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The effect of potassium deficiency on the susceptibility of the kidney to infection

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by

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I. INTRODUCTION

Infection occurs when a pathogenic organism finds an environment favorable to its growth. Dubos and other investigators have shown that there may be certain metabolic determinants of susceptibility to infection. For example, animals starved for short periods of time were extremely susceptible to infection with an organism which caused no infection in the normal animal.[1,2] The precise mechanisms by which such metabolic disturbances affect resistance have yet to be demonstrated. Certain metabolic products such as keto acids have been incriminated as affecting host resistance.[1] Defects in glycolysis have also been suggested as possibly inducing susceptibility to infection.[1]

Structural changes may also influence susceptibility to infection. Guzé and Beeson[3] have shown that a coliform bacillus which does not affect the normal kidney of a rat will infect a kidney whose ureter is completely obstructed. De Navasquez[4] has shown that the extensive scarring caused by a previous staphylococcal pyelonephritis in rabbits could become the seat of infection with the normally benign coliform organism. Braude et al[5] have induced coliform pyelonephritis in the rat merely by external massage of the kidney before the introduction of bacteria to the blood stream.

Potassium deficiency has been shown to affect cellular function, metabolism and structure. Carone and Cooke[6] demonstrated that gastric secretory function was decreased in potassium deficiency. The importance of potassium in the early steps of the carbohydrate cycle in rat muscle was demonstrated by Boyer.[7] Gardner[8] and associates showed that potassium deficiency interfered with normal

glycogenesis in rats. Schrader et al[9] in 1934 demonstrated that, in potassium deficiency, certain structural changes occurred in the kidney. Since that time, many investigators have described lesions of potassium deficiency although their descriptions have sometimes varied in details.[10-14] In the kidney fatty, vacuolar, hydrophic and necrotic changes of the tubular cells, as well as epithelial hyperplasia, cystic dilatation of the tubules and peritubular fibrosis, have all been described. Much of the confusion about the nature and location of these lesions has been cleared by Oliver et al,[13] who investigated the lesions of potassium deficiency in rats using a microdissection technique. They found that, in the early phases of potassium depletion, the lesions occurred in only two locations, the collecting tubules and the proximal convolutions. The distal tubule showed only the passive changes of dilatation and cellular compression which were the result of primary obstructive changes lower in the nephron system.

Lesions affecting the collecting tubules were of two varieties, (1) a severe swelling and hyperplasia of the tubular epithelium with associated degenerative, necrotic and fibrotic changes, predominantly in the outer third of the medulla, and (2) intracellular accumulation of granule droplets which was limited to the inner zone of the medulla. The lesions of the proximal tubule were similar, but only occasional nephrons were affected. The prolific regenerative hyperplasia of the collecting tubules was severe enough to produce obstruction in the outer third of the medulla and resultant intrarenal hydronephrosis in the tubules proximal to the obstruction.

Clinically, pyelonephritis has been reported in patients with severe potassium deficiency due to other causes. Relman and Schwartz[15] report one such case in five patients with potassium deficiency. This was a 25-year old woman whose deficiency probably extended for approximately two years and whose renal biopsy showed old pyelonephritic scarring. Milne et al,[16] in their study of two cases of primary aldosteronism, describe a 55-year old female with a deficiency of at least fifteen years who had repeated attacks of acute pyelonephritis and whose biopsy showed changes compatible with chronic pyelonephritis.

Both metabolic and structural changes have been shown to alter susceptibility to infection. In potassium depletion, both metabolic and structural changes occur. Pyelonephritis has been reported in patients with severe depletion of this ion. These observations might lead one to suspect that the potassium deficient kidney might be more susceptible to infection than the normal kidney and, indeed, this is the opinion expressed by several investigators from both clinical and experimental observation.[17, 18] The purpose of this study was to investigate this hypothesis in experimental potassium deficiency and to study the occurrence of infection in humans with moderate potassium depletion.

II. MATERIALS AND METHODS

Animals: The rats used were white males of the Sprague Dawley strain, weighing 150 to 300 grams. The mice used were white males of the Swiss strain, weighing 15 to 30 grams.

Diet: The potassium deficient diet was in artifical vitamin-supplemented diet consisting of sucrose 79.1%, casein 15%, corn oil 5%, and choline, cysteine and salts 0.9%. The salt mixture contained Ca, P, Fe, Mn, Zn, Cu, and Mg salts, but no Na, K or Cl. The animals on this diet were given 0.9% saline to drink ad libitum to supply Na and Cl requirements. The contol diet was essentially the same, but included Na and K salts in the salt mixture. The control mice were given Purina Lab Chow.

Bacterial Strains: The strain of Escherichia Coli used was the same strain as used by Guzé and Beeson.[3] The organism was cultured following passage through a series of rats with obstructed ureters in Beef Heart Infusion broth for four hours at 37° centigrade.

Injection of Organisms: The tail vein was used to inject both mice and rats. The volume of culture of E. Coli used was 0.5 ml. for rats and 0.25 ml. for mice. The rats received approximately 150 to 200 million organisms. The mice received approximately 75 to 100 million organisms.

Examination of Kidneys: The animals were killed by dislocation of the cervical vertebrae. The abdomen was opened aseptically and both kidneys were removed. One whole kidney was ground, with 9 ml. of 0.9% saline, in a Ten Broeck grinder until a homogeneous suspension was obtained. This represented the 1/10 dilution. Subsequent tenfold dilutions were made in saline and agar pour plates were made

from representative dilutions depending on the expected number of organisms. These were incubated for 48 hours and colony counts were taken. The other kidney was fixed in 10% formalin and histological sections stained with hematoxylin and eosin were made.

Blood Chemical Determinations: Random samples of sera were taken from each group and the concentration of potassium was determined on a Baird Internal Standard Flame Photometer.

Cases Studied: Fifteen patients with potassium deficiency for estimated periods of one to nine months who came to autopsy were selected consecutively from the autopsy files of the Grace-New Haven Hospital of the years 1952 to 1954. The case histories were reviewed as were the autopsy protocols and the original histological sections of the kidneys.

Experimental Procedure: The rats were fed the potassium deficient diet ad libitum for periods of one, two, three and seven weeks before injection of E. Coli. Six of these animals were pair fed with six normal animals receiving the control diet for a period of three weeks before injection. All of these animals were harvested one week after injection. Another group of animals was injected after three weeks of diet and harvested three days and two weeks after injection. Six animals were kept deficient for periods up to fourteen weeks and were harvested without injection to determine the incidence of spontaneous infection.

Normal mice were injected with E. Coli and harvested at intervals of from three hours to two weeks. Mice of the same strain were placed on the potassium deficient diet ad libitum for three weeks before injection with E. Coli. These animals were harvested at intervals ranging from eight hours to one week after injection.

III. RESULTS

1. RATS: Bacteriological Results (see Table I)

At one week or more after injection, the bacterial counts ranged from 0 to 168,000 in the deficient animals and 1,000 to 30,000 in the control animals. Guzé and Beeson[3] believed that counts greater than 100,000 constituted infection. The one potassium deficient animal with a count of over 100,000 showed no microscopic evidence of infection.

At three days following injection the deficient animals had counts ranging from 1,000 to 400,000. These values were in the normal range for a three day harvest.[3] The group of deficient animals harvested without injection had counts ranging from zero to 60. No animal in any of the groups except for the one deficient animal had colony counts sufficiently high to make a bacteriologic diagnosis of infection.

Histological Findings: Lesions of severe potassium deficiency were seen in the kidneys of the depleted animals. There was marked hyperplastic proliferation of the tubular epithelium in the outer zones of the medulla associated with some cellular necrosis and peritubular fibrosis. Intracellular accumulations of granule droplets were prominent, especially in the region of the papilla. There was an increase in the number of intercalated cells. Dilatation of the loops of Henle and the distal convolutions was present. No acute or chronic inflammation was present. Serum potassium determinations of representative animals in this group ranged from 1.7 meq. to 2.8 meq. per liter. The urine concentrating ability of four potassium-deficient rats was tested by

measuring urine osmolarity following water deprivation and subcutaneous pitressin injection. These animals showed concentrations ranging from 1732 to 2228 milliosmoles. Normal rats can concentrate to over 2800 milliosmoles.

2. MICE: Bacteriologic Results (see Table II)

Since rats are notoriously resistant to infection, the study was repeated in mice. First it was deemed advisable to study the effect of intravenous coliform organisms on the normal mouse kidney. At three hours, the bacterial counts ranged from 2,000 to 43,000 in the normal mouse. Approximately the same number of organisms were present at eight and 24 hours. In four days, the range was 100 to 3,000 and, in one week, two out of three animals had sterile cultures. In reviewing the colony counts, it was apparent that the mouse handled the organism in much the same way as the rat. The counts of the deficient animals paralleled closely the counts of the normal control animals. The colony counts at all intervals to four days were within the same range. In one week, six out of ten animals had counts of under 3,600 and the remaining four had sterile cultures. No major differences in the handling of organisms by the deficient animal and its normal control counterpart was apparent. There was no evidence of infection bacteriologically.

Histological Findings: The microscopic picture of the deficient mouse was essentially the same as seen in the deficient rat. Tubular hyperplasia and its associated changes occurred in the outer zone of the medulla and granule droplet accumulation was present in the cells of the papilla. No evidence of acute or chronic inflammation was seen in either the normal or deficient mouse kidney

in animals injected with E. Coli. The serum potassium concentrations of the deficient mice ranged from 1.7 meq. to 2.3 meq. per liter.

3. CASE STUDIES

Fifteen patients who died with unrelated pathology, but who had probable potassium deficiency of estimated periods of one to nine months, were studied with respect to their clinical course and their autopsy findings. The clinical picture in all of these individuals included extra renal potassium losses or poor dietary intake. Seven patients had disease of the upper gastro-intestinal tract which, by its nature, prevented adequate intake. Six patients had severe hepatic dysfunction which led to potassium deficiency as a result of vomiting, diarrhea or, in once case, the administration of sodium glutamate. Two patients had severe diarrhea due to ulcerative colitis. The disturbance in potassium metabolism was reflected in the serum potassium levels. Two-thirds of the patients had levels of less than 3.0 meq. per liter. All the patients were able to concentrate their urine at times during their hospital stay. Low specific gravities were recorded, however, when serum potassium levels were lower than 2.5 meq. per liter.

All but four patients received antibiotics at some time in the duration of their illness. All patients had evidence of acute infection elsewhere at the time of their demise. One patient had an indwelling catheter in place. In reviewing the pathology of the kidneys of these patients, the features which were looked for were signs of acute infection, the residuals of old or chronic infection, and evidence of potassium deficiency as exemplified by the lesions seen in experimentally deficient animals. There was

no evidence of acute infection in the kidneys of any of the patients. Five patients had subcapsular or cortical scarring, but there was no evidence of activity associated with these lesions such as a surrounding cellular infiltrate. None of the cases exhibited morphological evidence of potassium depletion such as was described in the experimental animals or in other reports.[15,16] In three cases, all of which had severe alterations in serum electrolytes other than hypokalemia, there was mild to marked hydrophic change and vacuolization of the epithelium of the proximal tubules. Cholemic nephrosis was seen in four cases who had severe hepatic failure.

	POTASSIUM DEFICIENT RATS					CONTROL RATS	
TIME INTERVAL AFTER INJ.	NUMBER OF ANIMALS	LENGTH OF DEFICIENCY	COLONY COUNTS	SERUM K meq.	URINE CONC. M.osmoles	NUMBER OF ANIMALS	COLONY COUNT
3 days	6	4 wks.	400,000			3	28,000
			151,000				19,200
			111,000				9,800
			11,000				
			10,000				
			1,000				
1 week	6	2 wks.	191				
			100				
			20				
			10				
			10				
			0				
1 week	5	3 wks.	300	2.4			
			200	2.6			
			10				
			0				
			0				
1 week	6	4 wks	168,000	1.7	1732	6	10,000
	pair		53,000	2.6	2024	pair	9,000
	fed		38,000	2.2	1320	fed	3,000
			16,000	2.1	2228		2,000
			15,000	2.3			1,000
			7,000				1,000
1 week	5	8 wks.	15,000	2.4			
			1,000	2.5			
			1,000	2.3			
			160	2.4			
			0				
2 weeks	6	4 wks.	680			3	0
			30				0
			20				0
			0				
			0				
			0				
Not inj.	6	8-14 wks.	60	2.6			
			50	2.6			
			0	2.5			
			0	2.5			
			0				
			0				

TABLE I

Experimental data on potassium deficient and control rats.

TIME INTERVAL INJECTION + HARVEST	MICE POTASSIUM DEFICIENT FOR FOUR WEEKS BEFORE INJ. NUMBER OF ANIMALS	COLONY COUNTS	SERUM K	NORMAL CONTROL MICE NUMBER OF ANIMALS	COLONY COUNTS
0	-	-	-	3	1,000,000 800,000 9,000
3 hrs.	-	-	-	3	43,000 34,000 2,000
8 hrs.	3	11,000 9,000 60	1.8	2	4,000 3,000
24 hrs.	3	74,000 9,000 2,000	2.3	3	600,000 270 0
4 days	3	24,000 9,000 240	2.1	3	260 140 100
7 days	10	3,700 1,760 760 150 130 50 0 0 0 0	1.7 1.8	3	1,000 0 0
2 weeks	-	-	-	3	40 40 0

TABLE II

Colony counts in deficient and normal mice.

Case No.	Hosp. No.	Diagnosis	Age	Sex	Duration of Deficiency	SERUM K meq.	SERUM NPN mg.%	URINE Sp. Gravity	MICROSCOPIC FINDINGS Infection	MICROSCOPIC FINDINGS Other
1	C53664	Portal fibrosis	34	F	7 wks.	2:1-3:5	64	1.012-1.024	0	Bile nephrosis, subcapsular scars
2	B24762	Viral hepatitis	29	F	10 wks.	2:4-3.2	57	1.010-1.017	0	(same)
3.	377650	Viral hepatitis	27	F	4.5 mos.	2.9-3.9	26	1.010-1.025	0	(same)
4	402447	Portal fibrosis	51	M	4 wks.	2.5-3.7	67	1.010-1.015	0	(same)
5	A19746	Ca jaw	58	M	3 mos.	2.8	65	-	0	Subcapsular scars
6	C32224	Portal fibrosis	50	F	5 mos.	1.9	24	1.008-1.023	0	-
7	421919	Hemachromatosis	44	M	4 mos.	1.8-3.5	53	1.005-1.025	0	Hydrophic change, prox. tubule
8	B45518	Ca stomach	59	F	7 mos.	3.4	30	1.012-1.022	0	-
9	43677	Ca stomach	60	M	4 mos.	4.0	37	1.022	0	-
10	411776	Ulcerative colitis	62	F	4.5 mos.	1.4-3.8	24	1.006-1.025	0	Hydrophic change, prox. tubule
11		3° burns	23	M	5 wks.	3.8-4.2	-	1.015-1.024	0	-
12	367096	Tracheo-esophageal fistula	3	M	4 mos.	3.4	23	1.016-1.030	0	-
13	403895	Esophageal stricture	48	M	9 mos.	4.1	58	1.025-1.028	0	Subcapsular scars
14	372593	Ca esophagus	69	M	2 mos.	2.3-4.1	30	1.016-1.023	0	-
15	A18985	Ulcerative colitis	28	M	5 mos.	2.5-4.2	27	1.030-1.034	0	Hydrophic change, prox. tubule

TABLE III

Clinical and histological data on patients with potassium deficiency.

IV. DISCUSSION

The results of these studies do not support the hypothesis that potassium deficiency makes the kidney more susceptible to infection. In spite of the structural changes produced by potassium depletion, there was no measurable difference between these animals and normal animals in the incidence of pyelonephritis as determined by bacteriological and histological findings.

It has been shown that only certain forms of structural damage may increase the susceptibility to infection. For example, Beeson et al[19] have demonstrated that scarring of the kidney cortex of rabbits by electrocautery before the injection of coliform organisms was not followed by infection, whereas scarring of the papilla almost invariably was. It has also been shown in rats that intrarenal obstruction of the distal collecting system by sulfadiazine or uric acid crystals was followed by infection, but that the necrosis, scarring, and subsequent obstruction caused by bichloride of mercury in the tubules near the corticomedullary junction had no such effect.[20] From these observations, it might be postulated that, in order to produce infection, the obstruction should be in the most distal portions of the collecting system and a lesion placed more proximally would have little or no effect. The lesions of potassium deficiency are found in the collecting tubules. Severe hyperplastic lesions associated with scarring and proximal obstruction occur in the ducts in the outer third of the medulla. The obstruction seen in potassium deficiency is slightly more proximal in the collecting system than the lesions caused by sulfadiazine and uric acid. The early severe lesions of potassium

depletion are primarily changes in the tubular epithelium and the obstruction seen is probably caused by the marked hyperplasia of the epithelium. It is possible that the obstruction is not as complete or as extensive as the obstruction seen in rats with sulfadiazine crystals. Because the rat is notoriously resistant to infection with E. Coli, similar experiments were carried out in mice with the same results. From the experimental observations reviewed here, it appears that the lesions of potassium deficiency do not increase the susceptibility of the rat or mouse kidney to infection with the strain of E. Coli used.

The young rat placed on a potassium deficient diet does not gain weight, as does an animal receiving a normal diet. Dubos and other investigators[1,2,21] have shown nutritional deficiency to be a factor in increasing the susceptibility of mice to infection with the staphylococcus and other organisms. In the present study pair-fed control animals with approximately the same weight gain as deficient animals reacted in a similar fashion to the animals on the deficient diet. Smith and Dubos[22] showed that the mouse in the early acute phase of starvation was more susceptible to infection than the mouse with an inadequate diet and subnormal weight gain over an extended period. This suggests that there might be a crucial time during dietary depletion when the animal is most susceptible to experimental infection. However, potassium-deficient rats challenged with bacteria at different stages of the development of potassium depletion showed no difference in the incidence of infection.

The patients studied here were all able to concentrate their

urine at times during their hospital stay. Recent studies show that the potassium deficient animal rapidly loses its ability to concentrate urine.[13] Findings in the experimental animals of this present study confirm this observation. This suggests the patients were not markedly depleted of potassium at the time when the high specific gravities were observed. That K deficiency was relatively mild is further reflected in the histological findings which did not show the parenchymal lesions found in the experimentally deficient animal. The three patients with hydrophic and vacuolar changes in the proximal tubule had either severe hyperchloremia or alkalosis associated with the hypokalemia. While some observers ascribe this type of lesion to human potassium depletion, others describe this lesion in association with electrolyte disturbances other than hypokalemia.[23] In these three cases it may be that these lesions are related to other electrolyte abnormalities rather than specifically to the hypokalemia since the remaining patients who had relatively normal serum electrolytes did not show these changes. The absence of acute or active pyelonephritis in these patients, all of whom had active infections elsewhere in their bodies, is compatible with the present observations in the experimentally depleted animal. Those cases of human potassium deficiency with associated pyelonephritis which have been reported[15-18] may have had either more severe potassium depletion than those studied here or pyelonephritis due to other causes. The observations in the experimental animals in the present study seem to support the latter possibility.

V. SUMMARY

An experimental study has been made of the effect of potassium deficiency on the susceptibility of the kidney to infection with a strain of E. Coli. Rats and mice were made potassium deficient and then injected with organisms. No bacteriological or histological evidence of infection was present in either potassium deficient animals or normal controls. The structural and functional changes of the kidney in potassium deficiency were observed.

Case studies of 15 patients with hypokalemia were reviewed in regard to clinical and autopsy findings. All suffered from moderate potassium deficiency. No patient had morphological evidence of potassium deficiency or infection in the kidneys. Three patients had hydrophic and vacuolar changes in the proximal tubules. These changes may have been secondary to electrolyte changes other than hypokalemia.

It is concluded that severe potassium deficiency in the rat and mouse has no effect on the susceptibility of the kidney to pyogenic infection with E. Coli, and that moderate potassium deficiency in man is not usually accompanied by renal infection.

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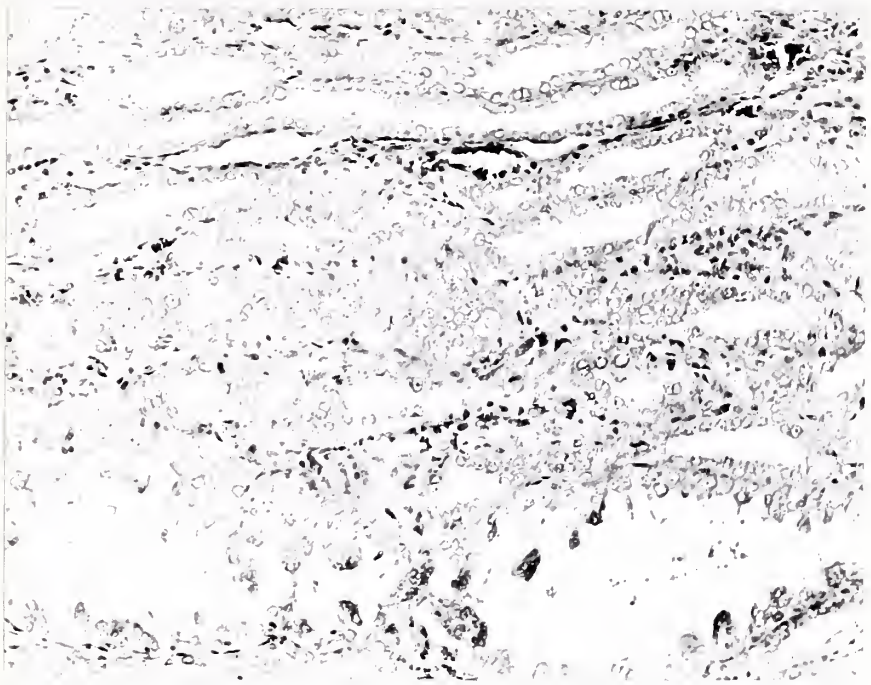

Fig. 1. Section of potassium depleted rat kidney showing hyperplasia of collecting tubular epithelium in outer medulla. X450

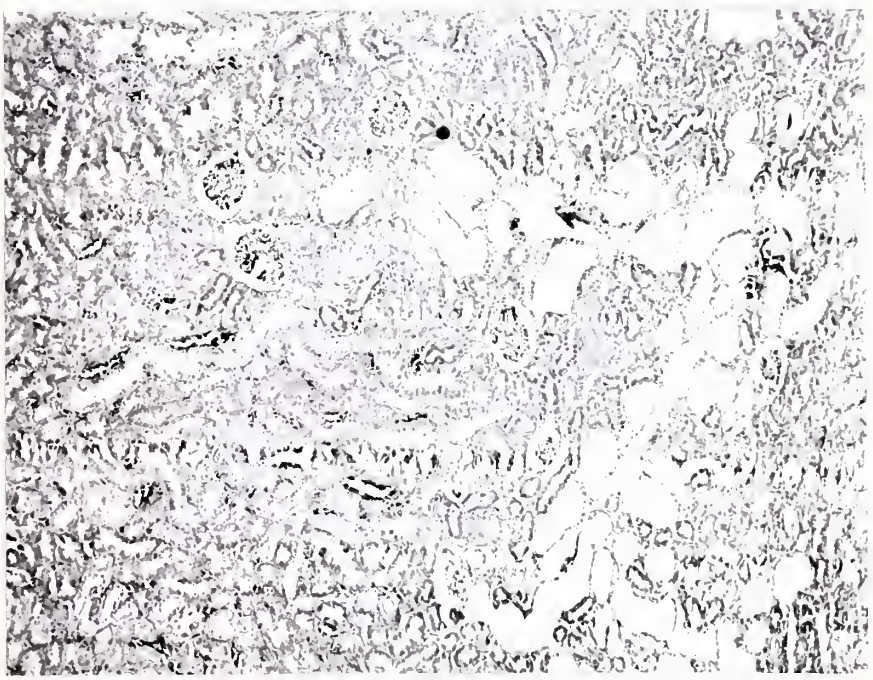

Fig. 2. Section of potassium depleted rat kidney showing dilatation of tubules in cortex. X100

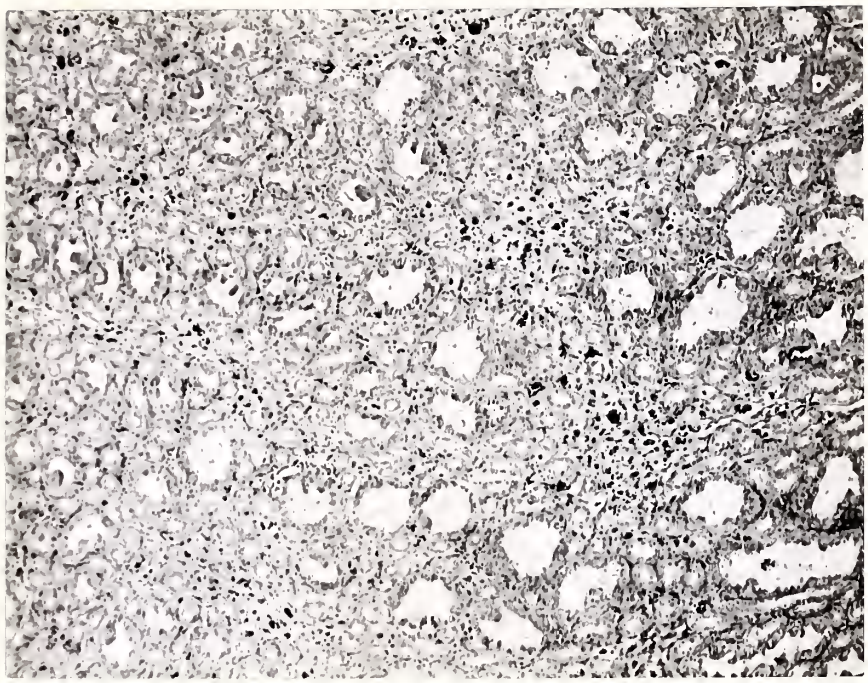

Fig. 3. Section of potassium depleted rat kidney showing peritubular fibrosis. X100

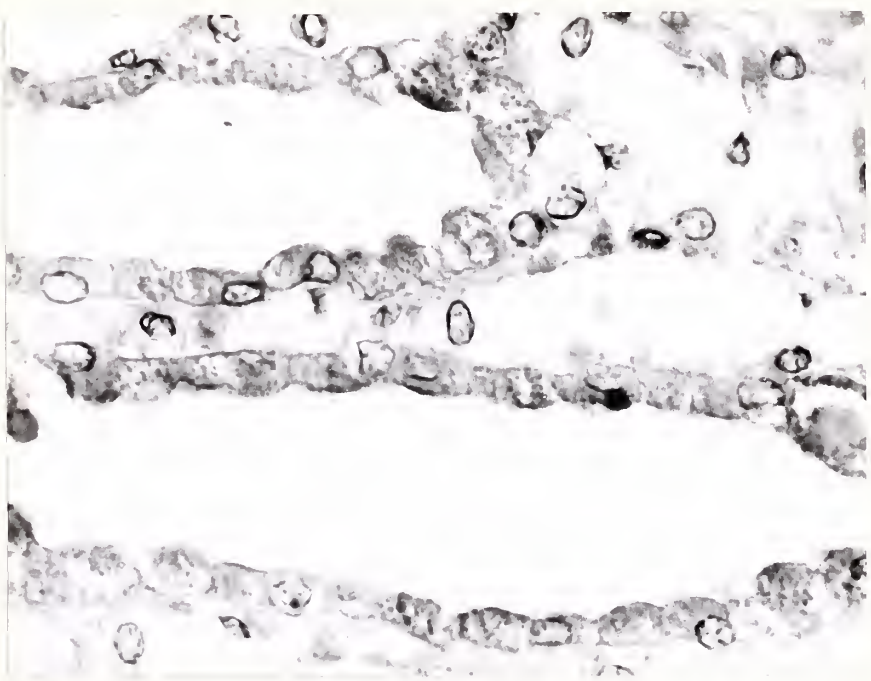

Fig. 4. Section of potassium depleted rat kidney showing granule droplets in tubular cells at papilla. X930

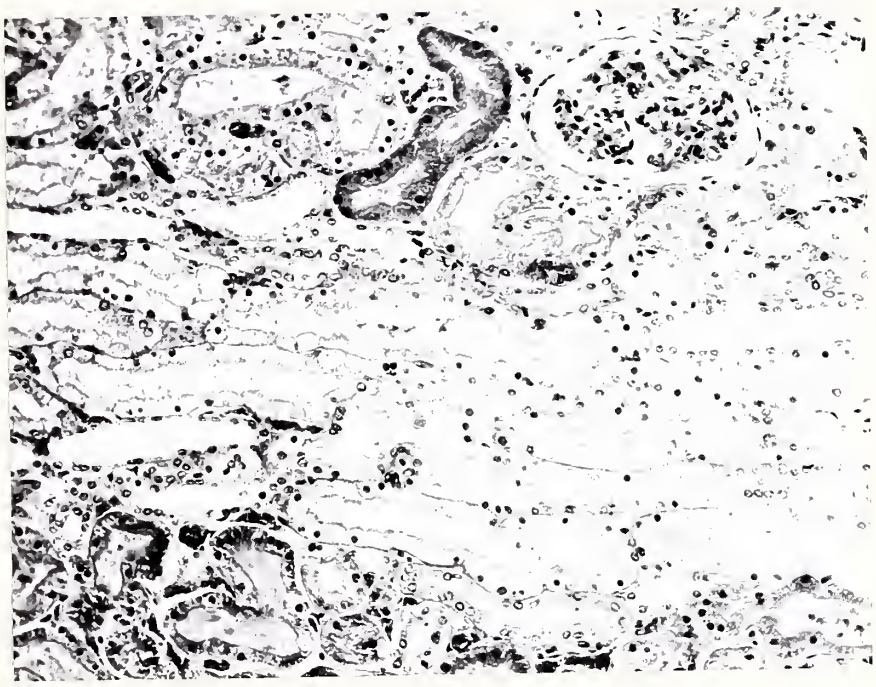

Fig. 5. Section of kidney from patient with ulcerative colitis showing moderately severe vacuolar change in proximal tubules. X450

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