[10] et al, in observing the plasma potassium level in 70 normal men, found that the mean plasma level was 4.41 mEq/l, with a fluctuation of from 3.7 to 5.3 mEq/l.

Ferrebee[11] et al, in 1941, stated that the normal potassium level in muscle tissue was 80 mEq/l. Best and Taylor[12] diagrammatically represent the potassium level as 320 mgms% in muscle tissue, and 420 mgms% in the erythrocytes. Expressed as milliequivalents, this amounts to about 82mEq/l of potassium in the muscle tissue, and 107 mEq/l in the erythrocytes.

More recent literature places the intracellular levels somewhat higher. Hoffman[13] schematically represents the distribution of body potassium in the following manner:



Smith Freeman[14] graphically represents the body concentrations of potassium as follows: (Numbers indicate milli-equivalents per liter)



Although there is still some discrepency between the results obtained by different investigators, much of this discrepancy can be explained by the great difficulty and inaccurate methods formerly used in intracellular potassium determinations. Further work with the flame-photometer will, no doubt, clarify this picture a great deal.

III

Intracellular depletion of potassium occurs in a variety of conditions. Elkinton, Winkler and Danowski[15] noted a loss of intracellular potassium in conditions of fasting, diarrhia, dehydration, and in diabetic coma. Of these, the first one involves a diminished intake of potassium; the second one involves an increased excretion of potassium (per rectum); and the third and fourth conditions involve primarily an internal readjustment, with renal excretion of potassium. According to these authors, potassium leaves cells in significant quantities only if it can be excreted, because they found that when some profound interference with the renal mechanism occurred, potassium does not leave the cells. Apparently the body has devised a scheme to protect the myocardium, which is extremely sensitive to changes in potassium in the perfusion fluid, from elevated serum levels.

Elkinton and Winkler[16] also noted in their experiments, that the release of potassium from the intact cell and its renal excretion was a general and reversible physiological response of the organism to severe water depletion, and that renal activity was essential to effect this intracellular loss of potassium. They

also noted a great resistance to change of the concentration of serum potassium, and that in subjects with intact kidneys, large amounts of intracellular potassium can be removed without any consistant or large change in the extracellular fluid concentration.

The liver also functions in potassium metabolism. By taking up and releasing potassium, it aids in maintaining the serum levels within normal limits. Danowski and Elkinton[17] found that deposition of glycogen in the liver is associated with potassium retention in the liver. Liver potassium also increases after muscle contractions, and after administration of potassium, whether orally or parenterally.

In apparent refutation of this observation, Elkinton, Tarail and Peters[18] studied 26 patients with kidney damage. They found that severe oliguria ar anuria appeared to be a prerequisite to elevation of the serum levels of potassium. The factors which determine the extracellular concentration are the volume of the extracellular fluid and the amount of extracellular potassium which results from exchanges with the cells on the one hand and the external environment on the other. Expansion of the extracellular fluid volume (without adding potassium) will result in transfer of some potassium from the cells.

Farber[19] et al, studied the potassium level in some disease states, and found that the plasma level does not change from normal in diabetes (without acidosis) and in congestive heart failure. They found an increase in plasma potassium in nephritis and a slight lowering of the level in hepatic failure. Alkalosis produced the most severe hypokaliemia.

Danowksi and Elkinton[20] observed that potassium leaves muscle cells during contraction; that it leaves cells following operations, following dehydration and starvation, with diarrhia and vomiting, as a part of Cushing syndrome, and with Doca therapy. It was further noted that at times the movements of cell potassium correlated very closely with nitrogen metabolism, and at other times the movements were in excess of such processes.

J.D. Nachmansohn,[20] in a paper presented to the 18th international physiology congress suggested that extensive transfers of potassium and sodium across the membrane of nerve fibers occur with electrical activity of the tissue. During excitation, the phase of inward current is accompanied by entry of sodium, and the more prolonged phase of outward current by a movement of potassium out of the fiber. When this occurs, there

there is an active expenditure of energy. These sudden changes of membrane permeability are initiated by the local action of acetylcholine on the protein of the membrane according to Dr. Nachmansohn.

Schilling, McCoord and Clausen[21] divided potassium losses and deficits into three general groups:

1. Chronic deficit associated with starvation.
2. Differential intracellular potassium deficits in which loss of water and electrolytes exceeds nitrogen loss, as occurs in intestinal obstruction.
3. Acute extracellular deficits as may occur in acute diarrhias, alkalosis and diabetic coma, in which sudden shifts of the potassium or sodium ions may occur and lead to dangerously low levels.

Danowski[22] et al, studied potassium metabolism in a series of children with such disorders as pyloric stenosis, diabetic acidosis and renal failure. They felt that dehydration was present in all the cases studied due to inadequate intake, and to vomiting. They found that when there was negative nitrogen balance, due to inadequate intake of carbohydrate and protein, that potassium was lost by the cells. In the patient with

diabetic acidosis, there was an additional potassium loss due to the potassium released with deglycogenation of the liver.

Gardner[23] found that in rats on potassium deficient diets, muscle electrolytes showed diminished potassium and increased sodium, calcium and magnesium concentrations. Liver electrolyte analysis showed diminished potassium values in only a small percentage of the animals, but liver sodium was increased in all. Their results indicated that magnesium and potassium compete for place in intracellular fluid of rat skeletal muscle.

Darrow,[24] who has done extensive research in potassium metabolism, found that increased excretion of potassium occurred when 1) DOCA, 2) Cortical hormone, 3) Estrogens, and 4) Testosterone were administered. These drugs all have the same steroid nucleus, and are all closely related if not actually the substance secreted by the adrenal cortex. The effect which the Adreno-cortico-like drugs have upon the potassium level can be amply appreciated by noting the effect which removal of the adrenals has upon it. As reported in Best and Taylor,[25] removal of the adrenals causes, among other things, a rise in potassium and calcium levels, and a fall in sodium level. The rise in potassium

concentration of serum is due to reduced excretion by the kidney, as well as to leakage from the cells into the extracellular fluid. This leakage is due to the bodies attempt to maintain isotonicity between intra- and extra-cellular fluids in the face of marked extra-cellular electrolyte changes, caused by the changed water balance.

Normal physiological changes in intracellular potassium levels are also demonstrable. Pulver and Verzar[26] showed that the addition of sugar to fasting yeast cells in a dilute potassium medium produced an uptake of both potassium and carbohydrate by the cells. Nerve fibers are especially rich in potassium. When a nerve is stimulated, or deprived of oxygen, potassium diffuses rapidly into the surrounding fluid.

Muscle fibers, in the process of contraction, lose potassium to the extracellular fluids. This was graphically shown by Farber[19] et al, who compared arterial plasma and venous plasma levels in individuals under a variety of conditions. They found that the plasma level of potassium in a vein which drained a working muscle showed an average increase from 4.3 to 5.0 mEq/l. Even slight exercise produced a marked increase. There was no corresponding increase in plasma levels of

venous return from other non-working muscles at the same time. Resting venous plasma levels were consistently close to arterial plasma levels, averaging about 0.1 mEq/l higher. This would suggest the possibility of an added margin of error in determining serum potassium levels due to the method of drawing blood for the determination. Patients who were adminished to "make a fist" in order to increase the prominence of the antecubital veins might have an increased serum potassium because of the activity.

IV

The differences between intracellular and extracellular levels of potassium have been explained on the basis of the semi-permeable membrane and the Donnan equilibrium. This implies that the cations inside the cell membrane, which are mostly potassium, cannot get out, and the cations outside the cell cannot get in. Osmotic pressures are balanced because the product of the concentrations of the intracellular cations equals the product of the concentrations of the extracellular cations. This would imply that the potassium that is within the cell membrane has always been there, but such is not the case, because the cell is constantly undergoing changes in the process of metabolism.

Krebs, Eggleston and Terner;[27] in studying the in-vitro turnover rate of potassium found that there is a constant interchanging of potassium. They came to the conclusion that the high concentration gradient of potassium cannot be due to an inanimate semi-permeable barrier alone, but that there are two processes in operation: 1) Leakage from the cell, which tends to even out the gradient, and 2) Active transport into the cells, which would involve an energy-fed process. They concluded that normally the two processes balanced,

thus providing an equilibrium between intra- and extra-cellular levels.

Fenn[28] found that there is a great deal of variation in the velocities at which different tissues exchanged potassium. In general, visceral organs exchange potassium much faster than skin, muscle or erythrocyte.

Raker and Taylor[29], using "tagged" potassium, found that the exchange rate in human cells is unaltered by increasing the plasma potassium concentration, but that there was a correlation between the exchange rate and the intracellular amount of the element.

Wener, Hoff, Scott and Winter[30] suggested that the discrepency between intra- and extra-cellular levels of potassium might be maintained as a "balance" which is regulated by hormonal factors, similar to the regulation of serum and bone calcium by the parathormone. They studied the effect of ergotamine sympatholysis on the distribution of injested potassium in thirteen dogs, but the results were inconclusive, and more work will be necessary before this theory can be presented.

Miller[31] studied a group of rats under various conditions, to determine the causes of changes in muscle potassium. Conditions produced included: 1) trauma by scalding, 2) fasting, 3) adrenalin injections, and

4) intraperitoneal glucose injections. Computations were made on the basis of 100 grams of fat-free solid. They found an increase in the potassium, phospherous, and nitrogen levels in the muscle cells of the rats. Glycogen levels had not changed, and shifts of the three elements from other tissues and extracellular fluid had not occurred, and there was no urinary retention of the elements. This suggested that some solid substance was leaving the cell, or being oxidized. Although they ruled out glycogen as this solid, they suggested that some other carbohydrate may be involved.

Studies made on erythrocytes by Harris[32] presented evidence indicating that potassium and sodium distribution is greatly influenced by the metabolism of the erythrocytes, and that the factors responsible for the original accumulation of potassium in the cells is also responsible for its maintenance. This maintenance is referred to as a "dynamic equilibrium", in which there is constant potassium exchange across the cell membrane. When metabolic activity is lowered, both potassium and sodium move with their concentration gradient, and restoration of metabolic activity will partially reverse the migration, even without the addition of other substances. In summing up his experiments, he noted that:

1) During storage of erythrocytes at 2 to 5 degrees Centigrade, potassium leaves the cells, and sodium enters the cells. Normal calcium concentration and the presence of preservatives did not alter this phenomenon. 2) When such stored blood was warmed to 25° and 37°, there was a reversal of this flow, and some potassium re-entered the cell, against a concentration gradient. 3) Addition of glucose augmented this return of potassium to the cells. 4) Sodium and potassium diffusion were not always reciprocal in nature. In some instances both potassium and sodium diffused into the cell. When glucose was added, however, sodium diffused out in about the same quantity as potassium diffused in. This would indicate that some metabolite is necessary for maintenance of the concentration gradient.

Terner, Eggleston and Krebs[33] made a detailed study of tissue potassium. They found that brain tissue was most satisfactory, because other tissues disintegrated under the procedures involved. Ox retinas were also very satisfactory. They reported that slices of brain tissue and pieces of retina maintain their normal potassium content when kept in a saline medium containing oxygen, glucose and l-glutamate. If one

substrate is absent, potassium leaves the tissue. When the missing substrate is added, the potassium is restored. In examining the procedure, they found that when ox retina stood in saline for one and onehalf hours at zero Centigrade, it lost one half of its potassium. When the glucose, l-glutamate and Oxygen were added, the potassium was restored to its original level. They also found that lactate or pyruvate could be used in place of glucose, and l-aspartate could be used in place of l-glutamate, but that it would be converted to glutamate in the system. They found that glutamate and potassium were taken up in equivalent amounts, and suggested that l-glutamate serves a function in potassium transport, and that the glucose is used for energy only. In studying in vitro losses, they found them to be most marked immediately following section of the tissue, and postulated that in vivo, losses may readily occur as a result of injury, surgical operations, asphyxia or shock.

Danowski and Elkinton[17] also reported that breakdowns in anionic complexes, increasing their electrostatic force, can cause increased intracellular potassium. This change is associated with an increase in glucose-l-phosphate, and a decrease in glucose-6-phos-

phate and fructose-6-phosphate. This is further evidence of the dependence of potassium exchanges on carbohydrate metabolism, especially in the phosphoryllation cycle. In conjunction with this finding, Gardner[23] et al, found that potassium depletion retards glycogenesis, and that potassium is a factor in the reaction of actomyosin with adenosine-triphosphate.

Scott and Jacobsen[34] also found that carbohydrate metabolism was associated with the accumulation and retention of potassium. They added glycolytic inhibitors in the form of iodoacetic acid and sodium fluoride to the cellular perfusion fluid, and demonstrated an increased loss of potassium, but the proportion was not constant. The increased loss was accompanied by an increased cellular permeability to sodium. They found that if pyruvate was given before the sodium fluoride, it reduced the loss of potassium from the cell.

Farber[10] et al, found that plasma potassium was reduced by the administration of glucose in normal individuals, but not in diabetics. The administration of insulin reduced the plasma potassium level in all subjects.

Ferrebee[11] and co-workers administered desoxycorticosterone acetate to laboratory animals in an

effort to determine its effect on muscle potassium. He found that protracted treatment produced muscle paralysis and a pseudo-diabetes insipitus. The muscle paralysis was accompanied by a decrease in potassium and a corresponding increase in muscle sodium. The chloride, water, and nitrogen balances remained essentially the same, so that there was a 1:1 ratio of exchange of sodium for potassium in the muscle cell. The authors felt, from the experiments, that it seems more accurate to speak of potassium being replaced by sodium, rather than the high sodium serum concentration "displacing" the potassium. Sodium only goes in when potassium comes out, and does not cause the potassium to come out.

Bourdillon[35] administered large single oral doses of NH_4Cl, KCl and NaCl, and found that the chloride stays in the extracellular fluid, and the potassium distributes to all fluids. He concluded that when potassium enters the cell, it must be accompanied by some anion, and that bicarbonate is probably the only one that can permeate the wall freely.

Elkinton[36] found that there were extensive intracellular changes in electrolytes during metabolic alkalosis. Potassium deficits were noted in all cases.

They found that bicarbonate levels fell to normal concurrently with the restoration of intracellular potassium levels.

Marks[37] studied a patient with pyloric obstruction and extensive vomiting. He found that with the development of an alkalosis, potassium migrated out of the cells in excess of the potassium-nitrogen ratio of 2.45 mEq's potassium per gram of nitrogen, with a concurrent drop in the serum level to 2.75 mEq-per-liter. With correction of the alkalosis, there was increased retention of potassium and a shift back to the potassium-nitrogen ratio of 2.4 mEq's potassium per gram of Nitrogen.

V

Potassium excretion has been generally considered to be primarily a process of glomerular filtration, with small quantities being lost via the intestinal route. Undoubtedly a large percentage of the plasma potassium is filtered through the glomerulus, since most electrolytes are, and then selectively resorbed through the proximal tubule. However, Berliner, Kennedy and Hilton[38] on the basis of their findings, concluded that potassium excretion is due to both glomerular filtration and to tubular secretion. They found that in man, up to 130 micro-equivalents per minute of potassium are secreted by the tubules. They computed this secretion by determining inulin clearances simultaneously with the potassium determinations. Since inulin is not secreted or resorbed by the tubules, the ratio of serum inulin to urinary inulin is an indication of the rate of glomerular filtration. Any difference between this ratio and the ratio of serum potassium to urinary potassium made at the same time, would indicate a secretive or absorptive process, whichever way the ratio deviated. They found that this secretory phenomenon can be more easily demonstrated when there is an impaired rate of filtration. Excesses of excreted over filtered potassium

are more marked by 1) restriction of sodium intake, and 2) administration of salts whose anions are rapidly excreted, carrying with them an equivalent amount of cation. In dogs, it was necessary to give potassium salts for a short time prior to testing in order to get a demonstrable increase of excreted over filtered potassium. This suggests a tolerance which the animal develops to potassium administration. In rats, numerous sublethal doses increased the lethal dose requirement. The development of a potassium tolerance is not associated with continuous high levels of potassium excretion, nor is it due to heightened adrenal activity because the administration of DOCA did not increase the tubular secretion in dogs.

They also found that the extent to which secretion exceeds filtration is affected to a considerable extent by the anion with which the potassium is administered. Since cation excretion is directly related to anion excretion, if the chloride ion is used, excretion will vary, because chloride can be resorbed. If, on the other hand, thiosulphate is used, it not only is not resorbed, but is also able to breakdown into two inns of sulphate, and would be able to excrete two times as many cations as had been administered.

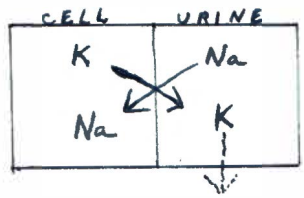
Mudge[39] also found that there is active secretion of potassium by the tubules, because the amount of potassium recovered in the urine was greater than the amount filtered. In further study of the renal secretion of potassium in dogs[40] it was found that potassium infusion is the most potent stimulus for initiating renal secretion of the drug; that kaliuria is increased by cellular hypertonicity; and that changes in the rate of potassium excretion occurs independently of the plasma concentration of potassium. Leaf and Camara[41] studied four patients with chronic renal insufficiency and found that they all actively secreted potassium from the renal tubules, in some instances in such quantities as to contribute to a deficiency of body potassium. Marks[37] also concluded that there was a minimal renal rate of excretion of potassium. He was unable to find any evidence of reabsorption of potassium against a concentration gradient in the tubules.

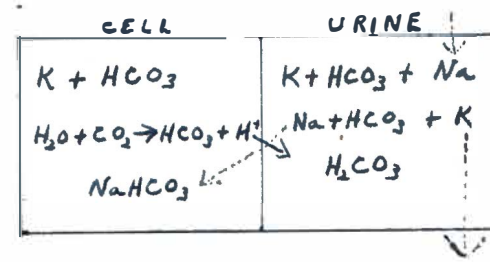
Tarail and Elkinton[42] in studying negative potassium balance, suggested that cellular metabolism played an important role in determining total exchanges of potassium, but emphasized the role of renal excretion. They noted that renal excretion continued in the presence of diminished intake, and that increased intake caused

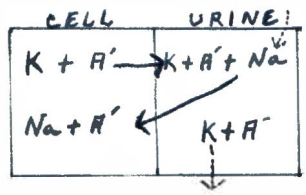
increased excretion. They further found no positive correlation between intake, serum concentration, and excretion, during periods of cellular depletion. Urine concentration was never found to be lower than serum concentration, and they could find no evidence that potassium could be reabsorbed against a concentration gradient. Their conclusion was that the normal kidney has a limited minimal rate of excretion of potassium (below which it cannot go), which is an important factor in producing a potassium deficit.

Cationic exchange has been found to play a major role in the reabsorption of the cations essential to maintenance of homeostasis. It has been proposed that acidification of urine is due to an exchange of hydrogen for sodium ions, the hydrogen forming the organic acids that lower the pH of the urine. Pitts and Alexander[43] state that there are two mechanisms for the production of an acid urine, the first being the exchange of sodium for hydrogen and the return of $NaHCO_3$, NaCl and NaH_2PO_4 to the blood, and the second being the formation of ammonia by the renal tubular cells. In addition to this exchange of sodium for hydrogen, there is also an exchange of potassium for sodium, according to Berliner, Kennedy and Hilton.[38] In an experiment

performed on a dog, they gave a primary injection of creatinine and sodium ferrocyanide, followed by an injection of creatinine and potassium ferrocyanide. After a wait of 90 minutes for excretion to become stabilized, ten clearance periods were obtained. The excretion of Na, K, NH_4, Cl, HCO_3, ferrocyanide, inorganic sulfate, and phosphate was measured, and the plasma levels of creatinine and potassium were determined. The minimum amount of excreted potassium exceeded by 100 to 300 micro-equivalents per minute the sum of all anions excreted except for ferrocyanide. Since ferrocyanide is not secreted or reabsorbed by the tubules, it indicates that secreted potassium must have been exchanged with a filtered cation so that for each mole of potassium added to the tubular urine, a mole of some other cation is removed. This could be accomplished by three possible mechanisms:







Increasing the potassium excretion is accompanied by a tendency for the urine to become alkaline.

Berliner, Kennedy and Orloff[44] noted that the administration of potassium salts leads to the production of an alkaline urine, and acidosis of body fluids, while depletion of potassium was found to be associated with the production of an acid urine, even with an accompanying increase in plasma pH and bicarbonate. They felt that this phenomenon was due to a competition between the potassium and hydrogen ion at some common point in their secretory pathways. Using a drug (No. 6063) which inhibits carbonic anhydrase, and thus prevents the functioning of the system by which hydrogen ions are made available for exchange, they found that they could obtain an increased excretion of potassium and an alkaline urine, even when there was a definite acidosis.

Berliner[38] et al, also showed the relationship between potassium excretion and an alkaline urine. They administered creatinine and sodium ferrocyanide to a dog at a steady rate, and when a steady state was reached, potassium ferrocyanide was gradually substituted for the sodium salt, over a prolonged period, with no change in the administration rate. As the

potassium excretion increased, there was a marked rise in the pH, and in Cl and HCO_3 excretion. This could be due to a change from the total reabsorption of $NaHCO_3$ to the cationic exchange of Na for K, and the subsequent excretion of $KHCO_3$. Since potassium has been shown to be secreted by the proximal tubules, this could easily occur. Another possibility is that, with the potassium load, there is a decreased reabsorption of potassium, with the associated anions. If there were not a proportional increase in sodium reabsorption, the result would be an increase in excretion of bicarbonate and chloride.

Renal tubular cells, like other cells in the body, contain potassium as the main cation. Consequently, even though the passage of potassium from the tubular epithelium into the proximal tubule could be explained on a simple gradient theory, the replenishing of the intracellular potassium from the interstitial fluids would occur against a concentration gradient, thus showing that the entire process is one of active secretion.

VI

In studying the observations and proposals made by the various workers in the field of potassium physiology, one is struck by the amount of research still to be done before the final chapter can be written. Even on the matter of potassium levels in the intra- and extra-cellular fluids, one finds disagreement among the results reported. Very likely many of these discrepancies were due to differences in quantitative methods of determination, to differences in tissues used (erythrocyte and muscle, for example), and perhaps in a small part, to differences between species of animal studied, such as the rat, rabbit, dog and man. Standardized procedures in flame photometry will undoubtedly help to clarify the human limits of normal in the various body fluid compartments.

Conditions which cause losses of intracellular potassium are numerous and varied, and include: Diabetic acidosis; diarrhia (especially that noted in infants); starvation; dehydration; post-operative conditions; normal physiological processes, as in muscle contraction; 17-keto-steroid therapy; chronic disease conditions, including Cushing's syndrome; and anoxia. These conditions can eventually have a profound effect on the intracellular potassium level, but those that mediate their

effect through extracellular levels are much more gradual in their production of clinical symptoms.

In studying the causes of exchanges and changes at the cell membrane, several interesting observations have been made. There is general agreement that some energy-fed process is responsible for maintaining the intracellular level, and that the level is due to a balance between potassium leakage and this energy fed process. If this process diminishes, intake is less than leakage, and a net loss occurs. If the extracellular level is lowered, the gradient is increased and leakage is greater than intake, and again the result is a net loss. Usually this second mechanism is slower in evidencing itself than the one first mentioned. An important mechanism in making this a slow change is the kidney, which helps to maintain the serum level. The energy-fed process mentioned above seems to be closely related to carbohydrate metabolism, because experiments showed that glucose, l-glutamate, and l-aspartate could be used to effect in vitro increases in intracellular potassium. Other authors have associated it specifically with phosphorylation processes, which are a part of carbohydrate metabolism.

The kidney, which helps to control leakage from

the intracellular compartments by maintaining a relatively constant serum level through balancing intake and output, has been studied extensively in this capacity. It has been determined that there is a minimal rate of excretion of potassium, below which the kidney cannot go. If potassium intake is reduced below this critical level, the serum levels can be expected to drop somewhat. Radical changes are prevented by replacement from the intracellular supply.

Recent evidence indicates that the renal control of potassium is also a factor in acid-base balance, there being an increased acidosis with increased kaliuria. This is accomplished because of an exchange of potassium for hydrogen in the tubule, with an increased reabsorption of hydrogen ions. Potassium is also exchanged for sodium in the tubules, thus providing another control of the sodium level in the serum.

The exchange of potassium for hydrogen is made possible by carbonic anhydrase, which makes hydrogen available for the exchange. Suppression of this enzyme retains hydrogen in the system, and causes marked increases in potassium excretion, as well as acidosis.

VII

A short review of the literature has been presented, in an attempt to show our present knowledge of the role of potassium in cell physiology, as evidenced by the causative factors in intracellular changes. Material has been presented showing that potassium is intimately related to the processes of carbohydrate metabolism, especially those involving phosphorylation. Renal contral of the serum levels has been shown to include active secretion of potassium by the kidney tubules, and cationic exchanges of potassium for sodium and hydrogen in the kidney tubules, thus affecting not only the potassium levels, but the pH of the body as well.

The present status of our knowledge of potassium metabolism is well summarized by Overman[45] who said, "We have yet to solve the majority of problems regarding the intimate actions of many of these ions--the role of ion antagonism, of ion-enzyme catalysis, of ion binding of enzyme and substrate. For example, potassium is important for synthesis of phospho-pyruvate from phospherus and pyruvate."

In a similar vein, Sheppard[46] wrote, "It is left as a task for the future to establish how a cation interacts at the cell interface, how the energy is expended

in the movement of the ion into the cell, and how the ion later leaves the cell in exchange for another."

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