EXCHANGES OF POTASSIUM RELATED TO ORGANS AND SYSTEMS

T. S. DANOWSKI AND J. R. ELKINTON[1]

From the Dept of Research Medicine, University of Pittsburgh School of Medicine and the Dept. of Medicine, University of Pennsylvania School of Medicine

Received for publication October 9, 1950

Recently a number of original studies and review articles (28, 31, 39, 50, 76, 77, 168) have served to focus the attention of the investigator and the clinician on the element potassium which, as a cellular and extracellular cation, accounts for about one half of the extra-skeletal fixed base within the body. In view of the diversity of the physiological processes and disease states encompassed in these various reports, it has seemed advisable to us to try presenting these data as they apply to various organs and systems. It is hoped that this will point out both knowledge and ignorance. Emphasis will be placed upon exchanges of potassium which occur between a) the organism and its external environment and b) the extracellular fluid and the cells. In view of the limited number and the accessibility of routes ordinarily involved in the external exchanges (gastro-intestinal tract, kidney, and to a much lesser degree, the skin), these balance sheets can be drawn with fair assurance. Much less certainty is present, however, in discussing changes which take place between cells, such as those of liver, muscle and nervous system, and the pericellular fluid since many of the estimates of transfers are indirect or inferred.

A. GASTRO-INTESTINAL TRACT

1. Exogenous potassium. Under ordinary circumstances potassium enters the body only through this route. It is present in practically all foods, being particularly high in animal and plant cells, including extracts of these such as bouillon, coffee and cocoa (15). Public water supplies usually contain only a fraction of a milliequivalent per liter. The daily intake of potassium may be zero in patients who are starving and in those given only selected clear liquids, or 100 milliequivalents or more in an adult laborer on a substantial diet. Analyses of animal and vegetable foodstuffs cited above indicate moreover that the amount of potassium ingested may vary considerably, depending on the soil in which vegetables were grown, the cut of meat, mode of preparation or preservation, etc. The oral intake may also be augmented by the use of "salt substitutes" which usually contain potassium. In animals, an excessive administration of this cation as an inorganic salt produces pylorospasm (215). In humans, anorexia, vomiting, diarrhea, abdominal discomfort as well as paraesthesias have been at times observed with the ingestion of KCl in multi-gram dosage (45, 212).

About four fifths of the ingested potassium is absorbed under ordinary circumstances at levels proximal to the large bowel. This is reflected in the relatively low potassium content of formed stools (61, 62, 77, 167).

[1] Established Investigator of the American Heart Association.

2. Endogenous potassium. Several lines of evidence indicate that body potassium may be lost via the gastro-intestinal tract. The invariable presence of this electrolyte in saliva and gastric juice, in duodenal and small bowel secretions, in pancreatic juice and in bile has been demonstrated (3, 94, 127, 145, 175, 176). It is of particular importance to note that these fluids frequently contain potassium in concentrations in excess of those which prevail in extracellular fluid, though lower than those present in the water of cells. This characteristic suggests that cells contribute potassium to these secretions.

It is obvious that the actual potassium concentrations encountered at any particular level in the gastro-intestinal tract will be influenced by the intake, if any, by the volume and composition of secretions, by the rate at which the contents move, and finally by the degree to which water and solutes are reabsorbed. It is not surprising to learn, therefore, that during periods of even moderate losses of such fluids to the exterior, as in diarrhea or vomiting, considerable deficits of body potassium can be incurred (39). Obviously the net losses will be all the greater in disease states which interfere with the ingestion and absorption of the usual potassium intake. This combination of potassium inanition and negative balances of body potassium has been studied in considerable detail in infants with diarrhea (48, 49, 97, 123, 200), in pyloric stenosis of newborns (41, 150), in adult patients representing a variety of gastro-intestinal disorders (8, 9, 108, 135, 192), as well as in diabetic subjects in acidosis or coma (25, 47, 92, 102, 103, 121, 148, 161, 163, 164, 177, 179, 185, 198, 201, 202, 206). The bulk of potassium lost comes from cells, either directly, as in gastro-intestinal tract secretions, or indirectly in replenishing extracellular supplies. Deficits may involve as much as one fifth of the potassium in the body. Evidence has been brought forth indicating that these losses may be of sufficient magnitude to jeopardize survival (86, 92, 100, 144).

Recognition of these exchanges of potassium between the body, the gastro-intestinal lumen, and the external environment has logically led to their use in removing excessive accumulations of body potassium such as those which occur in renal failure. The older approach of purging has not been revived, however, since it results in undesired losses of other body constituents such as sodium, chloride, water, etc. The same criticism applies as well to the use of small bowel lavage, though it is obvious that in both instances any inadvertent loss of extracellular or cellular constituents can be replaced by parenteral routes. With the latter technic such losses can also be avoided by the use of solutions of appropriate composition. A newer approach involves the use of cation exchange substances which can be administered orally. These include zeolites as well as sulfonic and carboxylic resins (27, 35, 36, 60, 158). The last of these has undergone the most extensive trials in human subjects (38, 44, 128). The H^+ or NH_4^+ cycle carboxylic cation exchange resin removes both exogenous and endogenous potassium with subsequent loss in stools. Since these exchanges need not involve specific cations, care must be taken to avoid depletion of sodium, either by replacement or by the use of a Na^+ cycle resin, alone or in combination with NH_4^+ or H^+ charged resin. Dramatic removal of accumulations of extracellular or cellular potassium by resin

enema may also be achieved, although the effectiveness of this procedure varies considerably (64).

B. LIVER

The cells and the surrounding fluid of the liver represent a store of body potassium second in magnitude only to that in muscle. In several ways this organ can be looked upon as a way-station in the travels of both exogenous and endogenous potassium. Ingested potassium entering the portal system accumulates in the liver in increments which are higher than those recorded in other sites (129, 165). This appears to be related in part to the preferential position of this organ, anatomically speaking. This interpretation is bolstered by the demonstration that, with intra-arterial injections into one of the limbs, the greatest increases are those observed in the muscles supplied by the subdivisions of such a vessel (217). Further support for this point of view is available in the finding that injections of isotopic potassium into the antecubital veins produce maximal rises in cardiac muscle (37).

Evidence is available, on the other hand, that the liver participates in a more specific manner in the metabolism of this electrolyte. Thus, it should be noted that this tendency for potassium accumulation in the liver occurs even when this electrolyte is injected intravenously (63). Furthermore, potassium which is released during muscular contraction is in part taken up by the liver (75). Whether or not these are purposeful processes, it is clear that they do serve to temper any sudden influx of potassium into the extracellular fluid. If this is kept in mind, it is not unreasonable to suggest that the heretofore described congregation of orally given exogenous potassium in the liver may be more than fortuitous.

Published data indicate that deposition of glycogen in the liver is associated with a proportionate retention of potassium and other cations (74, 79). Furthermore, unavailability of these electrolytes in optimal proportions under *in-vitro* conditions results in less than maximal glycogen formation (109). Preliminary studies have indicated, however, that a complete absence of these electrolytes by no means abolishes the glycogenetic process in isolated rat diaphragm (183). Nonetheless it is obvious that the formation or the breakdown of glycogen is in general associated with increases and decreases, respectively, in liver potassium. Finally, though specific evidence is lacking, it is probable that, as in the case of muscle (*v. infra*), a protein-potassium ratio is present with gains or losses of potassium as the liver nitrogen content varies.

Certain studies do suggest, however, that this tissue does not always follow the pattern of potassium exchange characteristic of other tissues. Thus, desoxycorticosterone acetate (DOCA) administration does not produce depletion of liver potassium nor does adrenalectomy raise the liver content of this electrolyte (29, 52, 106). Also, the liver of potassium-depleted animals does not show the large electrolyte and potassium changes evident in muscles (113). With extensive hemorrhage, however, liver potassium is lost, presumably as a result of interruption of processes which maintain cell potassium levels intact (51).

C. MUSCLE

The bulk of body potassium is located within the voluntary muscles. This prepondernant distribution is related primarily to the mass of this tissue rather than to any unusual concentration of potassium in these cells. Actually, in view of the predominantly intracellular position of this ion, the cells of many other tissues and organs, including bone, contain potassium in levels much higher than those in extracellular fluid and as high as those in muscle (110, 146).

The mechanisms responsible for this disparate distribution remain as obscure as they were at the time the difference was first established. They are maintained by energy-linked processes, since with anoxia or death potassium pours out of cells (26, 56, 80, 81, 91, 211, 220). This fact, however, serves merely to confirm the reality of the difference rather than to trace its origins. The advent of isotopic potassium has served to establish that the potassium in cells is not absolutely segregated since it exchanges in a matter of hours with administered K^{42} (24, 104, 114, 129, 143, 165).

There are other observations which point to the transferability of potassium through membranes into or out of cells, including those in muscles. The occurrence of such migrations has been established in several ways for blood cells (40, 46, 57, 105, 137, 141). Similarly in muscle it has been shown, as cited earlier (75), that during contraction potassium is released from the cells and enters the extracellular fluid. The relative constancy of muscle potassium concentrations in itself is sufficient proof that a replacement of this lost fraction must subsequently occur. Losses of tissue potassium following operations (14, 16, 166, 172), during dehydration and starvation (10, 67, 69, 205, 210), diarrhea (86), vomiting (150), Cushing's syndrome (136, 208), or DOCA (53, 83, 140) or other steroid therapy (65, 88, 149, 182) result in reversible deficits of muscle potassium. It has been shown too that the entry of potassium into muscle cells may occur even when the stores of this cation are not depleted (78, 204, 218). Moreover, the lowered volumes of distribution of injected potassium salts in adrenalectomized animals or in humans or dogs with far advanced renal failure suggest that intracellular potassium concentrations are increased under these conditions (133, 216). This has been confirmed by muscle analyses (22, 29, 33, 52, 106, 156). Finally, the movement of potassium from extracellular fluids into cells in association with an attack of periodic paralysis provides another example of such transfers (42, 82, 99, 170, 187, 189). In this last entity it is not certain whether the muscle potassium stores are normal.

From the above observations it is clear that extensive transfers of potassium take place into and out of living tissue cells under a wide variety of physiological and pathological conditions, but the mechanisms by which these transfers are effected are not completely delineated. Experimental evidence has been adduced (19, 34) to support the theory that in skeletal muscle potassium passively diffuses into the cell to neutralize the nondiffusible intracellular anions, sodium being excluded. Since it was found that the extrusion of sodium is independent with respect to the time of entry of potassium and must perforce be an active transport

against a high concentration gradient, even this theory makes the transfer of potassium dependent on energy-producing processes within the cell. From additional data (29, 33) it has been calculated that in the adrenalectomized animal potassium accumulates within the muscle cell as a result of the breakdown of anionic complexes which produce an increase in their electrostatic force. This change in the state of intracellular organic anions is associated with an increase in glucose-1-phosphate and a decrease in glucose-6-phosphate and fructose-6-phosphate, and is further evidence of the dependence of potassium exchanges on metabolic processes, especially the carbohydrate phosphorylation cycle.

Other experiments confirm this interdependence. It has been shown in the isolated living rat diaphragm that both glucose utilization and potassium uptake are increased by the addition of insulin (130, 207). It is not a reciprocal obligatory relationship, however, since, as mentioned previously, the absence of potassium in the external medium does not prevent glycogenesis in such a preparation (183). In intact rats, however, potassium depletion retards glycogenesis (98). Similarly in the cells of *E. coli* in which the major portion of potassium appears to exist as salts of hexose phosphate (17) potassium deficiency diminishes the incorporation of radioactive phosphate into phospholipids and nucleic acids in the presence of glucose, hexose phosphates, and other substrates (173). *In-vitro* studies (188) have shown that potassium conditions the reaction of actomyosin with adenosine triphosphate, but the exact mechanism by which this occurs is unknown.

It is customary to differentiate between movements of cell potassium occurring in conjunction with the anabolism or catabolism of protein and those in excess of such processes (1, 67, 69, 71). These subdivisions of the external and internal balances of this electrolyte are justified in view of the characteristic proportions in which K and N are lost from tissues during starvation (95). They point to the existence of potassium transfers independent of nitrogen metabolism. Studies of cation and water balances in various experimental and clinical situations have indicated a) that extensive transfers of potassium in excess of nitrogen may occur (41–43, 47, 49, 71, 102, 108, 124, 150, 169, 172, 192, 200), b) that frequently these are associated with reciprocal though not necessarily equivalent movements of sodium (34, 54, 66, 71, 83, 112, 152, 184), and c) that at times the base within cells (potassium as well as sodium) may vary in osmotic activity (70, 71, 203). Since muscle potassium makes up the bulk of the cellular phase of this electrolyte it is obvious that these processes will, from the quantitative point of view at least, occur preponderantly in this tissue. It should be pointed out that the failure to demonstrate alterations in the concentration of potassium in this or in other tissues does not disprove the occurrence of increases or decreases in this ion. Experimental evidence is available indicating that in the cellular phase. just as in the extracellular phase, concentrations may remain intact as a result of water movements, whereas the total amounts of potassium may be actually decreased or increased (156).

It has been claimed that in organisms that have reached a state of biological equilibrium (intact renal function) transfers of intracellular sodium and potassium bear a relationship to extracellular bicarbonate and chloride concentration

(54). In experimental animals, extracellular hypochloremic alkalosis has been associated with a movement of potassium out of, and sodium into, the intracellular phase of skeletal muscle, this relationship holding whether the alkalosis or the potassium depletion was initiated first (54, 97, 98). Hypochloremic alkalosis is a common concomitant of hypokaliemia and intracellular potassium depletion in many clinical conditions (8, 23, 41, 65, 66, 124, 135, 155a, 166, 172, 192). It is not clear just how this relationship is effected, and some evidence has appeared which suggests that intracellular sodium or chloride shifts are more directly involved than are those of potassium (66). In any case the mechanisms involved will not be clarified until a much more complete description is at hand of the exchanges of both cations and anions in each phase occurring under these conditions.

D. CARDIAC ASPECTS OF POTASSIUM METABOLISM

Though cardiac and skeletal muscles are histologically related, potassium exchanges in these two tissues are not necessarily identical. It has already been indicated that skeletal muscle changes need not be representative of those occurring elsewhere in the body, for example, in the liver. Some of the difference between the heart and other striated muscle may represent only analytical limitations. Others can be adventitious; thus, the higher uptake of K^{42} by cardiac cells following intravenous injection probably represents a geographical advantage. However, at this time no organ other than the heart is known to respond as dramatically to alterations in extracellular potassium. With moderate increases in plasma or extracellular potassium, increments of only 1 or 2 milliequivalents per liter above the upper limit of control values, the T wave of the electrocardiogram becomes peaked; later the QRS may become prolonged (191, 213, 214). As the levels rise toward 10–12 milliequivalents per liter the P waves are lost, the QRS contour changes to intraventricular block, and cardiac standstill supervenes before respiratory arrest. Blood pressure is maintained (119). This sequence of events, first delineated in experimental situations, is frequently duplicated, as will be mentioned later, in patients with anuria and less often in subjects with far-advanced renal failure with maintained or even increased urine volumes. It may also be seen in untreated diabetic coma and in patients given KCl (21, 101, 162, 186). The importance of this sequence of events in clinical situations cannot be over-emphasized, since preventative or remedial procedures are now at hand. Even without the complicated technics and apparatus of vivo-dialysis, a high carbohydrate-fat, *no* protein diet in renal failure or anuria will tend to prevent potassium intoxication. If elevated levels are already present, cation exchange resins will reverse the trend (44, 64).

On the other hand it has been shown that potassium deficiency induced in one of several ways produces histological evidences of myocardial and, in some species, skeletal muscle necrosis (53, 87, 139, 181). Cardiac enlargement and symptoms of congestive failure have been described in potassium-depleted patients (92, 96). The fact that mortality figures in infants ill with diarrhea can be favorably affected by potassium therapy (86) may be related to functional or histological

sequelae in this tissue. It is not clear whether the S-T and T depression and the Q-T prolongation frequently associated with hypokaliemia represent alterations produced by decreases in the potassium outside of cells, inside, or both.

E. POTASSIUM AND THE NERVOUS SYSTEM

The cells of this tissue, in common with other cells in mammals, contain potassium in high concentrations. In spinal fluid, potassium concentrations are significantly lower than those in extracellular fluid (111). The significance of this disparity is not explicable by any known peculiarity of the extracellular-cellular phases of nervous tissue. It may be related, however, to the anatomical fact that the spinal fluid compartment is an analog of a bursa. Just as in other cells, adrenalectomy is associated with a rise in potassium in nervous tissue (115). Davenport, however, has indicated that in brain cells these changes do not take place, and that in this regard the brain, at least in rats, resembles liver in its behavior and contrasts sharply with skeletal muscle (54a). Another unusual feature of this organ is its ability to withstand the swelling of cells accompanying extracellular hypotonicity by releasing some of its own electrolytes (187a, 219).

Radioactive isotope distribution studies indicate that the penetration of tagged molecules occurs much more slowly in brain than in other tissues (165). This relatively slow interchange would suggest that acute phenomena associated with potassium administration are related to the peri- rather than the intracellular potassium. This view is in keeping with the paresthesia following potassium treatment (134), with the slowing of EEG observed with the injection of potassium as well as with the anti-curare (2, 18, 117, 122, 174) and perhaps the muscle anti-fatigue effects (120, 199) of injected potassium salts. In connection with this last group of studies it is of interest that hypokaliemia may mask hypocalcemic tetany (72, 73).

In common with the blood cell system, the loss of potassium occurring after incubation of brain tissue at body temperatures can be cancelled *in toto* by glucose in an anaerobic system and accelerated by fluoride (59). During aerobic incubation of brain slices this has been reported after glucose and l-glutamate but, following glucose alone, the suppression of potassium loss is only partial (194). Finally, perfusion of a local area of the cerebral cortex with high concentrations of potassium transiently raises its rate of oxygen consumption (55).

Extensive transfers of potassium and sodium across the membrane of nerve fibers occur in association with electrical activity in this tissue. By use of the radioactive isotopes Na^{24} and K^{42}, evidence has been obtained (116, 138) that during excitation of the giant nerve fiber of the squid, 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. This is not a simple exchange of the two ions by diffusion since these permeability changes are separated in time with the result that an action potential is produced during the cycle. Although sodium is moving down an electrochemical gradient during the initial phase, it must be actively transported against the gradient during the recovery phase. An expenditure of energy must therefore occur. It has been suggested

(160) that these sudden changes of membrane permeability are initiated by the local action of acetylcholine on the protein of the membrane. Electrolyte exchanges during excitation of this tissue are not restricted to peripheral nerves. Evidence of loss of potassium and gain of sodium by cerebral cortical neurones following convulsions induced in rats and rabbits by metrazol, electric shock, or sound has been obtained from micro-incineration and crystallographic analysis (30).

F. THE ROLE OF THE KIDNEY

The major role of the kidney in regulating the body fluids has been proven and emphasized repeatedly. Its importance in the excretion of potassium has been realized more clearly since the experimental demonstration that anuria following nephrectomy, ureteral ligation, and perhaps in some cases of $HgCl_2$ intoxication, results in death from potassium poisoning (118). More recent studies in patients with far advanced renal failure have indicated that even with continued urine output ECG changes and high extracellular fluid potassium levels appear in a minority of these subjects (68, 85, 131, 132, 147, 171, 180, 190). In the remainder, however, normal or even increased potassium excretion is encountered, sufficient at times to result in depletion (20, 23, 178). A number of studies provide reasonable explanations for this diversity of patterns. It has been shown in dogs that, either with an increased load of potassium presented to the kidneys for excretion or during an osmotic diuresis, there is tubular secretion of this electrolyte (12, 13, 89, 153–155). This finding makes it clear that potassium present in the urine can come from glomerular filtrate, tubular secretate, or both. It should not be surprising to find, therefore, that in nephron injury these two sources can be unequally affected, and as a matter of fact clinical data are available indicating that tubular secretion of potassium still occurs in chronically impaired kidneys (68, 142). This is based on the indirect evidence that in such subjects the glomerular filtrate, even when huge errors in the measurement of its rate of formation are assumed, cannot account for all of the potassium in the urine. This obviously need not be solely the result of activity of aglomerular nephrons, though such may be present.

Another function of renal tubules to be mentioned is the removal of potassium from glomerular filtrate (151, 157, 193). In view of the fact that water can only be abstracted but not added to the filtrate it is obvious that the occurrence of urine-plasma ratios of potassium lower than unity is evidence of "active" reabsorption of potassium. Though this is often cited as evidence for movement of potassium against a concentration gradient in plasma, a moment's thought makes it apparent this is not the case. Actually the initial transfer of the ion is against the high levels of potassium prevailing in cells, in this case, the proximal tubular epithelium (32). Hence *any* reabsorption of potassium which occurs when concentrations of this electrolyte in filtrate are lower than that in tubular cells must represent a transfer against a gradient.

These considerations raise important questions as to (a) the renal mechanisms involved in the excretion of potassium under maximal and minimal stimuli,

and (b) the means by which the kidney interprets and responds to these stimuli. From the experimental work quoted above it is clear that active tubular reabsorption and active tubular secretion of potassium occur under minimal and maximal stimuli. It has been suggested that both mechanisms are active simultaneously in the excretion of a variety of substances, including potassium (6, 35). Although there are no unequivocal data as yet concerning the overlap of these two mechanisms between the two conditional extremes, the inhibitory actions of mercury on tubular reabsorption during water diuresis and on tubular secretion during potassium loading strongly suggest that filtered potassium is mostly reabsorbed and that facultative excretion is a secretory process (153).

Whatever may be the mechanism of the renal excretion of potassium in any particular instance, it is interesting to speculate on the way in which needs of the body for the ion are made known to the kidney. Under conditions of potassium deficit renal conservation may occur. It is hardly comparable to the abrupt renal conservation of sodium; urinary losses of potassium continue in the face of inadequate intake for many days (47), and reach a minimum only slowly, if at all (192). The stimulus does not appear to be simply the low concentration of potassium in plasma and extracellular fluid, since such low levels are often already present when the excretion rate is relatively high (192). Furthermore, the lowest urine-plasma ratios are observed after extracellular fluid levels have returned to normal (151). Likewise when potassium is administered in large amounts to potassium-depleted subjects and taken up by cells of the body, the renal excretion rate may not rise until several days after the plasma concentration has risen to normal or high levels (151, 192). These data suggest that the kidney responds to depletion and replenishment of potassium in the intracellular phase of tissues. It has been suggested that the specific site of stimulus may be either in the cells of the adrenal cortex (209) or in the renal tubule.

A similar interpretation is possible in regard to the stimulus for maximal excretion of the ion. Elevation of the plasma level is not the only correlate. Chronic dehydration is one of the strongest stimuli for the excretion of potassium (67). Under such conditions it is unrelated to the plasma level, filtered load, or rate of urine flow, and is accomplished at least in part by tubular secretion (155). These data again suggest that at least one stimulus to potassium excretion is the content or concentration of potassium in tissue cells.

G. ADRENAL CORTEX AND POTASSIUM METABOLISM

The accumulation of potassium in plasma, in extracellular water and in cells during adrenal cortical insufficiency (22, 29, 33, 52, 106, 107, 156, 221, 222), as well as the excessive urinary loss of potassium in extensive DOCA therapy (83, 84, 90, 93) or in Cushing's syndrome (159), has long since established the importance of this gland in the metabolism of potassium. Furthermore, clear cut morphological changes in the adrenal cortex accompany, at least in the rat, alterations in the potassium intake. Thus on a low intake of an inorganic salt of this cation the cortex is narrowed; with increased levels of intake it greatly increases in size with associated evidences of augmented secretory activity

(4, 5, 58). These alterations in form are accompanied by predictable changes in function. Thus urinary potassium losses rise with increased intake of this electrolyte and cortical hypertrophy, and under the opposite circumstances the converse is true. These alterations are presumably related to increases and decreases, respectively, in the secretion of DOCA-like steroids. It is of interest that these adjustments can occur in the absence of the anterior pituitary (11).

In view of these facts it would appear to be logical to assume that similar correlations exist during periods characterized by smaller fluctuations in potassium intake. If this be true, hormonal control of the urinary excretion of this cation can be postulated as a homeostatic mechanism. At present, however, there is no convincing evidence that any such precise relationship exists between the adrenal and its neighbor, the kidney. Despite this lack of direct evidence it should be emphasized that a variety of exogenous and endogenous steroids, the latter produced under the stimulation of administered ACTH, do modify the urinary excretion pattern of potassium. Whether the different effects which have been recorded, varying both in intensity and in direction, are the result of a direct action of any particular compound on the tubular epithelium or represent merely a secondary change is not known at present (7, 88, 125, 126, 149, 195–197). In behalf of the latter prospect it should be noted that a vast body of experimental facts is now being accumulated indicating that compounds with the steroid configuration do exert a variety of effects totally unrelated to adrenal function.

CONCLUSION

Potassium is a substance ubiquitous in living organisms. It plays a role in the physiological processes of nearly every type of tissue and organ; its pharmacological effects are legion. The wide scope of activities of this ion has been indicated by the experimental observations set forth in the foregoing pages.

The role of potassium in physiological processes is so extensive that this review is admittedly incomplete. Indulgence is begged for the fact that many papers have been either omitted from the review, inadequately criticized, or perhaps misinterpreted.

REFERENCES

1. Albright, F., Reifenstein, E. C. Jr. and Forbes, A. P.: Does potassium move with nitrogen? Conference on Metabolic Aspects of Convalescence. Josiah Macy Jr. Foundation, 11: 25, 1945.
2. Altamirano, M. and Huidobro, F.: Some actions of potassium chloride at the neuromuscular junction. Am. J. Physiol., 152: 53–65, 1948.
3. Austin, J. H. and Gammon, G. D.: Gastric secretion after histamine: sodium and potassium content and pepsin estimation. J. Clin. Investigation, 10: 287–307, 1931.
4. Bacchus, H.: Ketosteroid and ascorbic acid cytochemistry observed in the adrenal cortices of rats flooded with either sodium or potassium chloride, or given prolonged injections of DCA. Federation Proc., 9: 7, 1950.
5. Badinez, O. and Croxatto, H.: Effect of potassium chloride and sodium chloride on the weight of rat adrenals. Bol. soc. biol., 5: 37–40, 1948.
6. Barclay, J. A., Cooke, W. T. and Kenney, R. A.: Evidence for a three component system of renal excretion. Acta med. Scandinav. 128: 500–507, 1947.
7. Bartter, F. C., Fourman, P., Forbes, A. P., Jeffries, W. M. and Dempsey, E.: A quantitative analysis of the effects of adrenocorticotropic hormone (ACTH) on potassium (K) and phosphorus (P) metabolism. J. Clin. Investigation, 28: 769, 1949.
8. Bellet, S., Nadler, C. S., Gazes, P. C. and Lanning, M.: Effect of vomiting due to intestinal obstruction on the serum potassium. Chemical and electrocardiographic observations in fifteen cases. Preliminary report. Am. J. Med., 6: 712–724, 1949.
9. Bellet, S., Nadler, C. S., Gazes, P. C. and Lanning, M.: Effect of vomiting due to intestinal obstruction on serum potassium. Gastroenterology, 12: 49–56, 1949.

10. Benedict, F. G.: A study of prolonged fasting. Carnegie Inst. of Wash., Public. #203.
11. Bergner, G. E. and Deane, H. W.: Effects of pituitary adrenocorticotropic hormone of the intact rat, with special reference to cytochemical changes in the adrenal cortex. Endocrinology, 43: 240-260, 1948.
12. Berliner, R. W. and Kennedy, T. J., Jr.: Renal tubular secretion of potassium in the normal dog. Proc. Soc. Exper. Biol. & Med., 67: 542-545, 1948.
13. Berliner, R. W., Kennedy, T. J., Jr. and Hilton, J. G.: Renal mechanisms for excretion of potassium. Am. J. Physiol., 162: 348-367, 1950.
14. Berry, R. E. L., Iob, V. and Campbell, K. N.: Potassium metabolism in immediate postoperative period. Arch. Surg., 57: 470-478, 1948.
15. Bills, C. E., McDonald, F. G., Niedermeier, W. and Schwartz, M. C.: Sodium and potassium in foods and waters. Determination by the flame photometer. J. Am. Dietetic Assoc., 25: 304-314, 1949.
16. Blixenkrone-Møller, N.: Potassium metabolism in connection with operations. Acta chir. Scandinav., 97: 300-312, 1949.
17. Bolton, E. T.: Potassium compounds associated with carbohydrate metabolism of *Escherichia coli*. Federation Proc., 9: 153-154, 1950.
18. Boulet, L. and Boulet, M. A.: Antagonism between barium and potassium on excitability of the vagus. Comp. rend. Soc. de biol., 141: 1226, 1947.
19. Boyle, P. J. and Conway, E. J.: Potassium accumulation in muscle and associated changes. J. Physiol., 100: 1-63, 1941.
20. Brown, M. R., Currens, J. H. and Marchand, J. F.: Muscular paralysis and electrocardiographic abnormalities resulting from potassium loss in chronic nephritis. J. Am. M. A., 124: 545-549, 1944.
21. Bryant, J. M. Effect of potassium on the ventricular deflections of the electrocardiogram in hypertensive cardiovascular disease. Proc. Soc. Exper. Biol. & Med., 67: 557-558, 1948.
22. Buell, M. V. and Turner, E.: Cation distribution in the muscles of adrenalectomized rats. Am. J. Physiol., 134: 225-239, 1941.
23. Burnett, C. H., Burrows, B. A. and Commons, R. R.: A mechanism of potassium deficiency in alkalosis. J. Clin. Endocrinol., 9: 676, 1949.
24. Burrows, B. A. and Sisson, J. H.: The measurement of total body potassium by the radioisotope dilution technique. J. Clin. Investigation, 28: 801, 1950.
25. Butler, A. M., Talbot, N. B., Burnett, C. H., Stansbury, J. B. and MacLachlan, E. A.: Metabolic studies in diabetic coma. Tr. A. Am. Physicians, 60: 102-109, 1947.
26. Cattell, McK. and Civin, H.: The influence of asphyxia and other factors on the serum potassium of cats. J. Biol. Chem., 126: 633-644, 1938.
27. Ch'en, J. S. and Freeman, S.: The removal of cations from solutions and the rat's alimentary canal by H-form resins. J. Lab. & Clin. Med., 35: 99-110, 1950.
28. Cicardo, V. H.: Importancia Biologica Del Potasio. El Ateneo, Buenos Aires, 1947. Pages 1-254.
29. Cole, D. F.: Chemical changes in the tissues of the rat after adrenalectomy. Endocrinol., 6: 245-250, 1950.
30. Colfer, H. F. and Essex, H. E.: The distribution of total electrolyte potassium and sodium in the cerebral cortex in relation to experimental convulsions. Am. J. Physiol., 150: 27-36, 1947.
31. Conway, E. J.: Exchanges of K, Na and H ions between the cell and its environment. Irish J. M. Sc., Oct.-Nov., 593-609, 1947.
32. Conway, E. J., Fitzgerald, O. and MacDougald, T. C.: Potassium accumulation in the proximal convoluted tubules of the frog's kidney. J. Gen. Physiol., 29: 305-334, 1946.
33. Conway, E. J. and Hingerty, D.: The influence of adrenalectomy on muscle constituents. Biochem. J., 40: 561-568, 1946.
34. Conway, E. J. and Hingerty, D.: Relations between potassium and sodium levels in mammalian muscle and blood plasma. Biochem. J., 42: 372-376, 1948.
35. Conway, E. J.: Biological interlinkage of acid-alkali formation with ion transport and synthetic reduction. Irish J. M. Sc., 287: 787-800, 1949.
36. Crismon, J. M.: Sodium and potassium depletion in rats by means of cation exchange resins mixed with food. Federation Proc., 8: 30, 1949.
37. Crismon, J. M., Crismon, C. S., Calabresi, M. and Darrow, D. C.: Electrolyte redistribution in cat heart and skeletal muscle in potassium poisoning. Am. J. Physiol., 139: 667-674, 1943.
38. Currens, J. H., Counihan, T. and Rourke, M.: Observations on the administration of ammonium cation exchange resin to patients with cardiac edema. J. Clin. Investigation, 29: 807, 1950.
39. Danowski, T. S.: Newer concepts of the role of potassium in disease. Am. J. Med., 7: 525-531, 1949.
40. Danowski, T. S.: The transfer of potassium across the human blood cell membrane. J. Biol. Chem., 139: 693-705, 1941.
41. Danowski, T. S., Austin, A. C., Gow, R. C., Mateer, F. M., Weigand, F. A., Peters, J. H. and Greenman, L.: Electrolyte and nitrogen balance studies in infants following cessation of vomiting. Pediatrics, 5: 57-67, 1950.
42. Danowski, T. S., Elkinton, J. R., Burrows, B. A. and Winkler, A. W.: Exchanges of sodium and potassium in familial periodic paralysis. J. Clin. Investigation, 27: 65-73, 1948.
43. Danowski, T. S., Greenman, L., Gow, R. C., Weigand, F. W., Mateer, F. M., Peters, J. H., Cosgrove, E. F., Seiferth, W. and Davis, N.: Electrolyte and nitrogen balance studies in patients receiving a nitrogen mustard. J. Pharmacol & Exper. Therap., 98: 147-152, 1950.
44. Danowski, T. S., Greenman, L., Mateer, F. M., Peters, J. H., Weigand, F. A., Mermelstein, H. A., and Clarke, C. E.: Carboxylic cation exchange resin studies in animals and humans. J. Clin. Investigation 29: 807, 1950.

45. DANOWSKI, T. S., GREENMAN, L. AND PETERS, J. H.: Unpublished observations.
46. DANOWSKI, T. S., HALD, P. M. AND PETERS, J. P.: Sodium, potassium, and phosphates in the cells and serum of blood in diabetic acidosis. Am. J. Physiol., 149: 667-677, 1947.
47. DANOWSKI, T. S., PETERS, J. H., RATHBUN, J. C., QUASHNOCK, J. M. AND GREENMAN, L.: Studies in diabetic acidosis and coma with particular emphasis on the retention of administered potassium. J. Clin. Investigation 28: 1-9, 1949.
48. DARROW, D. C.: Congenital alkalosis with diarrhea. J. Pediat., 26: 519-532, 1945.
49. DARROW, D. C.: The retention of electrolyte during recovery from severe dehydration due to diarrhea. J. Pediat., 28: 515-540, 1946.
50. DARROW, D. C.: Tissue water and electrolyte. Ann. Rev. Physiol., 6: 95-122, 1944.
51. DARROW, D. C. AND ENGEL, F. L.: Liver, water and electrolytes in hemorrhagic shock. Am. J. Physiol., 145: 32-37, 1945.
52. DARROW, D. C., HARRISON, H. E. AND TAFFEL, M.: Tissue electrolytes in adrenal insufficiency. J. Biol. Chem., 130: 487-502, 1939.
53. DARROW, D. C. AND MILLER, H. C.: The production of cardiac lesions by repeated injections of desoxycorticosterone acetate. J. Clin. Investigation, 21: 601-611, 1942.
54. DARROW, D. C., SCHWARTZ, R., IANNUCCI, J. F. AND COVILLE, F.: The relation of serum bicarbonate concentration to muscle composition. J. Clin. Investigation, 27: 198-208, 1948.
54a. DAVENPORT, V. D.: Relation between brain and plasma electrolytes and electroshock seizure thresholds in adrenalectomized rats. Am. J. Physiol., 156: 322-327, 1949.
55. DAVIES, P. W. AND GRENELL, R. G.: Effect of high potassium on respiration and demarcation potential of a small locally-perfused area of cerebral cortex. Federation Proc., 9: 29, 1950.
56. DEAN, R. B.: Anaerobic loss of potassium from frog muscle. J. Cell. & Comp. Physiol., 15: 189-193, 1940.
57. DEAN, R. B., NOONAN, T. R., HAEGE, L. AND FENN, W. O.: Permeability of erythrocytes to radioactive potassium. J. Gen. Physiol., 24: 353-365, 1941.
58. DEANE, H. W., SHAW, J. H. AND GREEP, R. O.: The effect of altered sodium or potassium intake on the width and cytochemistry of the zona glomerulosa of the rat's adrenal cortex. Endocrinology, 43: 133-153, 1948.
59. DIXON, K. C.: Anaerobic leakage of potassium from brain. Biochem. J., 44: 187-190, 1949.
60. DOCK, W.: Sodium depletion as a therapeutic procedure: the value of ion-exchange resins in withdrawing sodium from the body. Tr. A. Am. Physicians, 59: 282-285, 1946.
61. DUNCAN, L. E., JR., MEYER, R. J. AND HOWARD, J. E.: Mineral balance during brief starvation. The effect on serum electrolytes and mineral balance of maintaining the intake of certain mineral constituents. J. Clin. Investigation, 27: 389-396, 1948.
62. DUNCAN, L. E., JR., MIRICK, G. S. AND HOWARD, J. E.: Total intravenous alimentation. Its effect on mineral and bacterial content of feces. Bull. Johns Hopkins Hosp., 82: 515-528, 1948.
63. EICHELBERGER, LILLIAN: The distribution of body water in skeletal muscle and liver in normal dogs following injections of potassium salts. J. Biol. Chem., 138: 583-595, 1941.
64. ELKINTON, J. R., CLARK, J. K., SQUIRES, R. D., BLUEMLE, L. W., JR. AND CROSLEY, A. P., JR.: Treatment of potassium retention in anuria with cation exchange resin. A preliminary report. Am. J. M. Sc., 220: 547, 1950.
65. ELKINTON, J. R., HUNT, A. D., JR., GODFREY, L., MCCRORY, W. W., ROGERSON, A. G. AND STOKES, J., JR.: Effects of pituitary adrenocorticotropic hormone (ACTH) therapy. J. Am. M. A., 141: 1273-1279, 1949.
66. ELKINTON, J. R., SQUIRES, R. D. AND CROSLEY, A. P.: Intracellular cation exchanges in metabolic alkalosis. J Clin. Investigation, 29: 811, 1950.
67. ELKINTON, J. R. AND TAFFEL, M.: Prolonged water deprivation in the dog. J. Clin. Investigation, 21: 787-794, 1942.
68. ELKINTON, J. R., TABAIL, R. AND PETERS, J. P.: Transfers of potassium in renal insufficiency. J. Clin. Investigation, 28: 378-388, 1949.
69. ELKINTON, J. R. AND WINKLER, A. W.: Transfers of intracellular potassium in experimental dehydration. J. Clin. Investigation, 23: 93-101, 1944.
70. ELKINTON, J. R., WINKLER, A. W. AND DANOWSKI, T. S.: Inactive cell base and the measurement of changes in cell water. Yale J. Biol. & Med., 17: 383-393, 1944.
71. ELKINTON, J. R., WINKLER, A. W. AND DANOWSKI, T. S.: Transfers of cell sodium and potassium in experimental and clinical conditions. J. Clin. Investigation, 27: 74-81, 1948.
72. ENGEL, F. L. AND MARTIN, S. P.: Hypokalemia masking the symptoms of hypocalcemia. Am. J. Med., 4: 455, 1948.
73. ENGEL, F. L., MARTIN, S. P. AND TAYLOR, H.: Relation of potassium to neurologic manifestation of hypocalcemic tetany. Bull. Johns Hopkins Hosp., 84: 285-301, 1949.
74. FENN, W. O.: The deposition of potassium and phosphate with glycogen in rat livers. J. Biol. Chem., 128: 297-307, 1939.
75. FENN, W. O.: The fate of potassium liberated from muscles during activity. Am. J. Physiol., 127: 356-373, 1939.
76. FENN, W. O.: Potassium. Sci. Am., 181: 16-21, 1949.
77. FENN, W. O.: The role of potassium in physiological processes. Physiol. Rev., 20: 377-415, 1940.
78. FENN, W. O. AND COBB, D. M.: The potassium equilibrium in muscle. J. Gen. Physiol., 17: 629-656, 1934.
79. FENN, W. O. AND HAEGE, L. F.: The deposition of glycogen with water in the livers of cats. J. Biol. Chem., 136: 87-101, 1940
80. FENN, W. O., KOENEMANN, R. H., FAVATA, B. V. AND SHERIDAN, E. T.: The role of lactic acid in the movements of potassium. Am. J. Physiol., 131: 494-508, 1940.

81. Fenn, W. O., Wilde, W. S., Boak, R. A. and Koenemann, R. H.: The effect of blood flow on potassium lib eration from muscle. Am. J. Physiol., 128: 139-146, 1939.
82. Ferrebee, J. W., Gerity, M. K., Atchley, D. W. and Loeb, R. F.: Behavior of electrolytes in familial periodic paralysis. Arch. Neurol. & Psychiat., 44: 830-840, 1940.
83. Ferrebee, J. W., Parker, D., Carnes, W. H., Gerity, M. K., Atchley, D. W. and Loeb, R. F.: Certain effects of desoxycorticosterone; the development of "diabetes insipidus" and replacement of muscle potassium by sodium in normal dogs. Am. J. Physiol., 135: 230-237, 1941.
84. Ferrebee, J. W., Ragan, C., Atchley, D. W. and Loeb, R. F.: Desoxycorticosterone esters. Certain effects in the treatment of Addison's Disease. J. Am. M. A., 113: 1725-1731, 1939.
85. Finch, C. A., Sawyer, C. G. and Flynn, J. M.: Clinical syndrome of potassium intoxication. Am. J. Med., 1: 337-352, 1946.
86. Flett, J., Jr., Pratt, E. L. and Darrow, D. C.: Methods used in treatment of diarrhea with potassium and sodium salts. Pediatrics, 4: 604-619, 1949.
87. Follis, R. H., Jr., Orent-Keiles, E. and McCollum, E. V.: The production of cardiac and renal lesions in rats by a diet extremely deficient in potassium. Am. J. Path., 18: 29-39, 1942.
88. Forsham, P. H., Thorn, G. W., Prunty, F. T. G. and Hills, A. G.: Clinical studies with pituitary adrenocorticotropin. J. Clin. Endocrinol., 8: 15-66, 1948.
89. Foulks, J. G., Mudge, G. H. and Gilman, A.: Effect of lithium on the renal excretion of potassium. Federation Proc., 9: 41-42, 1950.
90. Fourman, P., Kepler, E. J., Reifenstein, E. C., Jr. and Dempsey, E. F.: Effect of a single dose of desoxycorticosterone acetate on electrolyte metabolism. J. Clin. Endocrinol., 9: 660-661, 1949.
91. Fox, C. L., Jr. and Baer, H.: Redistribution of potassium, sodium, and water in burns and trauma and its relation to the phenomena of shock. Am. J. Physiol., 151: 155-167, 1947.
92. Frenkel, M., Groen, J. and Willebrands, A. F.: Low serum potassium level during recovery from diabetic coma with special reference to its cardiovascular manifestations. Arch. Int. Med., 80: 728-738, 1947.
93. Friedman, S. M., Polley, J. R. and Friedman, C. L.: Effect of desoxycorticosterone acetate on blood pressure, renal function, and electrolyte pattern in the intact rat. J. Exper. Med., 87: 329-338, 1948.
94. Gamble, J. L. and McIver, M. A.: A study of the effects of pyloric obstruction in rabbits. J. Clin. Investigation, 1: 531-545, 1925.
95. Gamble, J. L., Ross, G. S. and Tisdall, F. F.: Metabolism of fixed base during fasting. J. Biol. Chem., 57: 633-695, 1923.
96. Gamble, A. H., Wiese, H. F. and Hansen, A. E.: Marked hypokaliemia in prolonged diarrhea: possible effect on heart. Pediatrics, 1: 58-65, 1948.
97. Gardner, L. I., MacLachlan, E. A., Terry, M. L., McArthur, J. W. and Butler, A. M.: Chloride diarrhea and systemic alkalosis in potassium deficiency. Federation Proc., 8: 201, 1949.
98. Gardner, L. I., Talbot, N. B., Cook, C. D., Berman, H. and Uribe, R. C.: Effect of potassium deficiency on carbohydrate metabolism. J. Clin. Investigation, 28: 784, 1949.
99. Gass, H., Cherkasky, M. and Savitsky, N.: Potassium and periodic paralysis. A metabolic study and physiological considerations. Medicine, 27: 105-137, 1948.
100. Govan, C. D., Jr. and Darrow, D. C.: The use of potassium in the treatment of the dehydration of diarrhea in infants. J. Pediat., 28: 541-549, 1946.
101. Govan, C. D., Jr. and Weiseth, W. M.: Potassium intoxication. Report of an infant surviving a serum potassium level of 12.27 millimoles per liter. J. Pediat., 28: 550-553, 1946.
102. Greenman, L., Mateer, F. M., Gow, R. C., Peters, J. H. and Danowski, T. S.: Some observations on the development of hypokalemia during therapy of diabetic acidosis in juvenile and young adult subjects. J. Clin. Investigation, 28: 409-413, 1949.
103. Guest, G. M. and Rapoport, S.: Electrolytes of blood plasma and cells in diabetic acidosis and during recovery. Proc. Am. Diab. Assoc., 7: 95-115, 1947.
104. Hahn, L., Hevesey, G. and Rebbe, O. H.: Do the potassium ions inside the muscle cells and blood corpuscles exchange with those present in the plasma? Biochem. J., 33: 1549-1558, 1939.
105. Harris, J. E.: The influence of the metabolism of human erythrocytes on their potassium content. J. Biol. Chem., 141: 579-595, 1941.
106. Harrison, H. E. and Darrow, D. C.: The distribution of body water and electrolytes in adrenal insufficiency. J. Clin. Investigation, 17: 77-86, 1938.
107. Harrison, H. E. and Darrow, D. C.: Renal function in experimental adrenal insufficiency. Am. J. Physiol., 125: 631-643, 1939.
108. Harrison, H. E., Harrison, H. C., Tompsett, R. R. and Barr, D. P.: Potassium deficiency in a case of lymphosarcoma with the sprue syndrome. Am. J. Med., 2: 131-143, 1947.
109. Hastings, A. B. and Buchanan, J. M.: The role of intracellular cations on liver glycogen formation in vitro. Proc. Nat. Acad. Sc., 28: 478-482, 1942.
110. Hastings, A. B. and Eichelberger, L.: The exchange of salt and water between muscle and blood. I. The effect of an increase in total body water produced by the intravenous injection of isotonic salt solutions. J. Biol. Chem., 117: 73-93, 1937.
111. Helmsworth, J. A. and Keefer, M. L.: Potassium content of normal cerebrospinal fluid. J. Lab. & Clin. Med., 32: 1486-1490, 1947.
112. Heppel, L. A.: The diffusion of radioactive sodium into the muscles of potassium-deprived rats. Am. J. Physiol., 128: 449-454, 1940.

113. Heppel, L. A.: The electrolytes of muscle and liver in potassium-depleted rats. Am. J. Physiol., 127: 385-392, 1939.
114. Hevesy, G. and Hahn, L.: Exchange of cellular potassium. Det. Kgl. Danske Videnskabernes Selskab. Biologiske Meddelelser., 14: 1-27, 1941.
115. Hoagland, H. and Stone, D.: Brain and muscle potassium in relation to stressful activities and adrenal cortex function. Am. J. Physiol., 152: 423-435, 1948.
116. Hodgkin, A. L. and Huxley, A. F.: Ionic exchange and electrical activity in nerve and muscle. Abst. of Communications of XVIII Internat. Physiol. Congress, Copenhagen: Aug. 15 to 18, 1950: 36-38.
117. Hoff, H. E., Humm, D. G. and Winkler, A. W.: Concentration of potassium in serum and response to vagal stimulation in the dog. Am. J. Phy iol., 142: 627-632, 1944
118. Hoff, H. E., Smith, P. K. and Winkler, A. W.: The cause of death in experimental anuria. J. Clin. Investigation, 20: 607-624, 1941.
119. Hoff, H. E., Smith, P. K. and Winkler, A. W.: The relation of blood pressure and concentration in serum of potassium, calcium and magnesium. Am. J. Physiol., 127: 722-730, 1939.
120. Hoff, H. E., Winkler, A. W. and Smith, P. K.: Recovery of fatigued muscle following intravenous injection of potassium chloride. Am. J. Physiol., 131: 615-618, 1940.
121. Holler, J. W.: Potassium deficiency occurring during the treatment of diabetic acidosis. J. Am. M. A. 131: 1186-1189, 1946.
122. Holmes, P. E. B., Jenden, D. J. and Taylor, D. B.: Interaction between curare and the potassium ion at the motor end-plate. Nature, 162: 217, 1948.
123. Holt, L. E., Courtney, A. M. and Fales, H. L.: The chemical composition of diarrheal as compared with normal stools in infants. Am. J. Dis. Child., 9: 213-224, 1915.
124. Howard, J. E. and Carey, R. A.: The use of potassium in therapy. J. Clin. Endocrinol., 9: 691-713, 1949.
125. Ingle, D. J., Li, C. H. and Evans, H. M. The effect of adrenocorticotrophic hormone on the urinary excretion of sodium, chloride, potassium, nitrogen and glucose in normal rats. Endocrinology, 39: 32-42, 1946.
126. Ingle, D. J., Prestrud, M. C., Li, C. H. and Evans, H. M. The relationship of diet to the effect of adrenocorticotrophic hormone upon urinary nitrogen, glucose and electrolytes. Endocrinology, 41: 170-176, 1947.
127. Ingraham, R. C. and Visscher, M. B. Inverse concentration ratios for sodium and potassium in gastric juice and blood plasma. Proc. Soc. Exper. Biol. & Med., 30: 464-466, 1932.
128. Irwin, L., Berger, E. Y., Rosenberg, B. and Jackenthal, R. The effect of a cation exchange resin on electrolyte balance and its use in edematous states. J. Clin. Investigation, 28: 1403-1411, 1950.
129. Joseph, M., Cohn, W. E. and Greenberg, D. M. Studies in mineral metabolism with the aid of artificial radioactive isotopes. II. Absorption, distribution, and excretion of potassium. J. Biol. Chem., 128: 673-683, 1939.
130. Kamminga, C. E., Willebrands, A. F., Groen, J. and Blickman, J. R. Effect of insulin on the potassium and inorganic phosphate content of the medium in experiments with isolated rat diaphragms. Science, 111: 30-31, 1950.
131. Keith, N. M. and Burchell, H. B. Clinical intoxication with potassium: its occurrence in severe renal insufficiency. Am. J. M. Sc., 217: 1-12, 1949.
132. Keith, N. M., King, H. E. and Osterberg, A. E.: Serum concentration and renal clearance of potassium in severe renal insufficiency in man. Arch. Int. Med., 71: 675-701, 1943.
133. Keith, N. M. and Osterberg, A. E.: The tolerance for potassium in severe renal insufficiency: a study of ten cases. J. Clin. Investigation, 26: 773-783, 1947.
134. Keith, N. M., Osterberg, A. E. and Burchell, H. B.: Some effects of potassium salts in man. Ann. Int. Med., 16: 879-892, 1942.
135. Kennedy, T. J., Jr., Winkley, J. H. and Dunning, M. F.: Gastric alkalosis with hypokalemia. Am. J. Med., 6: 790-794, 1949.
136. Kepler, E. J., Sprague, R. G., Clagett, O. T., Power, M. H., Mason, H. L. and Rogers, H. M.: Adrenal cortical tumor associated with Cushing's syndrome. Report of a case with metabolic studies and remarks on the pathogenesis of Cushing's syndrome. J. Clin. Endocrinol., 8: 499-531, 1948.
137. Kerr, S. E.: Studies on the inorganic composition of blood: III. The influence of serum on the permeability of erythrocytes of potassium and sodium. J. Biol. Chem., 85: 47-64, 1929.
138. Keynes, R. D. and Lewis, P. R.: The movements of sodium and potassium during nervous activity. Abst. of Communications of XVIII Internat. Physiol. Congress, Copenhagen: Aug. 15 to 18, 1950: 298-299.
139. Kornberg, A. and Endicott, K. M.: Potassium deficiency in the rat. Am. J. Physiol., 145: 291-298, 1946.
140. Kuhlmann, D., Ragan, C., Ferrebee, J. W., Atchley, D. W. and Loeb, R. F.: Toxic effects of desoxycorticosterone esters in dogs. Science, 90: 496-497, 1939.
141. Kurnick, N. B.: Permeability of the human erythrocyte to sodium and potassium. J. Biol. Chem., 140: 581-595, 1941.
142. Leaf, A., Camara, A. A. and Albertson, B.: Renal tubular secretion of potassium in man. J. Clin. Investigation, 28: 1526-1533, 1949.
143. Levitt, M. F. and Gaudino, M.: Use of radioactive isotopes to measure intracellular cation concentrations in the normal dog. Am. J. Physiol., 159: 67-72, 1949.
144. Logsdon, C. S. and McGavack, T. H.: Death, probably due to potassium deficiency, following control of diabetic coma. J. Clin. Endocrinol. 8: 658-665, 1948.
145. Lorincz, E. and Nador, K.: Chemistry of human saliva. Orvosi Hetilap, 89: 567-571, 1948.
146. Manery, J. F. and Hastings, A. B.: The distribution of electrolytes in mammalian tissues. J. Biol. Chem., 127: 657-676, 1939.

147. MARCHAND, J. F. AND FINCH, C. A.: Fatal spontaneous potassium intoxication in uremia. Arch. Int. Med., 73: 384-390, 1944.
148. MARTIN, H. E. AND WEETMAN, H.: Serum potassium, magnesium, and calcium levels in diabetic acidosis. J. Clin. Investigation, 26: 217-228, 1947.
149. MASON, H. L., POWER, M. H., RYNEARSON, E. H., CIARAMELLI, L. C., LI, C. H. AND EVANS, H. M.: Results of administration of anterior pituitary adrenocorticotropic hormone to a normal human subject. J. Clin. Endocrinol., 8: 1-14, 1948.
150. MATERR, F. M., GREENMAN, L., AUSTIN, A. C., PETERS, J. H., MERMELSTEIN, H. A., WEIGAND, F. A. AND DANOWSKI, T. S.: The use of potassium chloride in the pre-operative treatment of pyloric stenosis in infants. Am. J. M. Sc., In press.
151. MATERR, F. M., GREENMAN, L., PETERS, J. H., GOW, R. C. AND DANOWSKI, T. S.: The occurrence of potassium U/P ratios lower than 1.0. Federation Proc., 8: 107-108, 1949.
152. MILLER, H. C. AND DARROW, D. C.: Relation of muscle electrolyte to alterations in serum potassium and to the toxic effects of injected potassium chloride. Am. J. Physiol., 130: 747-758, 1940.
153. MUDGE, G. H., AMES, A. III, FOULKS, J. AND GILMAN, A.: Effect of drugs on renal secretion of potassium in the dog. Am. J. Physiol., 161: 151-158, 1950.
154. MUDGE, G. H., FOULKS, J. AND GILMAN, A.: The renal excretion of potassium. Proc. Soc. Exper. Biol. & Med., 67: 545-547, 1948.
155. MUDGE, G. H., FOULKS, J. AND GILMAN, A.: Renal secretion of potassium in the dog during cellular dehydration. Am. J. Physiol., 161: 159-166, 1950.
155a. MUDGE, G. H. AND VISLOCKY, K.: Electrolyte changes in human striated muscle in acidosis and alkalosis. J. Clin. Investigation, 28: 482-486, 1949.
156. MUNTWYLER, E., MELLORS, R. C., MAUTZ, F. R. AND MANGUN, G. H.: Electrolytes and water equilibria in the dog. II. Electrolyte and water exchange between skeletal muscle and blood in adrenal insufficiency. J. Biol. Chem., 134: 367-387, 1940.
157. MCCANCE, R. A.: Renal function in early life. Physiol. Rev., 28: 331-348, 1948.
158. MCCHESNEY, E. W. AND MCAULIFF, J. P.: Effects of some ion exchange resins on mineral metabolism of rats. Am. J. Physiol., 160: 264-276, 1950.
159. MCQUARRIE, I., JOHNSON, R. M. AND ZIEGLER, M. R.: Plasma electrolyte disturbance in a patient with hypercorticoadrenal syndrome contrasted with that found in Addison's disease. Endocrinology, 1: 762-772, 1937.
160. NACHMANSOHN, D.: The role of acetylcholine in the exchange of ions across axional surface membranes. Abst. of Communications of XVIII Internat. Physiol. Congress, Copenhagen, Aug. 15 to 18, 1940: 371-372.
161. NADLER, C. S., BELLET, S., DILLON, E. S., AND LANNING, M.: Studies on the serum potassium in diabetic acidosis. Proc. Am. Diab. Assoc., 9: 63-81, 1949.
162. NADLER, C. S., BELLET, S., AND LANNING, M.: Influence of the serum potassium and other electrolytes on the electrocardiogram in diabetic acidosis. Am. J. Med., 5: 838-848, 1948.
163. NEEDHAM, J. W.: The metabolism of potassium in diabetic acidosis. Yale J. Biol. & Med., 22: 39-55, 1949.
164. NICHOLSON, W. M., AND BRANNING, W. S.: Potassium deficiency in diabetic acidosis. J. Am. M. A., 134: 1292-1294, 1947.
165. NOONAN, T. R., FENN, W. O. AND HAEGE, L.: The distribution of injected radioactive potassium in rats. Am. J. Physiol., 132: 474-488, 1941.
166. PEARSON, O. H. AND ELIEL, L. P.: Postoperative alkalosis and potassium deficiency. J. Clin. Investigation, 28: 803, 1949.
167. PETERS, J. P.: The distribution and movement of water and solutes in the human body. Yale J. Biol. & Med., 5: 431-467, 1933.
168. PETERS, J. P. AND VAN SLYKE, D. D.: Quantitative clinical chemistry. Interpretations. The Williams & Wilkins Co., Baltimore, 1: Chap. 15, 1931.
169. PHILIPS, F. S., GILMAN, A., KOELLE, E. S., MCNAMARA, B. P. AND ALLEN, R. P.: Water and electrolyte balance in dogs intoxicated with nitrogen mustard. Am. J. Physiol., 155: 295-308, 1948.
170. PUDENZ, R. H., MCINTOSH, J. F. AND MCEACHERN, D.: The role of potassium in familial periodic paralysis. J. Am. M. A., 111: 2253-2258, 1938.
171. RABINOWITCH, I. M.: On the relative proportions of sodium, potassium, calcium, and magnesium in blood plasma in renal disease. J. Biol. Chem., 62: 667-673, 1925.
172. RANDALL, H. T., HABIF, D. V., LOCKWOOD, J. S. AND WERNER, S. C.: Potassium deficiency in surgical patients. Surgery, 26: 341-363, 1949.
173. ROBERTS, I. Z.: Role of potassium in cellular metabolism. Federation Proc., 9: 219, 1950.
174. RUBIN, M. A., HOFF, H. E., WINKLER, A. W. AND SMITH, P. K.: Intravenous potassium, calcium, and magnesium and the cortical electrogram of the cat. J. Neurophysiol., 6: 23-28, 1943.
175. SAEMUNDSSON, J.: Potassium concentration in human gastric juice. Acta med. Scandinav., 130: (Supp. 208): 1-139, 1948.
176. SCUDDER, J., ZWEMER, R. L. AND WHIPPLE, A. O.: Acute intestinal obstruction. Evaluation of results in two thousand, one hundred fifty case; with detailed studies of twenty-five showing potassium as a toxic factor. Ann. Surg., 107: 161-197, 1938.
177. SELDIN, D. W. AND TARAIL, R.: The metabolism of glucose and electrolytes in diabetic acidosis. J. Clin. Investigation, 29: 552-565, 1950.
178. SHERRY, S., EICHNA, L. W. AND EARLE, D. P.: The low potassium syndrome in chronic nephritis. J. Clin. Investigation, 27: 556, 1948.

179. Sinden, R. H., Tullis, J. L. and Root, H. F.: Serum potassium levels in diabetic coma. New England J. Med., 240: 502–505, 1949.
180. Smillie, W. G.: Potassium poisoning in nephritis. Arch. Int. Med., 16: 330-339, 1915.
181. Smith, S. G., Black-Schaffer, B. and Lasater, T. E.: Potassium deficiency syndrome in the rat and the dog. A description of the muscle changes in the potassium-depleted dog. Arch. Path., 49: 185–199, 1950.
182. Sprague, R. G., Power, M. H., Mason, H. L., Albert, A., Mathieson, D. H., Hench, P. S., Kendall, E. C., Slocumb, C. H. and Polley, H. F.: Observations on the physiologic effects of Cortisone and ACTH in man. Arch. Int. Med., 85: 199–258, 1950.
183. Squires, R. D., Marsh, J. B. and Elkinton, J. R.: Unpublished data.
184. Steinbach, H. B.: Sodium and potassium in frog muscle. J. Biol. Chem., 133: 695-701, 1940.
185. Stephens, F. I.: Paralysis due to reduced serum potassium concentration during treatment of diabetic acidosis: Report of case treated with 33 grams of potassium chloride intravenously. Ann. Int. Med., 30: 1272-1286, 1949.
186. Stewart, H. J., Shepard, E. M. and Horger, E. L.: Electrocardiographic manifestations of potassium intoxication. Am. J. Med., 5: 821-827, 1948.
187. Stewart, H. J., Smith, J. J. and Milhorat, A. T.: Electrocardiographic and serum potassium changes in familial periodic paralysis. Am. J. M. Sc., 199: 789–795.
187a. Swinyard, E. A.: Effect of extracellular electrolyte depletion on brain electrolyte pattern and electroshock seizure threshold. Am. J. Physiol., 156: 163-169, 1949.
188. Szent-Gyorgyi, A.: Chemistry of muscular contraction. Academic Press, Inc., New York, 1947.
189. Talbott, J. H.: Periodic paraly is; a clinical syndrome. Medicine, 20: 85–143, 1941.
190. Tarail, R.: Electrocardiographic abnormalities in a case of uremia manifesting hyperpotassemia. Am. Heart J., 35: 665–673, 1948.
191. Tarail, R.: Relation of abnormalities in concentration of serum potassium to electrocardiographic disturbances. Am. J. Med., 5: 828–837, 1948.
192. Tarail, R. and Elkinton, J. R.: Potassium deficiency and the role of the kidney in its production. J. Clin. Investigation, 28: 99-113, 1949.
193. Tarail, R. and Seldin, D. W.: Reabsorption of potassium by the kidney. Federation Proc., 8: 154, 1949.
194. Terner, C., Eggleston, L. V. and Krebs, H. A.: The role of glutamic acid in the transport of potassium in brain and retina. Biochem. J., 47: 139-149, 1950.
195. Thorn, G. W., Forsham, P. H., Frawley, T. F., Hill, S. R., Jr., Roche, M., Staehelin, D. and Wilson, D. L.: The clinical usefulness of ACTH and Cortisone. New England J. Med., 242: 783-793, 1950.
196. Thorn, G. W., Forsham, P. H., Frawley, T. F., Hill, S. R., Jr., Roche, M., Staehelin, D. and Wilson, D. L.: The clinical usefulness of ACTH and Cortisone. New England J. Med., 242: 824–834, 1950.
197. Thorn, G. W., Forsham, P. H., Frawley, T. F., Hill, S. R., Jr., Roche, M., Staehelin, D. and Wilson, D. L.: The clinical usefulness of ACTH and Cortisone. New England J. Med., 242: 865–872, 1950.
198. Tuynman, P. E. and Wilhelm, S. K.: Potassium deficiency associated with diabetic acidosis. Ann. Int. Med., 29: 356-361, 1948.
199. Walker, S. M.: Action potentials in rat muscle with twitch tension potentiated by KCl treatment, adrenalectomy, tetanus and treppe. Am. J. Physiol., 154: 63-72, 1948.
200. Wallace, W. M. and Moll, F. C.: Balance and electrocardiographic studies in potassium deficiency. Am. J. Dis. Child., 77: 132-133, 1949.
201. Weissberg, J., McGavack, T. H., Shearman, A. M. and Drekter, I. J.: Behavior of electrolytes during treatment of diabetic keto-acidosis. J. Clin. Endocrinol., 9: 673, 1949.
202. Weissberg, J., McGavack, T. H., Shearman, A. M. and Drekter, I. J.: Electrolyte balance in uncontrolled and controlled diabetic acidosis and ketosis. Proc. Am. Diab. Assoc., 9: 141-146, 1949.
203. Welt, L. G., Jr., Orloff, J., Kydd, D. M. and Oltman, J. E.: An example of cellular hyperosmolarity. J. Clin. Investigation, 29: 935-939, 1950.
204. Wilde, W. S.: The distribution of potassium in the cat after intravascular injection. J. Biol. Chem., 128: 309-317, 1939.
205. Wiley, F. H. and Wiley, L. L.: The inorganic salt balance during dehydration and recovery. J. Biol. Chem., 101: 83-92, 1933.
206. Willebrands, A. F., Groen, J. and Frenkel, M.: Potassium exchange during treatment of diabetic coma. Nederlandsch Tijdschrift v. Geneeskunde, 92: 3929-3940, 1948.
207. Willebrands, A. F., Groen J., Kamminga, C. E. and Blickman, J. R.: Quantitative aspects of the action of insulin on the glucose and potassium metabolism of the isolated rat diaphragm. Science, 112: 277-278, 1950.
208. Willson, D. M., Power, M. H. and Kepler, E. J.: Alkalosis and low plasma potassium in a case of Cushing's syndrome: a metabolic study. J. Clin. Investigation, 19: 701-707, 1940.
209. Wilson, H. E. C.: Observations on the clearance of potassium by the kidneys. Biochem. J., 43: xxxi (Proc.), 1948.
210. Winkler, A. W., Danowski, T. S., Elkinton, J. R. and Peters, J. P.: Electrolyte and fluid studies during water deprivation and starvation in human subjects, and the effect of ingestion of fish, of carbohydrate, and of salt solutions. J. Clin. Investigation, 23: 807–815, 1944.
211. Winkler, A. W. and Hoff, H. E.: Potassium and the cause of death in traumatic shock. Am. J. Physiol., 139: 686–692, 1943.
212. Winkler, A. W., Hoff, H. E. and Smith, P. K.: Cardiovascular effects of potassium, calcium, magnesium and barium. An experimental study of toxicity and rationale of use in therapeutics. Yale J. Biol. & Med., 13: 123–132, 1940.

213. WINKLER, A. W., HOFF, H. E. AND SMITH, P. K.: Electrocardiographic changes and concentration of potassium in serum following intravenous injection of potassium chloride. Am. J. Physiol., 124: 478–483, 1938.
214. WINKLER, A. W., HOFF, H. E. AND SMITH, P. K.: Factors affecting the toxicity of potassium. Am. J. Physiol., 127: 430–436, 1939.
215. WINKLER, A. W., HOFF, H. E. AND SMITH, P. K.: The toxicity of orally administered potassium salts in renal insufficiency. J. Clin. Investigation, 20: 119–126, 1941.
216. WINKLER, A. W., HOFF, H. E. AND SMITH, P. K.: Toxicity of potassium in adrenalectomized dogs. Am. J. Physiol., 133: 494–495, 1941.
217. WINKLER, A. W., HOFF, H. E. AND SMITH, P. K.: Unpublished observations.
218. WINKLER, A. W. AND SMITH, P. K.: The apparent volume of distribution of potassium injected intravenously. J. Biol. Chem., 124: 589–598, 1938.
219. YANNET, H.: Changes in the brain resulting from depletion of extracellular electrolytes. Am. J. Physiol., 128: 683–689, 1940.
220. ZWEMER, R. L. AND SCUDDER, J.: Blood potassium during experimental shock. Surgery, 4: 510–527, 1938.
221. ZWEMER, R. L. AND TRUSZKOWSKI, R. The importance of corticoadrenal regulation of potassium metabolism. Endocrinology, 21: 40–49, 1937.
222. ZWEMER, R. L. AND TRUSZKOWSKI, R.: Potassium: a basal factor in the syndrome of corticoadrenal insufficiency. Science, 83: 558–560, 1936.