Intracellular Granules of the Renal Medulla in a Case of Potassium Depletion Due to Renal Potassium Wasting

Electron Microscopic Comparison With Renal Medullary Granules in the Potassium-Depleted Rat

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An electron microscopic comparison was made of intracellular granules of the renal papilla and inner medulla in two types of potassium depletion: one in a 47-year-old white male with chronic potassium-wasting renal disease and the other in the experimentally depleted rat. The granules in both cases were composed of small and large vesicles; myelin figures; small particles; and dense bodies, with a partial, or complete, single limiting membrane. Ultrastructurally, the constituent elements of the granules were essentially the same in the two types of potassium depletion. It was concluded that the intracellular granules in the human tissue were the result of potassium depletion and a counterpart to those in the potassium-depleted rat. (Am J Pathol 91:299–312, 1978)

POTASSIUM-DEPLETED HUMANS AND RATS develop vasopressin-resistant hyposthenuria,[1-3] a form of nephrogenic diabetes insipidus; in the rat, conspicuous intracellular granules accumulate in the renal papilla and inner medulla.[4-6] The granules contain glycoprotein [5] and, by light microscopy, are periodic acid–Schiff (PAS)-positive,[4-6] diastase-resistant,[4,5] and argyrophilic.[7] They involve all principal cell types in the area (epithelium, endothelium, and interstitium);[4,6,8] the intensity of the lesion parallels the osmolar gradient of the renal papilla.[6] This peculiar, perhaps unique, cytologic finding has been reported only in association with potassium depletion and almost exclusively in rodents.[3] Thus, in humans, the renal histologic change commonly attributed to potassium depletion, ie, large vacuoles in epithelial cells of proximal tubules, is in the cortex.[1,3] Specifically, medullary granules characteristic of the potassium-deficient rat have not been a feature of the renal lesion in humans.[3]

By electron microscopy, these granules in the rat contain modified membrane in the form of vesicles, myelin figures, smaller particles, and

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amorphous dense bodies, the whole usually enclosed in a single limiting membrane.[8-10] When stained for acid phosphatase by Gomori's method, the granules show the lead reaction product.[8] This finding is associated with a significant rise in acid phosphatase activity of both the papillary homogenate [8,11] and the isolated granules.[11] With potassium repletion, most of the granules lose their limiting membrane, disintegrate, and soon disappear; a few, however, may remain in the form of residual dense bodies.[8,10] In 1964, on the basis of ultrastructure, glycoprotein content, and positive staining for acid phosphatase (associated with an increase in local tissue acid phosphatase) the granules were classified as lysosomes.[8] More recent studies of the rat inner medulla have shown that increasing synthesis of membrane phospholipid [12] and increasing acid hydrolase activity [11] parallel the duration of potassium depletion, and degradation of phospholipid remains unimpaired.[13] Other reports have increased our knowledge of the granules' ultrastructure.[14-17] In summary, these findings strongly support the view that the multivesicular bodies are a type of lysosome.

We have previously described renal medullary intracellular granules in 2 adult brothers [7] and a 4-year-old boy [18] in association with chronic potassium depletion due to renal potassium wasting; in each case the cytoplasmic granules, by light microscopy, were similar to those of the potassium-depleted rat. These 3 patients, we believe, were examples or variants of the syndrome of hypokalemic alkalosis, juxtaglomerular cell hyperplasia, hyperaldosteronism, and normal blood pressure, described by Bartter and his associates.[19-21]

At necropsy, in 1974, renal tissue from one of the brothers became available for electron microscopic examination. Thin sections showed numerous intracellular granules containing membranous material in the papilla and inner medulla of both kidneys. The purpose of the present study is to compare the ultrastructure of these cytoplasmic bodies with that of renal medullary granules from the potassium-depleted rat. In making this comparison, we recognize that the mechanisms causing potassium depletion in the two models are dissimilar: chronic renal wasting in humans and acute dietary deprivation in the rat. Nevertheless, we hope to show that the intracellular granules of the renal medulla in the patient and in the experimental rat have essentially the same ultrastructure.

Materials and Methods

Clinical Abstract

The white male in this study was 47 years old at the time of death. From the age of 22 he had noted symptoms of potassium depletion: initially, paresthesia, pain, and stiffness in

the feet, and, later, polyuria, polydipsia, and intermittent muscular weakness of the lower legs.[22] He was hospitalized on numerous occasions in an effort to evaluate and treat his potassium-wasting renal disease. On one such occasion, when the patient was receiving a high potassium intake (~250 mEq/24 hr), chemical analyses showed the following: hypokalemia (~2.5 mEq/liter), hyperkaluria (~220 mEq/24 hr), decreased muscle potassium (60% of normal), and normal stool potassium (~10 mEq/24 hr). Aldosterone excretion was sometimes normal and at other times high. Plasma renin activity was increased. Open renal biopsy, with the patient in a state of partial potassium repletion, showed enlargement of juxtaglomerular bodies and PAS-positive intracellular granules involving epithelium, endothelium, and interstitium of the inner medulla. Treatment, consisting largely of potassium supplement with occasional trials of spironolactone and triamterene, failed to maintain a satisfactory level of serum potassium after the patient returned home from his period of hospitalization. This lack of therapeutic success was attributed in part to the fact that the patient, a partially compensated schizophrenic, rarely took the full dose of prescribed potassium supplement when at home. In March 1974, he sustained an acute myocardial infarction, complicated by subsequent episodes of congestive heart failure; 5 months later he was found dead in bed. On the basis of history and postmortem findings, death was attributed to ischemic heart disease, with myocardial potassium depletion a possible contributing cause.

Human Tissue

Approximately 8 hours after death, necropsy was performed at the Baroness Erlanger Hospital, Chattanooga, Tenn., and 24 hours later, formalin-fixed portions of each kidney were taken to the Veterans Administration Hospital, Nashville, Tenn. Forty-eight hours after original formalin fixation, tissue for electron microscopy was transferred from formalin to glutaraldehyde. For light microscopy, paraffin-embedded sections were stained with hematoxylin and eosin, with PAS reagent, and by Gomori's methenamine–silver technique. Portions of papilla and inner medulla were processed for electron microscopy.[23–25]

In addition, thin sections were stained for glycoprotein by Rambourg's method:[26,27] essentially, a light microscopic, methenamine–silver technique modified for electron microscopy. In our procedure, tissue which had been prefixed in glutaraldehyde and transferred to phosphate-buffered sucrose was embedded in araldite without postfixation in osmium tetroxide. Thin sections were placed on nickel grids and, following oxidation, were immersed in the heated methenamine–silver solution. Care was taken to ensure that unoxidized control sections received the same silver staining procedure as the oxidized sections.

Rat Tissue

The electron microscopic pattern of renal medullary intracellular granules for the potassium-depleted rat is well documented and highly reproducible.[10,12,16] For comparison with the human tissue, 4 normal Long-Evans rats, 2 males and 2 females weighing between 160 and 210 g, were used in the present study. One male and 1 female were given free access to a potassium-deficient diet (10 mEq K^+/kg; Teklad Mills Test Diets, Madison, Wis.) and to deionized distilled water. As controls, 1 male and 1 female were given free access to normal rat chow (350 mEq K^+/kg; Wayne Lab-Blox, Allied Mills, Inc., Chicago) and to tap water. At the end of 4 weeks, both groups of rats were anesthetized with sodium pentobarbital and, after removal of tissue, killed by exsanguination. For examination by light microscopy, portions of one kidney from each rat were fixed in 20% neutral buffered formalin and embedded in paraffin; sections were stained as described in *Human Tissue*. For examination by electron microscopy, portions of the opposite kidney were fixed in glutaraldehyde and processed as described in *Human Tissue*.

Leg muscle was analyzed for potassium content. From each rat, two samples (each weighing approximately 2 g) were dried *in vacuo*, given three 10-minute washings in ethyl ether to remove superficial triglycerides, and dried again to a constant weight. Each dried sample of muscle was digested in 15 ml of concentrated nitric acid. After removal of small lipid residue, the solution was transferred to a 100-ml volumetric flask and brought to volume with deionized distilled water. Five milliliters of the dilute solution was neutralized with concentrated ammonium hydroxide (approximately 0.8 ml was required) and analyzed for potassium in a Beckman Klina flame photometer. The value for the electrolyte (mEq/liter) was recalculated to express potassium as mEq per 100 g of muscle dry solids.

Results

Potassium Content of Rat Muscle

Evidence for potassium depletion in the 2 rats maintained on a potassium-deficient diet is shown in Table 1. Compared with a control rat of the same sex, the male showed a deficit of 43% of muscle potassium and the female showed a deficit of 41% of muscle potassium.

Rat Tissue: Light Microscopy

In the 2 rats maintained for 4 weeks on a potassium-deficient diet, intracellular PAS-positive, diastase-resistant, argyrophilic granules were present in epithelial, endothelial, and interstitial cells of the renal medulla and papilla. Although the granules were most conspicuous in the papilla and the intensity of the lesion paralleled the osmolar gradient from the inner medulla to the papillary tip, small collections of endothelial and interstitial cells containing PAS-positive granules were present in the outer medulla up to a narrow zone just under the corticomedullary junction. The overall pattern, ie, types and distribution of cells containing PAS-positive granules, was essentially identical to that described by others for the potassium-depleted rat.[4,6,8] The lesion was not seen in tissue from the 2 rats maintained on a normal diet.

Table 1—Potassium Content of Rat Muscle

Rat (category)	Diet* (mEq K^+/kg chow)	Sex	Muscle sample		
			No. 1†	No. 2†	Mean†
Control	350	M	47.7	49.5	48.6
Control	350	F	45.8	44.6	45.2
K^+-depleted	10	M	28.5	27.2	27.9
K^+-depleted	10	F	25.9	27.2	26.6

* All animals were on dietary regimen for 28 days.
† mEq K^+/100 g dry solids.

Rat Tissue: Electron Microscopy

In rat papilla (Figures 1, 3, and 5), intracellular granules induced by potassium depletion showed an internal structure similar to that previously described by others.[10,16] Cytomembranous material was present in the form of vesicles and myelin figures, together with small particles, amorphous dense bodies and, usually, a single limiting membrane. The granules were easily distinguished from mitochondria (Figures 1 and 8). Occasionally, smaller aggregates of membranous material (consisting largely of vesicles) were characterized by an irregular outline, absence of limiting membrane, and a close proximity to endoplasmic reticulum (Figures 1 and 3). The possibility was strongly considered that these small aggregates were immature granules or manifestations of autosequestration.

As was the case in sections studied by light microscopy, intracellular granules, characteristic of potassium depletion, were not seen in the electron micrographs of tissue from the 2 rats maintained on a normal diet.

Human Tissue: Light Microscopy

Observations are restricted to those which supplement a previously reported renal biopsy.[7] The lesion (intracellular PAS-positive granules of the papilla and medulla) was present in both kidneys. As in the rat, small scattered groups of endothelial and interstitial cells containing PAS-positive granules were present in the outer medulla up to, but not including, a narrow zone just beneath the corticomedullary border. In the human tissue, however, PAS-positive cells in the inner medulla and papilla tended to lie in longitudinal streaks parallel to the medullary rays. As a result, a uniform intensity of the lesion at a given horizontal level, as seen in the rat, was seldom present. Interstitial hyperplasia was more conspicuous in the human tissue, and, in contrast to the rat, a moderate amount of interstitial fibrosis was present in the area of the papillary tip. A number of the tubules were somewhat dilated. The concentration of PAS-positive cells was much greater than that seen previously at renal biopsy, and necropsy tissue demonstrated that cells with typical cytoplasmic granules were present in the body and tip of the papilla. Although many of the interstitial cells contained vacuoles, or vacuoles in combination with PAS-positive granules, the degree of vacuolization as judged by the number of foam cells was much less than that seen in the 4-year-old child previously described.[18] In the cortex, many of the juxtaglomerular bodies were moderately enlarged.

Human Tissue: Electron Microscopy

Electron micrographs of the human renal medulla showed autolytic effects of delayed fixation. Mitochondria were swollen, with only remnants of cristae remaining. Nuclear detail was absent. However, intracellular granules corresponding to those seen in light microscopy (despite some degree of swelling and partial loss of limiting membrane) were, for the most part, well preserved. A majority of epithelial, endothelial, and interstitial cells contained these granules, and in many cells the inclusions occupied a large proportion of the cytoplasm. The lesion was present in both kidneys. Granules contained modified membrane in the form of vesicles and myelin figures, together with small particles and residual dense bodies (Figures 2, 4, and 6). These intragranular structures appeared essentially identical to those seen in the potassium-depleted rat (Figures 1, 3, and 5).

Electron Microscopy: Silver Staining for Granule Glycoprotein

In both rat and human tissues, cytoplasmic granules showed a high content of silver reaction product when stained with methenamine–silver following oxidation (Figures 7 and 8). Control sections, not oxidized prior to silver staining, contained granules which were so faintly stained as to be barely discernible by electron microscopy.

Discussion

In the present study, specific cytoplasmic granules of the renal medulla in a case of chronic potassium deficiency were compared with those seen in the potassium-depleted rat. By light and electron microscopy, the granules were essentially similar in the two species. However, the overall histologic patterns differed in several details. In the human tissue, PAS-positive cells, although numerous, lacked the uniform distribution seen in the rat. Interstitial hyperplasia, in association with conspicuous foam cells containing PAS-positive granules and clear vacuoles, was a prominent feature in only the human tissue. Interstitial fibrosis, present to a moderate degree in the papilla of the man, was not seen in the rat. These differences may represent species variation or may reflect the basic dissimilarity in the manner in which potassium depletion was produced in the two models: recurring deficiency and repletion over many years in the man and acute dietary deprivation for a relatively short period in the rat. The possibility existed that a low-grade, intermittent, chronic infection (rather than the reaction to potassium depletion) may have been responsible for the interstitial fibrosis noted in the human papilla.

Several recent reports have described histologic changes of the renal

medulla in Bartter's syndrome.[28-30] Tissue obtained at biopsy showed hyperplasia of interstitial cells; in 1 case, hyperplasia was described as massive, with PAS-positive, argyrophilic, cytoplasmic granules in epithelial, endothelial, and interstitial cells.[29] In addition, inhibitors of prostaglandin synthesis have been found to improve the renal potassium wasting, nephrogenic diabetes insipidus, and hypokalemia of Bartter's syndrome.[29-31] The relationship of renal medullary interstitial cell hyperplasia and prostaglandin excess to the intracellular inclusions under discussion is unclear. However, we believe the evidence supports the concept that the granules are induced by potassium depletion, whether the result of renal potassium wasting in humans or dietary deprivation in the rat, and that they are a type of lysosome.

The following hypotheses regarding the origin of the granules presuppose that they are autophagic secondary lysosomes and that the cells of the renal papilla and inner medulla are, for unknown reasons, uniquely susceptible. In the first hypothesis, potassium deficiency renders certain intracellular membranes defective, causing the cell to reject the membranous material which must then be sequestered as an autophagosome. Increased membrane synthesis occurs in response to increased sequestration. Newly formed, potassium-deficient membranes are also defective and are sequestered in increasing quantities. In the cell, the result is an accumulation of large secondary lysosomes containing membranous material, often in the form of characteristic small vesicles. The second hypothesis requires the inactivation of lysosomal acid hydrolases as the direct or indirect result of potassium deficiency, perhaps through an alteration of intracellular hydrogen ion concentration. This enzyme inactivation prevents digestion of the products of normal sequestration within secondary lysosomes and thus leads to an accumulation of these organelles within the cell. Potassium repletion reactivates the hydrolytic enzymes and brings about a dissolution of the lysosomal aggregates. Either hypothesis, we believe, is compatible with the finding of increased membrane phospholipid synthesis during potassium depletion.[12] With regard to the finding of increased lysosomal acid hydrolase activity during potassium depletion,[11] the second hypothesis would presuppose a reactivation of the enzymes during the analytic procedure.

Conclusions

We have examined intracellular granules of the renal papilla and inner medulla in two examples of potassium depletion: an adult white male with chronic potassium-wasting renal disease of unknown origin and the experimentally depleted rat. Comparison of electron micrographs showed

that the cytoplasmic granules in the human and rat tissues were, with regard to their ultrastructure, composed of similar elements.

We believe that the granules observed in the human tissue were the result of potassium depletion and a counterpart to those in the potassium-depleted rat. We consider them to be autophagic secondary lysosomes, probably the result of accelerated sequestration of defective intracellular membrane or the result of inactivation of lysosomal acid hydrolase. However, the true origin and function of the granules, as well as the reason for their unique location along an osmolar gradient, remain to be determined.

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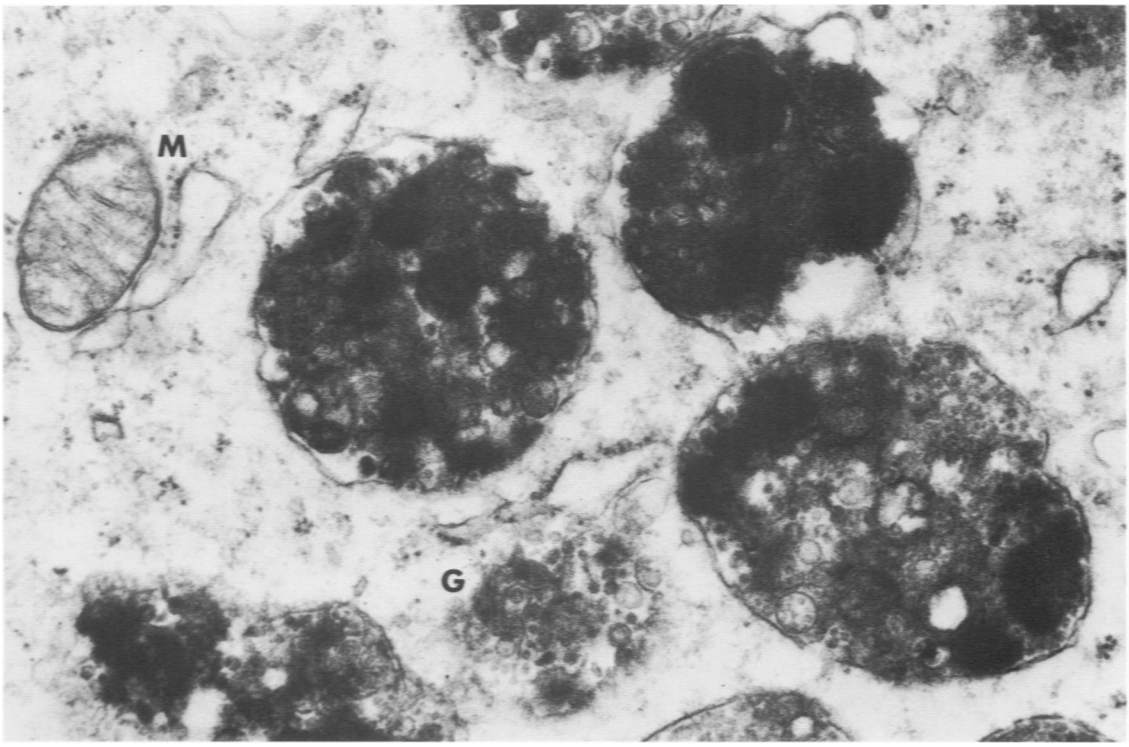
[*Illustrations follow*]



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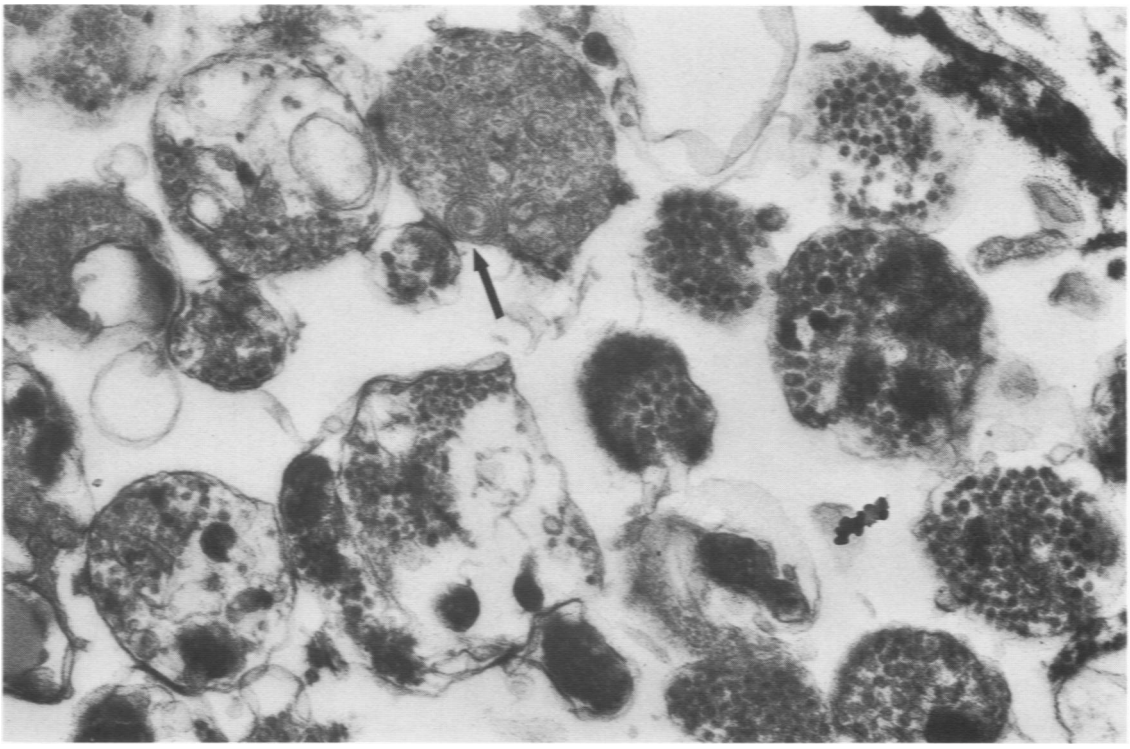

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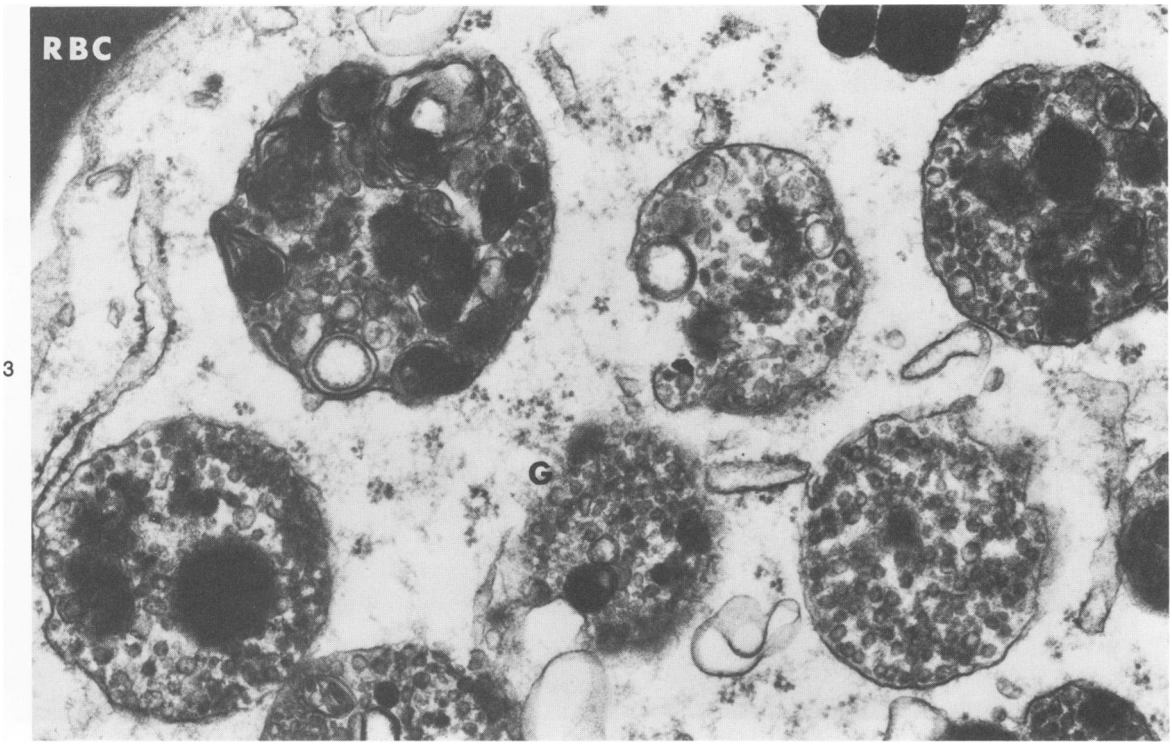
Figure 1—Epithelial cell from renal terminal collecting duct of rat receiving potassium-deficient diet for 28 days. Granules consisting of small and large vesicles, small particles, and dense bodies are characteristic of potassium depletion. Single limiting membrane is present but not always complete. Smaller granule (*G*) devoid of limiting membrane and in close proximity to endoplasmic reticulum may represent immature form. *M*, mitochondrion. (Uranyl acetate and lead citrate, ×37,500) **Figure 2**—Epithelial cell from renal terminal collecting duct of potassium-depleted patient described in text. Granules consist of small and large vesicles, small particles, and dense bodies. Membranous material in one granule suggests a myelin figure (*arrow*). Elements contained in granules appear structurally identical to those in granules from potassium-depleted rat (Figure 1). (Uranyl acetate and lead citrate, ×37,500)



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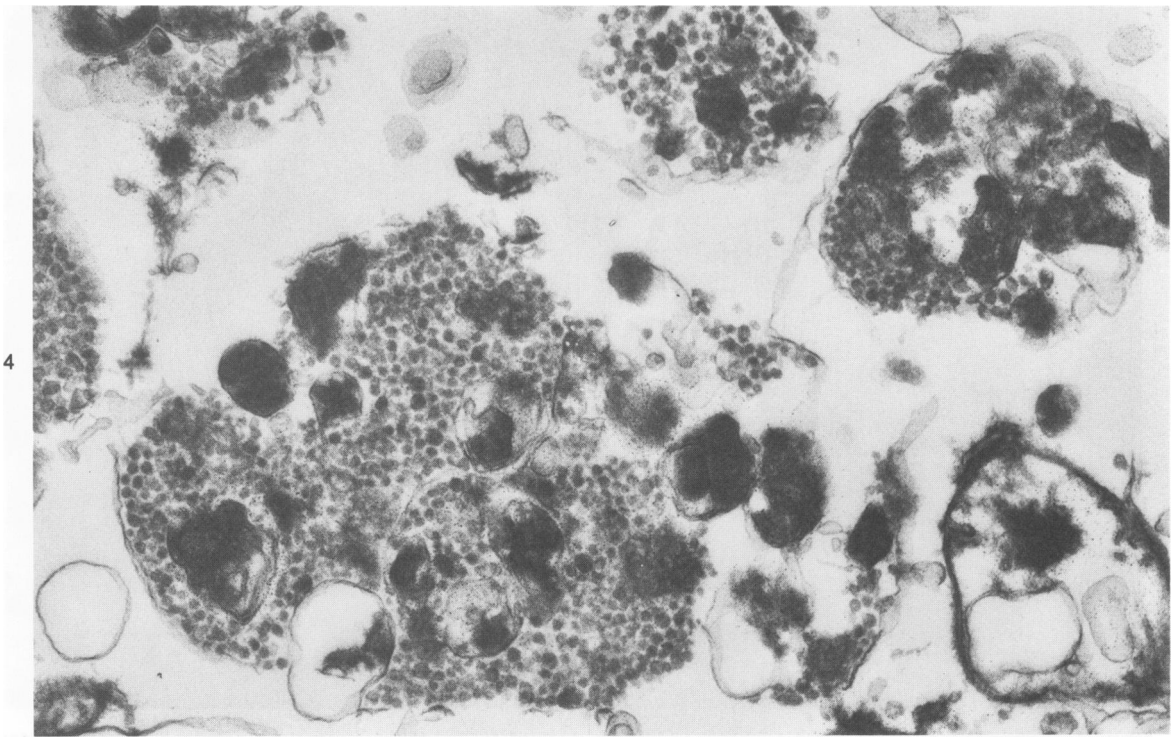

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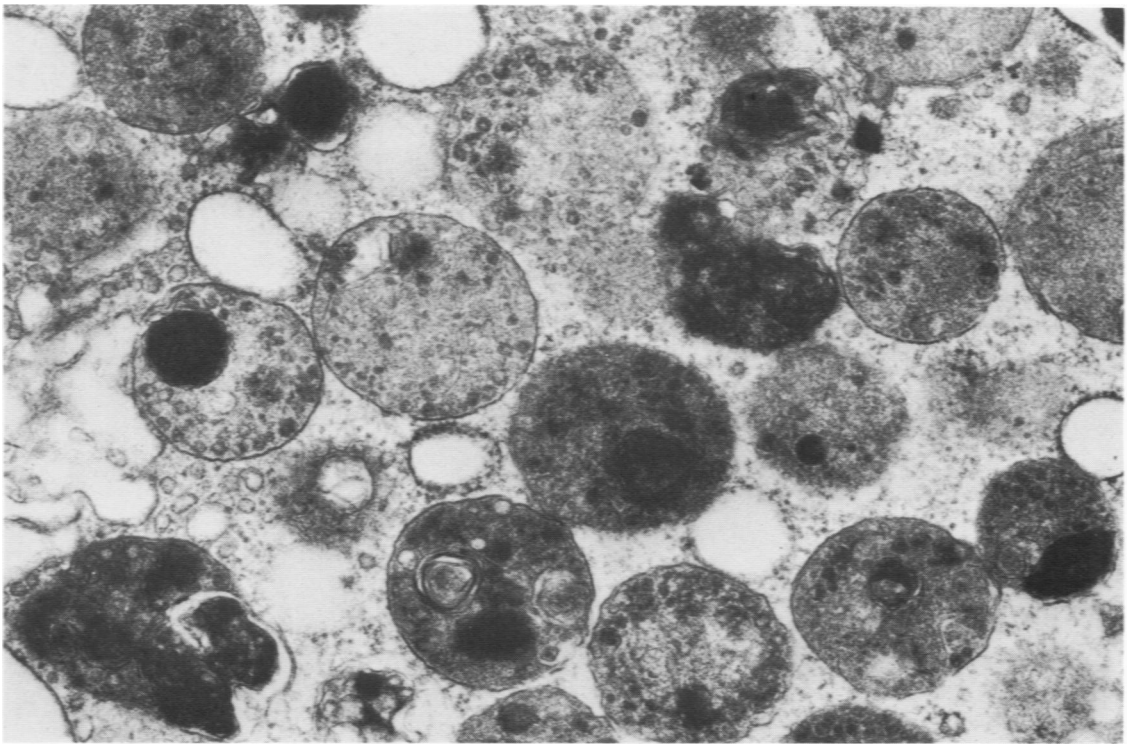
Figure 3—Endothelial cell from renal papilla of potassium-depleted rat. Granules, including possible immature form (*G*), are similar to those in epithelial cell (Figure 1). *RBC*, red blood cell. (Uranyl acetate and lead citrate, ×37,500) **Figure 4**—Endothelial cell from renal papilla of potassium-depleted patient. Granules, although larger, contain elements similar to those in epithelial cell (Figure 2). Increase in size of granules may represent aggregation of several smaller units. Small intragranular vesicles are especially numerous. (Uranyl acetate and lead citrate, ×37,500)



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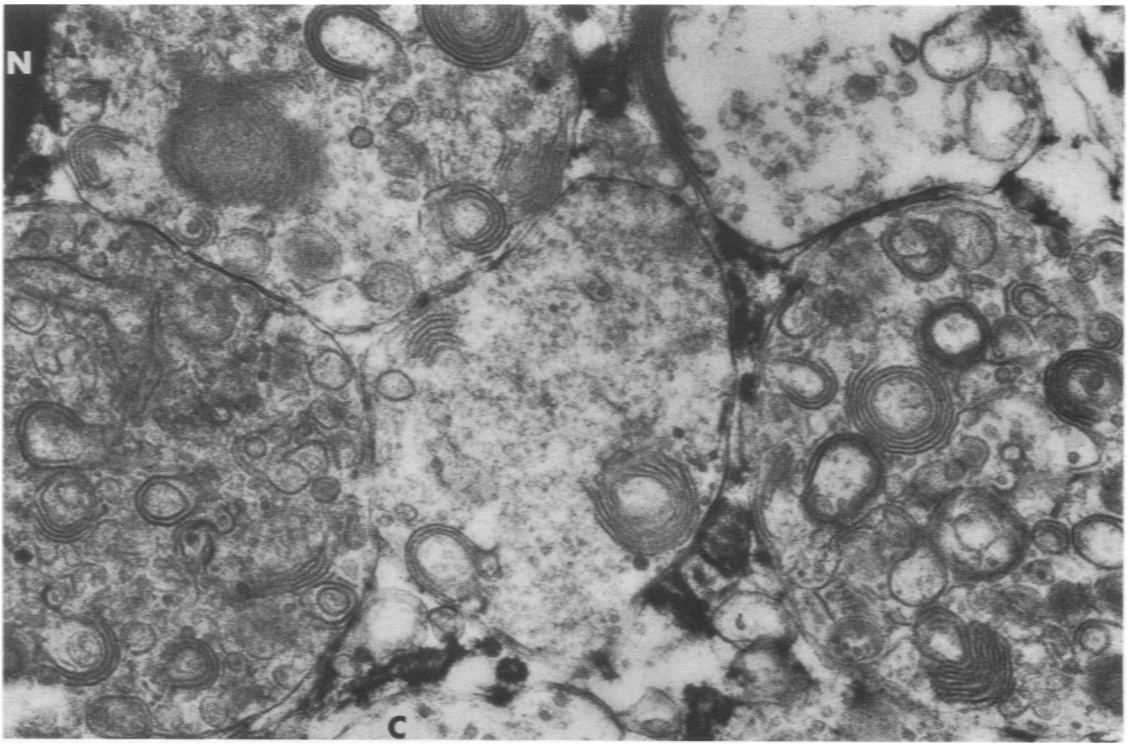

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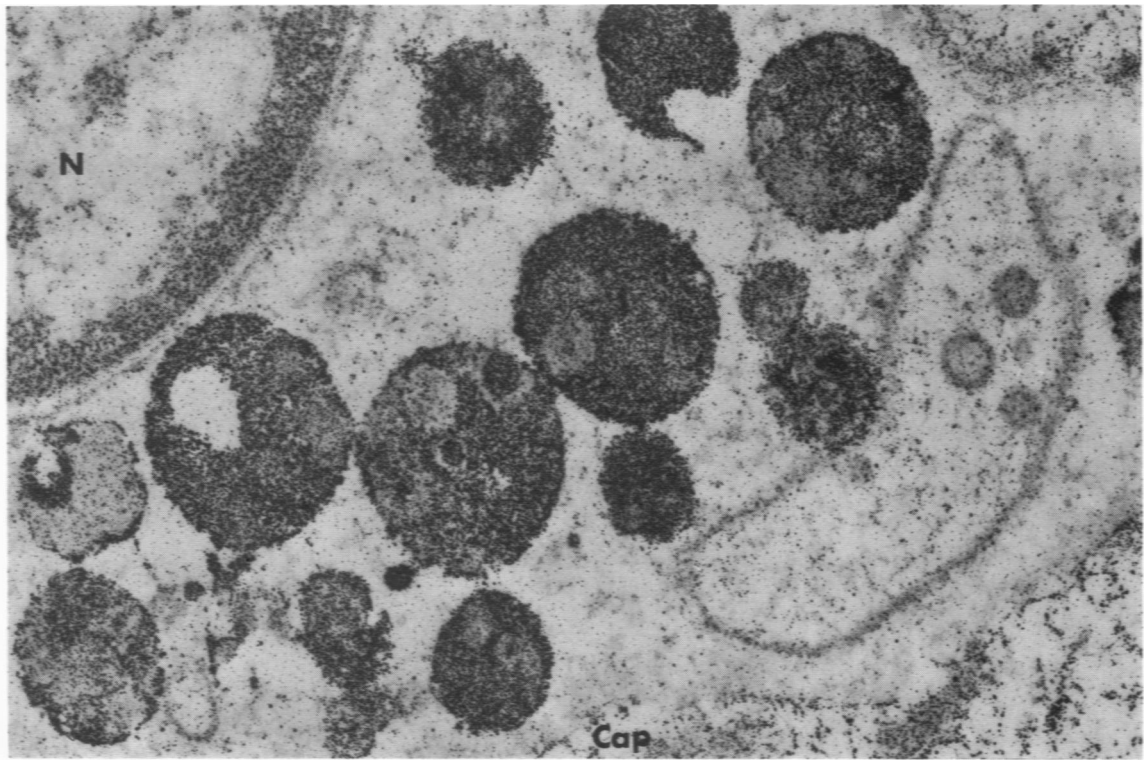
Figure 5—Interstitial cell from renal papilla of potassium-depleted rat. Granules contain vesicles, myelin figures, small particles, and dense bodies. Most of the granules show a single limiting membrane. Note dilated endoplasmic reticulum. (Uranyl acetate and lead citrate, ×37,500) **Figure 6**—Interstitial cell from renal papilla of potassium-depleted patient. Myelin figures predominate in large granules which fill most of the cytoplasm. *N*, nucleus; *C*, collagen. (Uranyl acetate and lead citrate, ×37,500)



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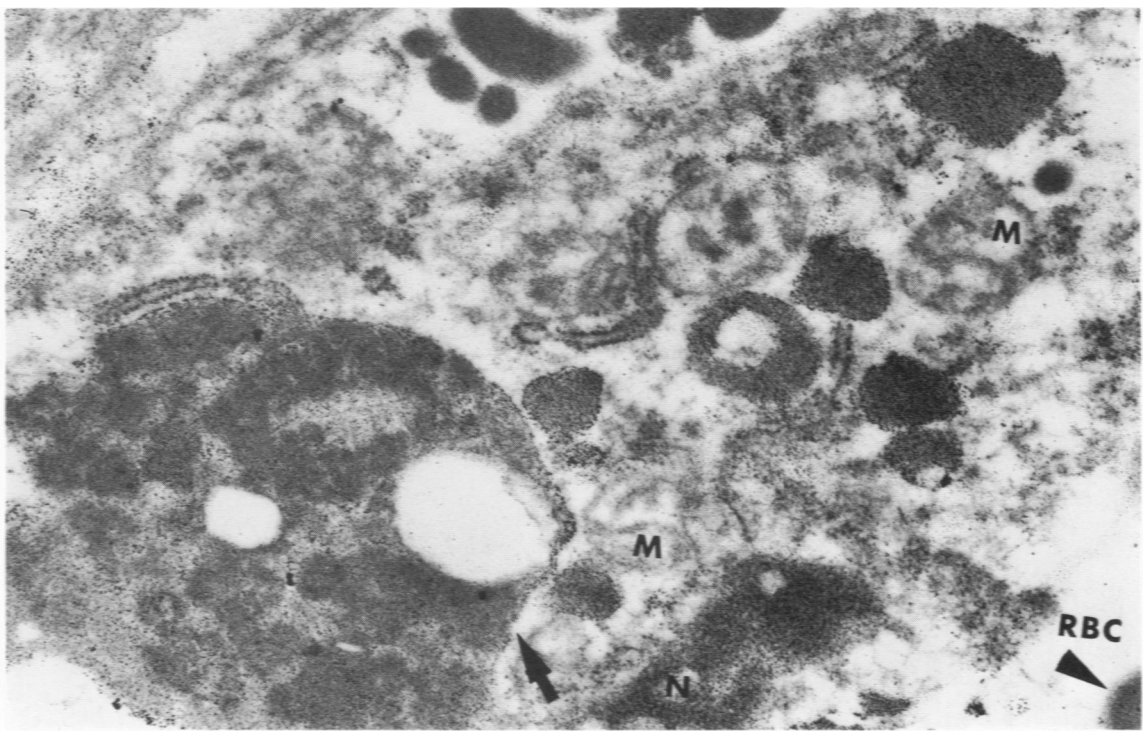

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Figure 7—Endothelial cell from renal papilla of potassium-depleted rat. Granules similar to those in Figures 1, 3, and 5 demonstrate argyrophilia. Silver reaction product is believed to indicate glycoprotein. *N*, nucleus; *Cap*, capillary. (Methenamine-silver with prior oxidation, ×37,500) **Figure 8**—Endothelial cell from renal papilla of potassium-depleted patient. Argyophilic granules are similar to those seen in potassium-depleted rat (Figure 7). *N*, nucleus; *M*, mitochondria; *arrow*, conglomerate granule; *arrow head, RBC*, red blood cell. (Methenamine-silver with prior oxidation, ×37,500)