ARTICLES

Factors Affecting the Excretion of Potassium *

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Since, under normal conditions, the kidneys are the only route of significant potassium output, it is apparent that the kidneys must excrete an amount of potassium approximately equal to the intake. The intake may be considered to be of the order of 100 mEq/day, although depending upon the type of diet consumed the actual amount of potassium taken in and excreted in the urine may vary over a wide range. One of the striking aspects of the normal mechanism for potassium excretion is its change over a very wide range — from a very few milliequivalents to several hundreds each day — with only minimal changes in the potassium content of the body. These wide extremes indicate an unusual flexibility in excretion rate. This does not mean that the rate of potassium output is always closely adjusted to intake under all conditions. Conditions of stress and disease may modify potassium excretion in a manner unrelated to potassium intake and upset potassium balance—most often in a negative direction.

The central point of this discussion will be concerned with the mechanism in the kidney by which potassium excretion is carried out and those factors which, taken together, determine the rate of potassium excretion.

When we consider that an average normal individual forms some 175 liters of glomerular filtrate each day, each liter containing a little over 4 mEq of potassium, we may calculate that a total of some 700 mEq of potassium enters the glomerular filtrate each day. Since, on the average, only about 15% of this amount appears in the urine, it is obvious that the renal tubules must have a mechanism for reabsorbing potassium and returning it to the blood and that most of the filtered potassium must be reabsorbed. Because of these quantitative relationships and because it had generally been assumed that if the renal tubules reabsorbed a particular substance they did not secrete it, and vice versa, several scattered observations suggesting that potassium might also be secreted by the tubules from the blood directly into the urine [1, 2] were largely disregarded. However, about 10 years ago several systematic investigations showed that a tubule mechanism for addition of potassium to the urine must be present, since

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it could be shown that amounts of potassium far in excess of that filtered could be excreted in the urine [3, 4].

With the demonstration of the existence of a tubule mechanism for potassium secretion, the earlier filtration-reabsorption view of potassium excretion had become inadequate and the potassium excretion mechanism became the most complicated which had been encountered, since it must be considered, at least potentially, as the resultant of three separate processes. However, as I shall show, the actual mechanism which need be considered is considerably simpler than would appear at first sight because it is possible to eliminate two of these three processes from consideration.

When the potassium secretion mechanism was first demonstrated there was a general tendency to consider it a reserve capacity to be turned on only when the complete cessation of reabsorption was insufficient to maintain an adequate excretion rate. However, Mudge and Gilman concluded that secretion contributed to the potassium appearing in the urine under normal conditions even though the total rate of potassium excretion is well below the rate of potassium filtration [5]. This conclusion was based on the observation that mercurial diuretics, which inhibit potassium transport, frequently depress potassium excretion even though potassium excretion is well below the rate at which potassium is filtered before the mercurial diuretic is administered.

Since that time evidence has accumulated that a major part of the potassium excreted in the urine is normally derived from the secretory process. Several years ago we proposed that it was convenient to consider all of the filtered potassium to be reabsorbed and all of the excreted potassium to be derived from secretion by the tubules [6]. This was done for two reasons: first, this view was compatible with all we knew about potassium excretion and second, and most important, it greatly simplified consideration of the mechanism by eliminating reabsorption and, for most purposes, glomerular filtration from consideration.

We believe that recent experiments strongly support this view which was originally adopted largely as a matter of convenience. I should like to describe briefly the experiments on which these conclusions are based. They were done by Drs. Norman Levinsky, Douglas Davidson and me [7] in dogs utilizing a preparation which makes it possible to use one kidney as a control for the other in the trained unanesthetized animal. The bladder is divided into two pouches, each containing one ureteral orifice and each pouch is connected permanently to the outside

through a nylon funnel from which urine can be collected. A small inflatable cuff of silicone rubber contained within a tantalum clip is placed around the right renal artery and connected to the outside through a fine polyethylene tube. The cuff can be inflated with air and made to constrict the renal artery, reducing the rate of glomerular filtration and, to a lesser extent, the renal blood flow. The undisturbed left kidney serves as a control[8].

The plan of the experiments was based on the assumptions, suggested by earlier work and supported by the experiments themselves,

HIGH RATE OF SODIUM EXCRETION

INFUSION .85% NaCl INULIN SALYRGAN 12 cc / MIN.

GFR cc / Min.		Na^+ EXCRETION µEg / Min.		K^+ EXCRETION µEg / Min.	
R	L	R	L	R	L
59	58	954	929	15	18
63	57	1200	1081	17	18
57	56	1470	1370	19	22
CUFF INFLATED RIGHT RENAL ARTERY					
40	64	816	1420	52	55
43	63	911	1520	56	59
52	64	1270	1500	63	61
46	60	1019	1340	58	59

FIGURE 1. See text.

that: 1) the potassium secretion process is located distal to the reabsorptive process, and 2) potassium secretion consists of an exchange of potassium ions from the tubule cells for sodium ions from the fluid in the tubule lumen. If this is the case and if the filtered potassium is completely reabsorbed, then, provided adequate amounts of sodium reach the exchange mechanism, it might be possible to reduce the filtered potassium considerably without affecting the rate of potassium excretion. To be certain that adequate amounts of sodium were available to the exchange mechanism, diuretics of different types were

LOW RATE OF SODIUM EXCRETION

INFUSION GLUCOSE MANNITOL INULIN 5 cc / Min.

GFR cc / Min.		Na^+ EXCRETION μEg / Min.		K^+ EXCRETION μEg / Min.	
R	L	R	L	R	L
34	35	38	39	35	39
33	35	37	38	42	45
33	34	37	38	43	44
CUFF INFLATED RIGHT RENAL ARTERY					
22	35	18	176	53	79
14	38	1	192	14	92
28	38	8	99	53	76
21	35	5	54	32	67

FIGURE 2. See text.

administered. Similar results were obtained with several types of diuretics — mercurials, diamox, sodium sulfate, and simply the rapid infusion of sodium chloride.

A typical experiment in which a mercurial diuretic was combined with a rapid infusion of sodium chloride is shown in Figure 1. The first three periods are controls and indicate that glomerular filtration rate, sodium excretion and potassium excretion are virtually identical in the two kidneys. When the cuff is inflated glomerular filtration is reduced up to 35 or 40% below the control kidney and sodium excretion is correspondingly, or somewhat more markedly decreased. Potassium excretion, however, remains equal in the two kidneys. It is important that, although reduced, sodium excretion in the experimental kidney remains considerable.

An experiment in which no attempt was made to maintain sodium excretion is shown in Figure 2. Here again in the control periods the function of the two kidneys is virtually identical. However, now when glomerular filtration is reduced sodium virtually disappears from the urine and there is a decrease in potassium excretion. This decrease in

potassium excretion we interpret as due, not to a decrease in the amount of potassium filtered, but to a decrease in the amount of sodium available, at the proper place in the distal tubule, for exchange with potassium.

The only reasonable interpretation for these experiments is: 1) the filtered potassium makes no appreciable contribution to the potassium in the urine; 2) the reabsorption occurs higher up in the tubule than the secretion and 3) the maintenance of potassium secretion is dependent upon the availability of adequate amounts of sodium.

One of the interesting and striking characteristics of the potassium secretion mechanism is its relationship to the hydrogen ion secretion mechanism described by Dr. Pitts [9]. Circumstances which depress the capacity to secrete hydrogen ion increase the secretion of potassium, those which enhance the secretion of hydrogen ion depress the secretion of potassium. Conversely, conditions which enhance potassium secretion depress hydrogen ion secretion and those associated with low potassium yield high rates of hydrogen ion secretion. These facts led us to propose that potassium and hydrogen ion are secreted, at least in part, by the same mechanism and are in a form of competiton in the process [10]. I would like to show two experiments which, I believe, demonstrate rather nicely some of the aspects of potassium secretion and its relationship to hydrogen ion. Although they do not show any new phenomena they demonstrate established phenomena a little more directly and elegantly than before. These experiments were done by Drs. Orloff and Davidson [11] in our laboratory and utilize the chicken as an experimental animal according to a techique devised by Sperber in Upsala, Sweden. The chicken possesses a renal portal system as do all the vertebrates except the mammals. The renal portal vein is to the kidney what the hepatic portal vein is to the liver. Blood draining the somatic portions of the rear half of the body enters the renal portal vein which enters the kidney, breaks up into a peritubular capillary circulation, joining the postglomerular blood derived from the renal artery, and is then collected into the renal vein which empties into the inferior vena cava. For this reason material infused into a vein of the leg is delivered first to the peritubular capillaries of the kidney on the same side without access to the glomeruli which it reaches only from the general circulation and then equally on the two sides. Thus the glomerular filtrate is identical on the two sides, but the peritubular environment can be made to differ. The effect of such differences can then be evaluated because each ureter empties separately and directly into the cloaca where

the ureteral orifice is relatively easily accessible for collection of urine from each kidney.

The effect of an infusion of potassium salts into a vein of one leg in a chicken is shown in Figure 3. During the control periods the excretion of potassium is quite low and equal on the two sides. When the infusion is started, the excretion of potassium on the side of the infusion increases rapidly to high levels and then remains fairly constant although the estimated concentration in the peritubular blood continues to rise throughout the experiment. This suggests that the mechanism for secreting potassium has reached some sort of maximum capacity and is saturated. On the control side the rate of potassium excretion increases gradually as potassium escaping excretion by the infused kidney gradually raises the amount of potassium available in the rest of the animal.

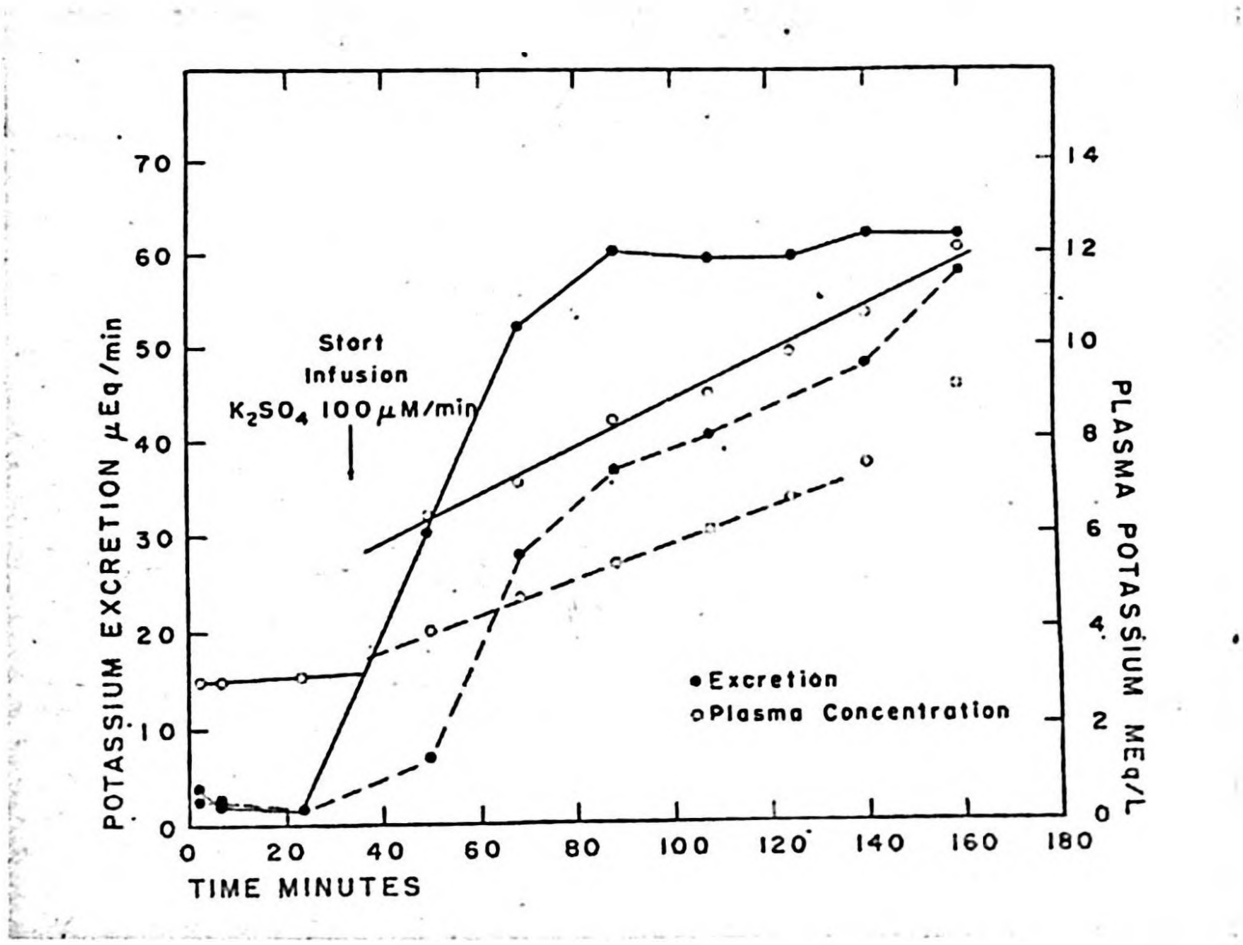

FIGURE 3. Effect of infusion of potassium sulfate in a leg vein of the chicken on the excretion and plasma concentration of potassium. Continuous lines: kidney on same side as infusion. Broken lines: contralateral kidney. The concentation of potassium in the plasma perfusing the experimental kidney is estimated by adding to the concentration in peripheral blood the amount infused divided by the estimated plasma flow to the experimental kidney. The latter is the unilateral clearance of p-aminohippurate simultaneously infused in a wing vein.

Figure 4, which illustrates dramatically the relationship between acid and potassium excretion, shows an experiment beginning more or less where the last one ended. Here the chicken had been receiving an infusion of K_2SO_4 in one leg for almost an hour before the indicated observations were made. As a consequence, the rate of potassium excretion is markedly increased, particularly on the side of the infusion. Note that the urine is also less acid on the side of the infusion —an indication of inhibition of hydrogen ion secretion by the high potassium concentration. At this point, in addition to the continued infusion of potassium, acetic acid at the rate of 100 microequivalents per minute is infused in the same vein. When acid is added to the bicarbonate containing blood, the acetic acid reacts with bicarbonate to yield sodium acetate and carbonic acid. The carbonic acid is dehydrated to water and carbon dioxide but, being contained within a vein, the carbon dioxide can not escape until the first capillary circulation is reached. These capillaries are the peritubular capillaries of the kidney on the infused side and here the escape of carbon dioxide from the

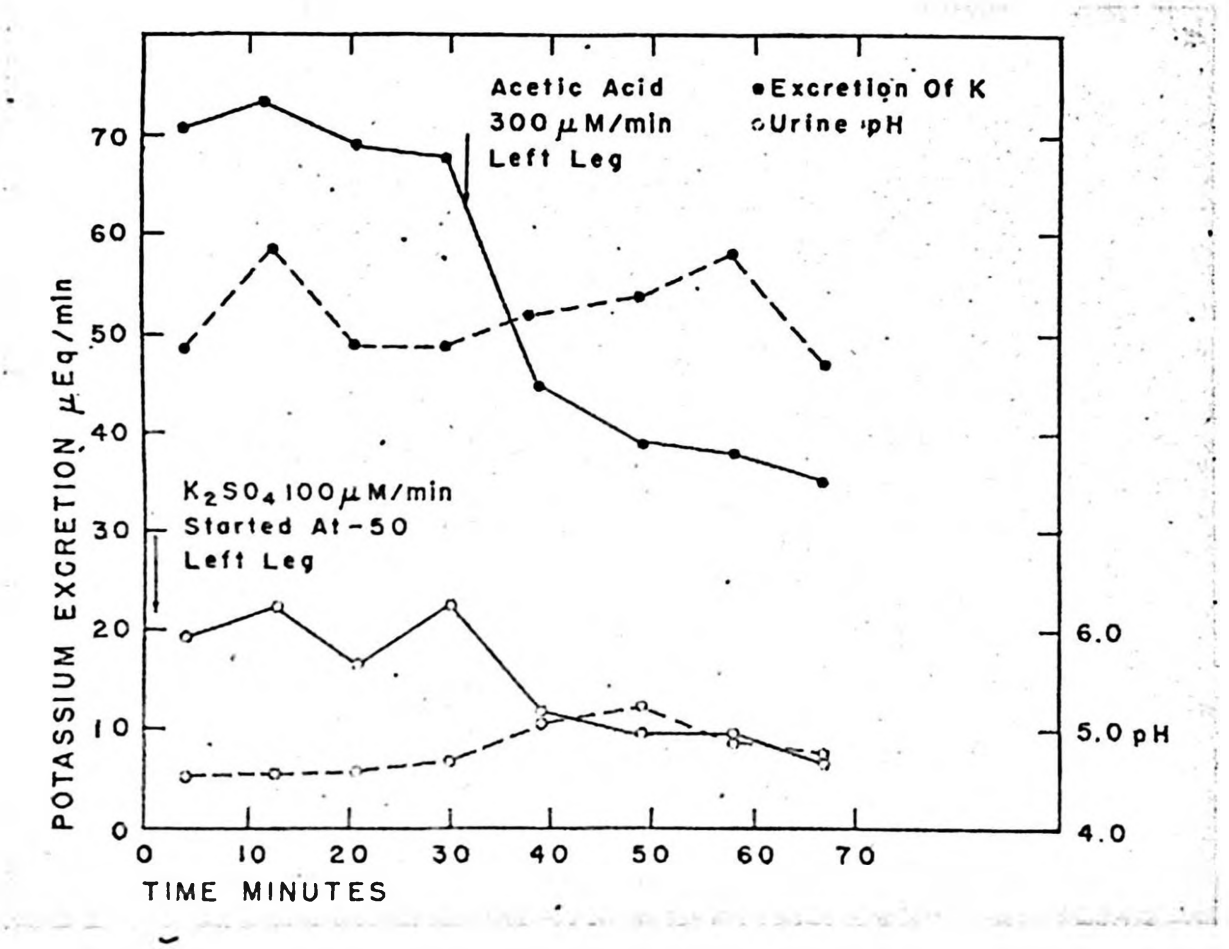

FIGURE 4. Effect of infusion of acetic acid in a leg vein of the chicken on the excretion of potassium and urine pH. Solid lines: experimental (left) kidney. Broken lines : control (right) kidney, Infusion of potassium sulfate, 100 μM per min., in left leg started 50 minutes before time O.

blood raises the carbon dioxide tension of the tubule cells, lowering their pH and yielding what might be considered to be unilateral renal respiratory acidosis. Note that despite the persistence of a higher potassium concentration the rate of potassium excretion immediately drops well below that of the control kidney and the urine pH falls to the level of the control which is about as acid a urine as can be produced by the chicken under these circumstances. This is, I believe, a rather nice demonstration of the inverse relation between potassium and hydrogen ion secretion.

I should like to mention two sets of conditions in which potassium and hydrogen ion secretion may change in the same rather than opposite directions. These are: 1) when there are changes in the amount of adrenal steroids available and 2) when there are changes in the amount of sodium available to the common mechanism for exchange. The effect of adrenal steroids is presumably an increase in the total capacity of the mechanism which the two types of ion share so that there is simultaneously more room for both. However, there is no obligatory effect of the salt-active adrenal steroids on potassium excretion since no deficit of potassium is produced no matter how large a dose of steroid is administered if the sodium available for exchange is kept low by rigid restriction of the salt intake [12].

The other factor which may change the secretion of both acid and potassium in the same direction is a change in the amount of sodium delivered to the exchange mechanism. If these two ions can be secreted only in exchange for sodium, as appears to be the case, then it does not matter how great the capacity for secreting each if the amount of sodium delivered to the mechanism is insufficient to utilize this capacity. Thus a change in sodium excretion from low to high levels will usually be accompained by an increase in potassium excretion.

Considering now those factors which determine the rate of potassium excretion, we have already mentioned several including 1) the rate of sodium excretion, 2) the availability of adrenal steroids with aldosterone-like activity, and 3) the state of acid-base balance. The rate of glomerular filtration we have mentioned as relatively unimportant except to the extent that: 1) changes in glomerular filtration may change the amount of sodium available to the exchange mechanism, and 2) that changes in glomerular filtration may, under some conditions, represent complete loss of the contribution of some of the nephrons.

The rate of potassium excretion is also poorly related to the plasma potassium concentration except to the extent that the plasma potas-

sium concentration reflects the potassium concentration in cells. This, of course, is appropriate since potassium is mainly an intracellular ion and its rate of excretion might well be expected to be related to its concentration inside rather than outside of cells.

The final figure illustrates diagramatically some of the circumstances affecting potassium excretion and may help in visualizing how various changes come about. This is, of course, strictly diagrammatic and not to be interpreted too literally. The figure represents one of the distal tubule cells involved in the ion exchange process. It is represented

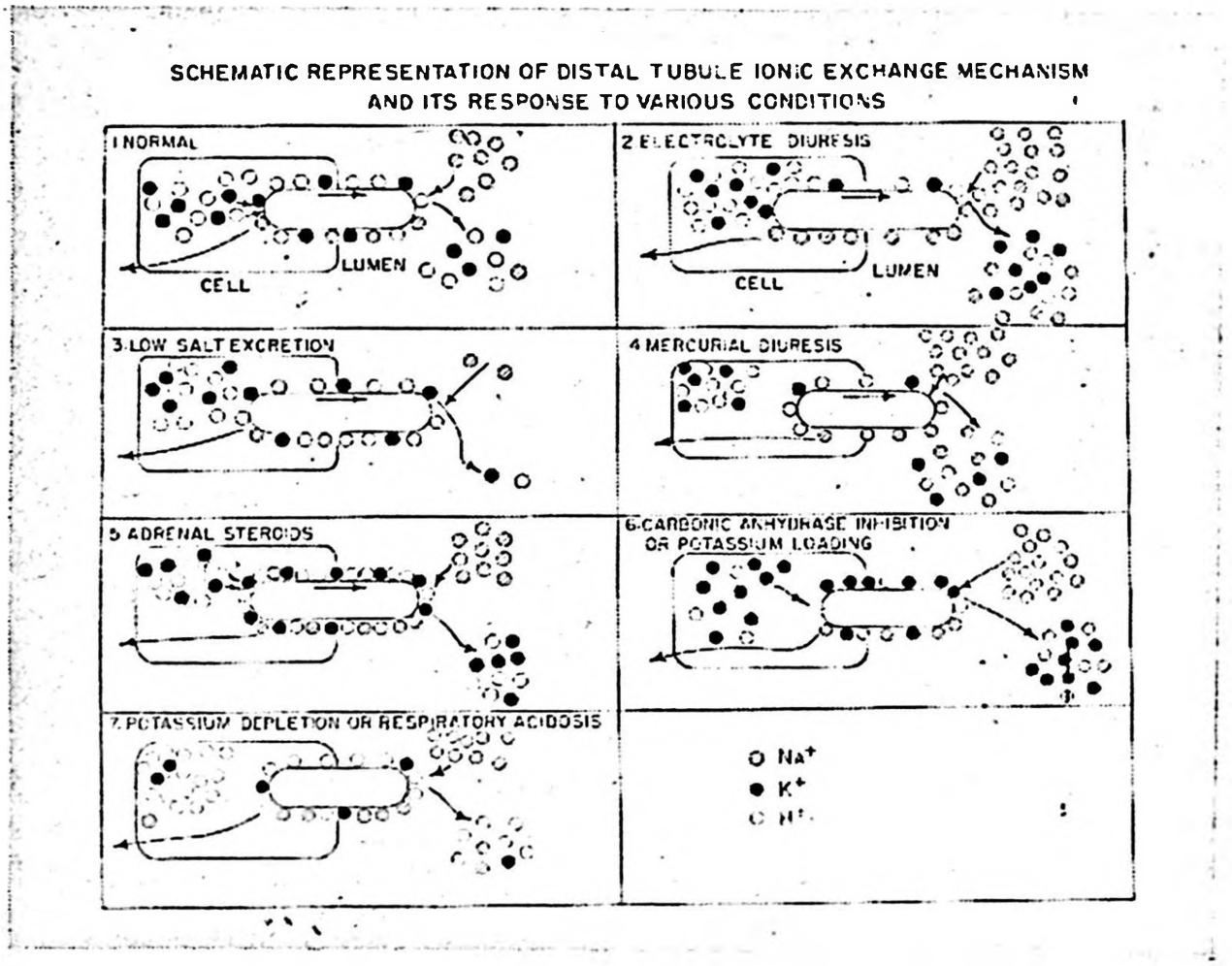

FIGURE 5. See text.

as containing a certain number of potassium and hydrogen ions. The exchange mechanism is represented by a conveyor belt which picks up potassium and hydrogen ions inside the cell and carries them into the lumen where they are replaced by sodium ions derived from the fluid in the lumen of the tubule. The sodium ions carried into the cell are dropped off in exchange for more potassium or hydrogen ions and the sodium is then extruded into the interstitial fluid.

Under average normal circumstances we visualize the amount

of sodium reaching the mechanism as moderate—only a little escapes being picked up by the exchange, but the amount that is picked up is not enough to load the inbound side of the belt with sodium. The rate of secretion of potassium and hydrogen ions is considerably less than capacity because there is not enough sodium to utilize this capacity.

Now suppose that without changing the composition of the cells or the characteristics of the exchange process we increase the delivery of sodium to the exchange mechanism. This we might do by administering some salt whose anion is poorly reabsorbed by the tubules, such as sodium sulfate, or by the administration of large amounts of sodium chloride. This effect is represented in diagram No. 2. Now a large amount of sodium is available to the exchange mechanism. Consequently, although considerably more sodium escapes into the urine, the return cycle of the carrier is now loaded with sodium and the excretion of potassium and hydrogen ions is increased.

Conversely, if salt excretion is markedly reduced—as might be the situation in an individual on a very low salt intake or in cardiac failure—the amount of sodium reaching the exchange mechanism is very low. Consequently although the sodium is removed virtually completely from the urine, very litte potassium or hydrogen ion enters the urine in the process. Much of the capacity for secreting potassium or hydrogen ion is not used.

Now the administration of a mercurial diuretic decreases the capacity to secrete potassium ion, but does not eliminate it completely. At the same time, by its effects on sodium reabsorption higher in the tubule, the mercurial diuretic increases the delivery of sodium to the exchange mechanism. Consequently, the change in potassium excretion which follows the mercurial diuretic will depend on the previous state of sodium and potassium excretion. If it has been moderate as in diagram No. 1, there will be relatively little change, possibly a little up, possibly a little down. If it has been quite low, as the result of low salt intake or cardiac failure as in diagram No. 3, it will go up and sometimes quite markedly. On the other hand if it has been high because of an electrolyte diuresis or potassium loading or the administration of a carbonic anhydrase inhibitor such as diamox, potassium excretion will go down when a mercurial is administered.

The circumstances represented in the other diagrams have already been mentioned in some detail and require no further explanation.

To summarize briefly the major characteristics of the renal potassium excretion mechanism: 1) the tubule reabsorbs and secretes

potassium and both are continuous processes, 2) there is evidence to support the simpler view that all of the filtered potassium is reabsorbed and that excreted potassium is derived from the secretory process located in the distal tubule, 3) the mechanism operates by exchanging potassium ions for sodium ions, and 4) the rate of secretion depends on the capacity of the exchange mechanism, the relative availability of potassium and hydrogen ions within the cells, and the amount of sodium available to the mechanism for exchange.

Acknowledgment

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