TARTRATE NEPHRITIS, WITH ESPECIAL REFERENCE
TO SOME OF THE CONDITIONS UNDER WHICH IT
MAY BE PRODUCED.*

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PLATE 20.

The subcutaneous administration of sodium tartrate to rabbits and dogs may cause a pronounced disintegrative action upon the epithelium of the kidney. Associated with the change in the convoluted tubules there is to be noted a greatly diminished urine volume and a marked decrease in the elimination of certain of the urinary constituents.¹

In view of the fact that the changes induced in the kidney by tartrate are confined almost exclusively to the tubular epithelium, thereby affording a means of studying various phases of renal secretion with practically intact glomerular structure, an investigation has been made of some of the conditions under which this experimental nephritis may be induced. Such a study is of especial significance when it is recalled that tartaric acids or their salts may enter rather extensively into the dietary; that purgation is frequently induced by tartrates; and that, in certain instances of chronic kidney involvement, cream of tartar water is often prescribed for the promotion of diuresis.

METHODS.

In general we have employed the rabbit as our experimental animal, although in some instances dogs have been used. The tartaric acid injected was an old, beautifully crystallized product of

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¹ Underhill, F. P., *Jour. Biol. Chem.*, 1912, xii, 115.

Trommsdorf, and preparations made by Baker. The acid was of the racemic variety. The sodium salt was always injected, the free acid never being administered. The various methods followed in our work were those commonly in use and call for no especial explanation. Sections of the organs were preserved in Zenker's and Orth's fluids and in 5 per cent. formalin.

THE INFLUENCE OF DOSAGE UPON THE PRODUCTION OF TARTRATE NEPHRITIS IN FASTING PHLORHIZINIZED ANIMALS.

In a former paper² the general features of tartrate nephritis have been reviewed; but for the sake of completeness we have inserted here some of the experiments previously published with a different object in view. Our plan has been to study the phenomena provoked by tartrate injections, such as the changes in urine volume, changes in the elimination of characteristic urinary constituents, together with the histological picture presented. The results obtained from such an investigation may be of service in the interpretation of the conditions found in spontaneous renal involvement. It is well known that phlorhizin will provoke a significant glycosuria in an animal with intact kidney, but when the renal epithelium is impaired glycosuria either does not occur at all or else the amount of sugar appearing in the urine is markedly decreased. This phlorhizin action, therefore, has been in general use for a relatively long time as a test for renal efficiency.

RABBIT C.

Female Rabbit, Weighing 2,200 Grams, Received Daily Subcutaneous Injection of 0.25 of a Gram of Phlorhizin.

Date (1911).	Urine.					Remarks.
	Volume in c.c.	Specific gravity.	Reaction to litmus.	Total nitrogen in gm.	Dex- trose in gm.	
Nov. 21	85	1.026	Acid	0.95	1.88	Drank 80 c.c. water.
22	75	1.030	Acid	1.30	1.16	Drank 45 c.c. water.
23	75	1.030	Acid	1.18	0.87	Drank 50 c.c. water.
24	30	1.012	Alkaline	0.00	0.00	Subcutaneous injection of 1.75 gm. tartaric acid, neutralized with sodium carbonate, in 30 c.c. water. Drank 140 c.c. water.
25	40	1.015	Alkaline	0.07	0.00	Would not drink. Animal killed. Kidneys very pale and soft.

² Underhill, F. P., *loc. cit.*

Histological Examination. Kidney.—(Figure 1.) The majority of the convoluted tubules show necrosis of their epithelium. In some the necrotic cells remain and fill up the lumen as a granular mass; in others this mass has broken into fragments; in a few, vacuolated cell skeletons remain attached to the basement membrane. The early stage of the necrobiosis sometimes involves first the cytoplasm nearest the lumen, the nuclei persisting until all the cytoplasm has become thus altered. More often fragmentation and vacuolization of the cytoplasm and early loss of the nucleus is the chief change. The epithelium of the loops of Henle seems to escape injury, but these and the collecting tubules contain hyaline and granular casts. In the medulla the majority of the tubules contain granular and hyaline casts. No blood or epithelial casts are seen. The epithelium of the large collecting tubules is swollen in an almost spherical form, there being much vacuolation, especially about the nucleus. The glomerules seem entirely normal. There is no hemorrhage and no inflammatory reaction of any kind.

In the preliminary experiments the elimination of both total nitrogen and dextrose was followed before and after the administration of a single dose of sodium tartrate.

The protocols show the influence of a single dose of sodium tartrate upon the excretion of nitrogen and dextrose in a fasting phlorhizinized animal.

RABBIT D.

Female Rabbit, Weighing 2,200 Grams, Received Daily Subcutaneous Injection of 0.25 of a Gram of Phlorhizin.

Date (1911).	Urine.					Remarks.
	Volume in c.c.	Specific gravity.	Reaction to litmus.	Total nitrogen in gm.	Dex- trose in gm.	
Nov. 21	125	1.024	Acid	1.12	2.75	Drank 70 c.c. water.
22	60	1.036	Acid	1.17	1.28	Drank 25 c.c. water.
23	50	1.040	Acid	0.92	1.19	Drank 45 c.c. water.
24	18	—	Alkaline	0.05	0.00	Subcutaneous injection of 2 gm. tartaric acid neutralized with sodium carbonate, in 40 c.c. water. Animal drank 125 c.c. water.
25	2 drops	—	—	—	0.00	Urine clots in jelly-like mass.
26	3 drops	—	—	—	0.00	Would not drink.
27	0	—	—	—	—	Animal died in convulsions.

Histological Examination. Kidney.—The condition is the same as in rabbit C, except that the necrosis of the convoluted tubules is almost universal. In the cortex nothing but collecting tubules are seen containing nucleated cells, and also what may be distal convoluted tubules with swollen and fused epithelium retaining still their nuclei, but in a pyknotic condition. There are fewer casts

in the medulla than in the case of rabbit C. The glomerules and interstitial tissues seem to be normal. The vacuolation of the epithelium of the large collecting tubules is striking, the nuclei frequently being small, compact, and distorted.

RABBIT H.

Male Rabbit, Weighing 2,500 Grams, Received Daily Subcutaneous Injections of 0.25 of a Gram of Phlorhizin.

Date (1911).	Urine.					Remarks.
	Volume in c.c.	Specific gravity.	Reaction to litmus.	Total nitrogen in gm.	Dex- trose in gm.	
Nov. 29	100	1.024	Acid	0.56	2.30	Would not take water.
30	90	1.025	Acid	1.31	2.57	Would not take water.
Dec. 1	110	1.032	Acid	1.26	1.73	Drank 100 c.c. water.
2	5	—	Alkaline	0.018	0.015	Subcutaneous injection of 1.5 gm. tartaric acid neutralized with sodium carbonate dissolved in 30 c.c. water.
3	30	1.008	Alkaline	0.066	0.068	Drank 60 c.c. water.
4	20	—	Alkaline	—	Trace	

Histological Examination. Kidney.—A few segments of convoluted tubules have escaped necrosis, otherwise the specimen is similar to the sections previously discussed.

RABBIT I.

Female Rabbit, Weighing 2,300 Grams, Received Daily Subcutaneous Injection of 0.25 of a Gram of Phlorhizin.

Date (1911).	Urine.					Remarks.
	Volume in c.c.	Specific gravity.	Reaction to litmus.	Total nitrogen in gm.	Dex- trose in gm.	
Dec. 5	100	1.030	Acid	2.88	4.03	Drank 40 c.c. water.
6	200	1.020	Acid	1.73	3.45	Drank 125 c.c. water.
7	90	1.030	Acid	1.84	1.40	Drank 50 c.c. water.
8	10	—	Alkaline	0.075	0.076	Drank 125 c.c. water.
						Subcutaneous injection of 2 gm. tartaric acid neutralized with sodium carbonate, dissolved in 30 c.c. water.
9	0					Animal killed. Fluid in peritoneal cavity. Abdomen edematous. Surface of kidneys hemorrhagic.

Histological Examination. Kidney.—A large proportion, but not quite all of the proximal convoluted tubules show complete destruction of their epithelium, which remains as a coarse granular mass entirely filling the tubule. There is little tendency to cast formation in the convoluted tubules. The earliest stage of the process, which is seen also in the distal convoluted tubules, is a vacuola-

tion of the epithelium, with retention of nuclei. Glomerules and interstitial tissues show no changes, but there is blood in the pelvis of the kidney. The collecting tubules show little change, but the majority of the tubules in the pyramids show hyaline casts.

Liver.—Normal.

RABBIT G.

Female Rabbit, Weighing 2,400 Grams, Received Daily Subcutaneous Injection of 0.25 of a Gram of Phlorhizin.

Date (1911).	Urine.					Remarks.
	Volume in c.c.	Specific gravity.	Reaction to litmus.	Total nitrogen in gm.	Dex- trose in gm.	
Nov. 29	105	1.022	Acid	0.86	2.00	Would not take water.
30	60	1.035	Acid	1.04	1.49	Would not take water.
Dec. 1	85	1.036	Acid	1.36	0.98	Animal drank 80 c.c. water.
2	32	—	Alkaline	0.072	0.072	Subcutaneous injection of 1 gm. tartaric acid, neutralized with sodium carbonate, dissolved in 20 c.c. water. Animal drank 60 c.c. water.
3	3	0	Alkaline	0.007	Trace	Animal drank 30 c.c. water.
4	0					Animal killed. Tissues were not examined histologically.

RABBIT A.

Male Rabbit, Weighing 2,200 Grams, Received Daily Subcutaneous Injection of 0.25 of a Gram of Phlorhizin.

Date (1911).	Urine.					Remarks.
	Volume in c.c.	Specific gravity.	Reaction to litmus.	Total nitrogen in gm.	Dex- trose in gm.	
Nov. 14	90	1.040	Acid	1.85	2.72	
15	100	1.026	Acid	1.60	1.80	
16	100	1.030	Acid	1.99	1.43	
17	30	—	Alkaline	0.13	0.00	Subcutaneous injection of 3 gm. tartaric acid, neutralized with sodium carbonate, dissolved in 40 c.c. water.
18	8	—	Alkaline	0.00	0.00	Animal lies in deep coma.
19	0	—				Animal found dead.
20	0					Tissues were not examined histologically.

DOG I.

Full Grown Bitch, Weighing 9 Kilos, Received Daily Subcutaneous Injection of 1.5 of a Gram of Phlorhizin.

Date (1912).	Urine.					Remarks.
	Volume in c.c.	Specific gravity.	Reaction to litmus.	Total nitrogen in gm.	Dex- trose in gm.	
Feb. 6	220	1.070	Acid	6.42	32.82	Animal drank 120 c.c. water.
7	415	1.074	Acid	11.70	43.33	Animal drank 250 c.c. water.
8	600	1.053	Acid	11.98	40.06	Animal drank 70 c.c. water.
9	125	1.008	Acid	0.16	00.00	8 gm. tartaric acid, neutralized with sodium carbonate, were subcutaneously injected dissolved in 50 c.c. water.
10	10	—	Acid	0.075	00.25	Animal has lost control of muscles and lies in cage. Vomits water taken. Animal killed. All organs appeared normal at autopsy.

Histological Examination. Kidney.—Beneath the capsule the tubules have a large lumen and low cytoplasm which stain deeply. The lumen usually contains more or less coarse granular detritus and frequently degenerated cells. Farther in, most of the cells of the proximal convoluted tubules are greatly swollen and vacuolated, so that they fill the lumen with a mere framework of cell outline, the nucleus of the cells usually persisting near the base; in a few tubules no nuclei can be seen. The basement membrane and the interstitial tissue are unaltered. Except for an increase in the amount of open space there are no abnormalities to be seen in the glomerules. There is no definite necrosis anywhere, and there are almost no casts, an occasional small hyaline cast being seen. In the pyramids the epithelium is slightly vacuolated, but not extensively. The collecting and the distal convoluted tubules are practically unaffected, as well as the loops of Henle.

Liver.—The cells are greatly vacuolated and swollen, so that the normal arrangement of the cells is obscured, the vacuolation being more marked in the center than in the periphery of the lobule, but all the cells are more or less affected. There is no necrosis or other change.

Adrenal.—Normal.

The data given above demonstrate the detrimental influence of subcutaneous injections of sodium tartrate upon the secretory activity of the kidney in phlorhizinized animals, and the reports of the corresponding histological study of the renal tissue show that tartrate administered under the experimental conditions has a specific action upon the convoluted tubules in both rabbits and dogs. In the earliest stage vacuolization alone is in evidence. Necrosis rapidly follows and the dead epithelium thrown off may form plugs in the tubules.

In general the urine voided after a typical tartrate injection is water-clear, almost colorless, and may contain a trace of protein or even clot on standing, depending somewhat upon the volume. In other cases microscopic examination reveals the presence of large numbers of hyaline and granular casts together with typical renal cells.

DOG 3.

Full Grown Bitch, Weighing 11 Kilos, Received Daily Subcutaneous Injection of 1.5 of a Gram of Phlorhizin.

Date (1912).	Urine.					Remarks.
	Volume in c.c.	Specific gravity.	Reaction to litmus.	Total nitrogen in gm.	Dex- trose in gm. [†]	
March 5	240	1.070 ⁺	Acid	4.44	31.05	Drank 370 c.c. water.
6	240	1.070 ⁺	Acid	8.11	29.44	Drank 250 c.c. water.
7	307	1.060	Acid	8.79	29.75	Drank 290 c.c. water.
8	442	1.035	Acid	3.05	12.88	Subcutaneous injection of 10 gm. tartaric acid, neutralized with sodium carbonate dissolved in 50 c.c. fluid. After injection animal vomited repeatedly. Could not drink because of vomiting.
9	335	1.050	Acid	7.68	15.12	Animal in very weak condition. Killed. All organs seemed normal at autopsy.
10	209	1.045	Acid	1.27	04.06	
11	240	1.016	Acid	1.08	01.02	

Histological Examination. Kidney.—The section resembles that of dog 1 except that a large proportion of the tubules is affected. The subcapsular tubules are vacuolated fully as much as the others, and the collecting tubules show more vacuoles than do those in dog 1, although they are not swollen so much as the convoluted tubular epithelium. In the center of some of the convoluted tubules the remaining epithelial fragments are fused together into a dense mass, but there is little or no cast formation, there being a few granular casts in the pyramids.

Liver.—Centers of the lobules show many coarse vacuoles resembling fatty infiltration, with a few finer vacuoles towards the periphery.

The kidneys may be pale and watery, or hard with tiny hemorrhages on the surface. The first type is the more common and comparison of the weights of these kidneys with those of normal starving rabbits has shown that the pathological specimens weigh at least twice as much as the kidneys taken from normal fasting rabbits.

Inspection of the tables will show in a general way that the effect produced upon the composition of the urine is not closely related

to the amount of tartrate injected. Thus, rabbit A, weighing 2,200 grams, received three grams of tartaric acid, whereas a rabbit of 2,400 grams (rabbit G) was given only one gram of tartaric acid, and yet the influence upon the elimination of nitrogen and dextrose was practically the same in both cases. At times experiments have been carried out in which less than 0.5 of a gram of tartaric acid injected into rabbits weighing 2,000 to 2,500 grams has been sufficient to cause a practical cessation of urine flow, or at least an inhibition of the elimination of the typical nitrogenous constituents. Small doses may sometimes entirely fail to cause any noticeable effects. When small doses are effective there is apparently little difference either in degree or kind between these effects and those produced by large doses. On the other hand, the introduction of large doses of tartrates invariably causes marked reactions.

PRODUCTION OF TARTRATE NEPHRITIS DURING INANITION
WITHOUT PHLORHIZIN ADMINISTRATION.

It is conceivable that in the observations previously recorded a significant rôle may be played by phlorhizin in the induction of tartrate nephritis. Phlorhizin which has an alleged specific influence upon the kidney may render the tubular epithelium hypersensitive to the action of the tartrate, or the renal tubules may suffer damage by the combined influence of the two drugs for which neither alone could be held responsible. To obviate the effect of phlorhizin some of the experiments already outlined have been repeated exactly, with the exception that phlorhizin administration has been omitted throughout.

Since creatin is an almost constant constituent of rabbit urine during a period of starvation,³ the estimation of this substance together with the determination of creatinin and total nitrogen has been made the criteria by which renal efficiency has been measured.

Typical protocols illustrative of this point follow.

³ Mendel, L. B., and Rose, W. C., *Jour. Biol. Chem.*, 1911-12, x, 213. Myers, V. C., and Fine, M. S., *Jour. Biol. Chem.*, 1913, xiv, 9.

RABBIT E.

Male Rabbit, Weighing 2,200 Grams. No Phlorhizin Was Given.

Date (1911).	Volume in c.c.	Specific gravity.	Reaction to litmus.	Total nitrogen in gm.	Creatinin in mg.	Creatin in mg.	Remarks.
Nov. 22	105	1.012	Acid	0.85	84	9	Drank 150 c.c. water.
23	65	1.022	Acid	0.81	87	34	Drank no water.
24	70	1.020	Acid	1.22	78	63	Drank 25 c.c. water.
25	30	1.015	Alkaline	0.12	Trace; too small to estimate	Trace; too small to estimate	Subcutaneous injection of 3 gm. tartaric acid, neutralized with sodium carbonate in 40 c.c. water.
26	Less than 1 c.c.	—	—	—	—	—	Drank 100 c.c. water.
27	0						Drank 60 c.c. water.
28							Found dead.

Histological Examination. Kidney.—(Figure 2.) Necrosis of the convoluted tubules is almost universal, and the necrotic epithelium is generally disintegrated. The collecting tubules show little change and there are many casts. The glomerules and interstitial tissue seem unaffected.

RABBIT F.

Female Rabbit, Weighing 2,200 Grams. No Phlorhizin Was Given.

Date (1911).	Urine.						Remarks.
	Volume in c.c.	Specific gravity.	Reaction to litmus.	Total nitrogen in gm.	Creatinin in mg.	Creatin in mg.	
Nov. 22	115	1.011	Acid	0.74	90	21	Drank 90 c.c. water.
23	70	1.020	Acid	0.97	111	39	Drank no water.
24	60	1.025	Acid	0.90	84	48	Drank 50 c.c. water.
25	32	1.015	Alkaline	0.15	Trace; too small to estimate	Trace; too small to estimate	Drank 60 c.c. water.
							Subcutaneous injection of 3 gm. tartaric acid, neutralized with sodium carbonate.
26	Less than 5 c.c.						Drank 25 c.c. water.
27	0						Animal in light coma. Killed. Kidneys were pale and soft.

Histological Examination. Kidney.—The conditions are about the same as for rabbit E. In the pelvis is a mass of coagulated protein, apparently from highly albuminous urine.

In other instances experiments were planned so that urine volume only was recorded, the real object of these observations being the

histological study of the renal organs. Several protocols of this nature are appended.

Rabbit 5.—A rabbit weighing 1,900 grams was placed in a cage without food; water was given. The urine volume for twenty-four hours amounted to 120 c.c. The following day the animal received a subcutaneous injection of 1 gm. of tartaric acid dissolved in 15 c.c. of water and neutralized with sodium carbonate. The volume of urine eliminated during this twenty-four hour period was 20 c.c. The rabbit was killed the next morning. Autopsy revealed the typical soft, pale kidneys and a considerable amount of fluid in the peritoneal cavity.

Histological Examination. Kidney.—Nearly all the proximal convoluted tubules show complete destruction of their epithelium, which remains as a coarse granular mass entirely filling the tubule. Glomerules and interstitial tissues show no changes.

Liver.—Normal.

Rabbit 6.—A rabbit weighing 2,500 grams was maintained under conditions similar to those noted for rabbit 5. The volume of urine voided during the succeeding twenty-four hours amounted to 200 c.c. The next day 1.5 gm. of tartaric acid neutralized with sodium carbonate were injected subcutaneously. The urine volume for this day was 86 c.c. On the following morning the animal was killed. The kidneys seemed normal on autopsy, and fluid was absent from the peritoneal cavity.

Histological Examination. Kidney.—The tissue was relatively little affected. All the epithelium of the tubules shows more or less granular degeneration and vacuolation, but there is no necrosis. A few tubules contain corpuscles and in a few tubules in the pyramids granular casts are present. The glomerules are congested and swollen. There are no interstitial changes.

Rabbit 7.—A rabbit weighing 2,000 gm. was maintained under the previously cited conditions. For the first day the urine volume amounted to 124 c.c. On the following day the animal received a subcutaneous injection of 2.5 gm. of tartaric acid neutralized with sodium carbonate. On this day 70 c.c. of urine were voided. Autopsy on the next day revealed the characteristic pale, soft kidneys. A relatively large volume of fluid was found in the peritoneal cavity, and there was an area of subcutaneous edema at the site of the tartrate injection.

Histological Examination. Kidney.—This kidney shows considerable necrosis and vacuolation of the proximal convoluted tubules, with extensive cast formation.

Liver.—Normal.

The results of the experiments justify the conclusion that the disintegrative changes observed in the kidneys of phlorhizinized rabbits are due to the action of the tartrate. Although our experience with the dog under these conditions has been much more limited, the observations indicate that in this animal also the same statement holds true. Phlorhizin seems to be without significant

influence in the reaction; the same type and degree of response may be called forth by tartrate in animals that have not received phlorhizin. Tartrate exerts a specific action upon the kidney; neither the liver nor the adrenal is affected. The dose of tartrate introduced appears to bear no direct relation to the extent of damage done to the kidney epithelium.

THE INFLUENCE OF ORAL ADMINISTRATION OF TARTRATE UPON THE
KIDNEY OF FASTING RABBITS.

The widespread employment of tartrates in articles of diet, and the general employment of Rochelle salts as a purgative, make of particular interest an investigation of the influence of tartrates upon kidney structure and function when the salts are given by mouth. In order to use the results of the previous experiments as a standard of comparison the present observations were made with fasting animals. The protocols follow.

Rabbit 19.—A rabbit weighing 2,640 gm. was kept without food for three days. At the end of this period 10 gm. of tartaric acid (Baker, tested purity) neutralized with sodium carbonate were introduced into the stomach through a sound. The animal died in less than twelve hours. The organs appeared normal. Anuria has been in evidence for several hours.

Histological Examination. Kidney.—The epithelium of the convoluted tubules is fairly well preserved. There is slight vacuolation in some, and in others extensive desquamation. Most of the tubules contain granular, and in some instances, cellular debris, with occasional karyorrhexis. At the junction of the cortex and medulla is a narrow zone in which there are numerous tubules with epithelium entirely necrotic, swollen into a granular mass entirely filling the lumen. No such entirely necrosed tubules are found in either the cortex or the pyramids; in a few collecting tubules are hyaline casts, and in many convoluted tubules there is considerable nuclear fragmentation. The glomerules and interstitial tissues are normal. With Sudan III, there is found to be a diffuse slight fatty change in the convoluted tubule epithelium and a very severe fatty change in all parts of the loops of Henle. No fat is present in the collecting tubules or glomerules.

Liver.—There is a slight increase in the number of round cells in the interlobular connective tissue. The liver cells are considerably vacuolated in areas in various parts of the lobules, due to fat as shown by Sudan III. The cords are slightly narrowed as in a fasting animal.

Adrenal.—Normal.

Rabbit 21.—After a three days' fast a rabbit weighing 1,840 gm. was given 10 gm. of Rochelle salts (Merck's, crystalline product) by mouth, dissolved in 50 c.c. of water. The animal died in less than ten hours. The kidneys were large and hemorrhagic.

Histological Examination. Kidney.—Nearly all the secreting epithelium of all tubules has been destroyed by a process of vacuolation, which involves first the central part of the cytoplasm and spreads outwards until the entire cell is destroyed, the nucleus persisting last of all, becoming flat and pyknotic before disappearing. All stages of the process are present, but there are few cells in the convoluted tubules that are not somewhat affected; in some, only a narrow solid necrotic zone remains just inside the basement membrane. Henle's loops are less affected. The lumina of the tubules are full of loose cellular debris and occasional desquamated cells, but there is only occasionally any formation of casts, which are mostly granular. The glomerules show an extensive accumulation of granular material in the space, with the tufts much shrunken; there is some desquamation of endothelial cells into the glomerules, but no hemorrhage. Interstitial changes are absent, but there is edema of the areolar tissue about the hilum. With Sudan III, there is no trace of fatty change.

Liver.—Normal.

Rabbit 22.—After three days of inanition a rabbit weighing 1,660 gm. was given 8 gm. of Rochelle salts (Merck's crystalline) by mouth, dissolved in 50 c.c. of water. During the next twenty-four hours diarrhea was in evidence. The urine volume remained normal, although the nitrogen output was reduced from 0.88 to 0.31 gm. The rabbit lived about thirty-six hours. Just before death kidney secretion had stopped. The kidneys were hemorrhagic and the peritoneal cavity contained a relatively large volume of fluid.

Histological Examination. Kidney.—There is severe vacuolation of all the convoluted tubule epithelium, there being no normal cells, and most are entirely necrotic. Coagulation necrosis is prominent and cast formation is extensive. Henle's loops are generally filled with casts but the epithelium is usually well preserved. The collecting tubules are nearly all filled with hyaline casts. The glomerules occasionally contain a little granular debris, but most of them are normal. With Sudan III nearly all the tubules in the cortex show great numbers of fine fat globules; there is no fat in the collecting tubules, but the loops of Henle are very fatty. Occasionally a cast is found full of fat. There is but a trace of fat found in the glomerules.

Liver.—Normal.

Adrenal.—Normal.

Rabbit 23.—Following a three days' period of fasting, a rabbit weighing 1,480 gm. was given 5 gm. of Rochelle salts (Merck's crystalline) by mouth. The animal remained in apparently normal condition for a period of three days, when it was killed. At autopsy all tissues appeared to be normal.

Histological Examination. Kidney.—Almost normal. There is a little granular precipitate in some of the tubules, and a little granular change and vacuolation of the epithelium of a few of the convoluted tubules. No fat could be found by Sudan III.

Liver.—There is some connective tissue proliferation about the bile ducts and portal vessels. No stainable fat is present.

Adrenal.—Normal.

From the foregoing protocols it is apparent that tartrates administered by mouth to fasting rabbits are capable of calling forth pathological changes in the kidney similar in general to those produced by parenteral introduction. These observations also indicate that in order for tartrates given *per os* to produce effects at all comparable to those induced by subcutaneous administration, much greater doses are necessary.

THE ACTION OF ORAL ADMINISTRATION OF TARTRATES TO PHLORHIZINIZED RABBITS DURING FASTING.

In the previous section attention has been called to the fact that tartrates given by mouth to fasting rabbits produce pathological changes in the kidneys similar in kind to those provoked by subcutaneous introduction. Little opportunity for observance of change in urinary secretion was exhibited, since most of the animals died so soon after the ingestion of the salt. When the dose was sublethal the change in nitrogen elimination was not particularly well marked.

The present portion of this paper deals with the influence of tartrates when introduced *per os* to fasting rabbits, upon the rate and extent of elimination of water, urinary nitrogen, and dextrose, the excretion of the latter being induced by daily subcutaneous injections of phlorhizin. Examples of the results obtained follow.

RABBIT 12.

Rabbit, Weighing 1,720 Grams, Received Daily Subcutaneous Injection of 0.25 of a Gram of Phlorhizin.

Date (1912).	Urine.					Remarks.
	Volume in c.c.	Specific gravity.	Reaction to litmus.	Total nitrogen in gm.	Dex- trose in gm.	
March 25	90	1.030	Alkaline	0.80	1.79	10 gm. tartaric acid, neutralized with sodium carbonate, dissolved in 50 c.c. water given by stomach sound. Animal died in 18 hrs.
26	64	1.030	Acid	1.20	1.16	
27	47	1.040	Acid	1.14	1.04	
28	6 ⁴	—	Alkaline	0.07	0.00	

⁴ For eighteen hours.

Histological Examination. Kidney.—Extensive destruction of the epithelium of the convoluted tubules through vacuolation of the cytoplasm. The tubules immediately beneath the capsule are least affected, while the loops of Henle, especially at the junction with the medulla, show much coagulation necrosis. The glomerules show extensive exudation into the space with collapse of the tufts, while there are practically no casts in the tubules. With Sudan III there is no demonstrable fat in the epithelium, beyond a few droplets in the loops of Henle.

Liver.—Normal.

Adrenal.—Normal.

RABBIT 17.

Rabbit, Weighing 2,120 Grams, Received Daily Subcutaneous Injection of 0.25 of a Gram of Phlorhizin.

Date (1912).	Urine.					Remarks.
	Volume in c.c.	Specific gravity.	Reaction to litmus.	Total nitrogen in gm.	Dex- trose in gm.	
April 10	86	1.018	Acid	0.72	1.71	10 gm. tartaric acid, neutralized with sodium carbonate given by stomach sound.
11	104	1.025	Acid	1.14	2.58	
12	286	1.028	Alkaline	0.99	3.38	
13	56	1.024	Alkaline	0.62	1.24	Animal died at the end of 12 hrs.
14	17 ⁵		Acid	0.16	0.30	

Histological Examination. Kidney.—There are several areas of fibrosis beneath the capsule, which presents an irregular surface as if there had been some chronic inflammation. A few tubules have calcified epithelium, and a few others near the capsule show entirely necrotic epithelium which takes a faint basic stain. A few convoluted tubules and some of the Henle loops show recent necrosis of the epithelium, but these are rare. A few glomerules show fibrosed capsules. There are no casts. With Sudan III there is extensive, but not severe, fatty degeneration of the epithelium of practically all the convoluted tubules; there is very severe fatty degeneration of Henle's tubules, but the collecting tubules are practically free from fat. There is considerable fine fatty change in the interstitial tissue of the pyramids. The glomerules show no fat. This kidney is different from all the others in respect to the chronic changes present, which undoubtedly antedate our experiment.

Liver.—Much fine vacuolation of cells with fat in the center of the lobules; otherwise no changes are apparent.

Adrenal.—Normal.

⁵ For twelve hours.

RABBIT 13.

Rabbit, Weighing 1,680 Grams, Received Daily Subcutaneous Injection of 0.25 of a Gram of Phlorhizin.

Date (1912).	Urine.					Remarks.
	Volume in c.c.	Specific gravity.	Reaction to litmus.	Total nitrogen in gm.	Dex- trose in gm.	
March 25	110	1.020	Alkaline	0.96	1.12	5 gm. tartaric acid, neutralized with sodium carbonate, given by stomach sound.
26	80	1.035	Acid	1.44	1.79	
27	43	1.050	Acid	1.27	1.04	
28	130	1.035	Alkaline	1.04	2.24	
29	40	1.035	Alkaline	0.90	0.40	Animal killed.
30	38	1.032	Alkaline	0.90	0.80	

Histological Examination. Kidney.—A slight degree of vacuolation of the convoluted tubular epithelium, which is quite swollen generally and obliterates the lumen in many places. No other changes are noticeable. No casts. With Sudan III there is found a heavy fatty change in all the tubules at the junction of the cortex and medulla, but no fat is present in the cells outside this zone.

Liver.—Slight vacuolation of cells in the centers of the lobules, which is shown by Sudan III to be caused by fat.

Adrenal.—Normal.

RABBIT 14.

Rabbit, Weighing 1,480 Grams, Received Daily Subcutaneous Injection of 0.25 of a Gram of Phlorhizin.

Date (1912).	Urine.					Remarks.
	Volume in c.c.	Specific gravity.	Reaction to litmus.	Total nitrogen in gm.	Dex- trose in gm.	
March 25	140	1.020	Acid	0.96	2.00	Administered by stomach tube 2.5 gm. tartaric acid, neutralized with sodium carbonate. Ani- mal died in approximately 18 hrs. All organs seemed normal on autopsy.
26	50	1.032	Acid	1.14	1.63	
27	41	1.045	Acid	1.28	1.36	
28	29 ⁶	1.040	Alkaline	0.21	0.70	

Histological Examination. Kidney.—The epithelium of the convoluted tubules is much swollen and granular, obliterating the lumen of the tubules in most places. Wherever there is a lumen it contains granular detritus, and there is a little of the same in the glomerular spaces. No necrosis, casts, or interstitial changes. With Sudan III there is found to be a light diffuse staining of

⁶ For eighteen hours.

very fine granules in all the convoluted tubules, but the fatty change is severe only in the loops of Henle; and every tubule, except a few large collecting tubules at the junction of the cortex and medulla, is very fatty. There is no fat in the pyramids or in the glomerules.

Liver.—Normal.

Adrenal.—Normal.

RABBIT 20.

Rabbit, Weighing 2,020 Grams, Received Daily Subcutaneous Injection of 0.25 of a Gram of Phlorhizin.

Date (1912).	Urine.					Remarks.
	Volume in c.c.	Specific gravity.	Reaction to litmus.	Total nitrogen in gm.	Dex- trose in gm.	
May 1	70	1.015	Alkaline	0.58	1.40	10 gm. Rochelle salts (Merck) administered by stomach sound.
2	58	1.030	Acid	1.00	1.12	
3	60	1.032	Acid	1.25	1.40	
4	120	1.027	Alkaline	0.56	0.80	
5	80	1.030	Alkaline	1.00	1.16	Animal killed. Kidneys seemed small and shrunken.
6	58	1.030	Alkaline	1.24	0.54	

Histological Examination. Kidney.—Hyaline casts are very numerous in the loops of Henle, and in the proximal convoluted tubules. The epithelium is much better preserved than is usual in specimens showing so many casts, but nearly all the tubules show more or less granular detritus in the tubules. Glomerules and interstitial tissue are normal. Sudan III shows fat in a few isolated segments of Henle's loops, but no fat elsewhere.

Liver.—Normal.

Adrenal.—Normal.

A survey of the data given above leads to the conclusion that the introduction of tartrates by mouth to fasting rabbits, even in relatively large doses, is not nearly so effective in inhibiting the flow of urine and the excretion of urinary constituents as the administration of much smaller doses subcutaneously. There is an indication in some of the tables of a relatively slight diminution in the elimination of the urinary constituents under discussion. This reduction is not sufficiently marked, however, to lead one to assume the existence of any pathological change in the renal epithelium. Nevertheless, a glance at the respective histological reports will furnish sufficient evidence of a disintegrative action upon the convoluted tubules. The influence had apparently reached only the initial stages, which may account for the lack of noticeable change in the excretory

powers of the kidney. The influence upon the kidney seems hardly sufficient to account for the rapid intervention of death and it is suggested that the latter may be due to some secondary effect upon other organs or tissues.

THE INFLUENCE OF TARTRATES WHEN INTRODUCED BY MOUTH AND
SUBCUTANEOUSLY TO WELL FED RABBITS.

When tartrates are given by way of the mouth to well fed rabbits there is little evidence of a change in the elimination of urine, nor is the salt so toxic as when similarly introduced into animals when fasting. The following may be cited as examples illustrative of this point.

Rabbit 24.—A well fed female rabbit, weighing 2,800 gm., was taken from the stock pen and given by stomach tube 10 gm. of Rochelle salts dissolved in approximately 50 c.c. of water. From this time food was withheld. No symptoms of any sort, except a slight diarrhea, were noticeable for a period of three days. The volume of urine for the first day amounted to 72 c.c., for the second day to 36 c.c., and for the third day to 50 c.c. The specimens showed no differences that could distinguish them from normal rabbit urine. The animal was killed at the end of the third day and at autopsy all the organs and tissues seemed normal.

Histological Examination. Kidney.—There is a very little granular debris in some of the tubules, a little vacuolation in some of the epithelium cells, and a rare hyaline cast. Sudan III shows a severe fatty change involving all the tubules in the zone between the cortex and pyramids, stopping quite abruptly on either side. There is a very small amount of fat in some of the convoluted tubules (proximal) and almost none at all in the collecting tubules in the pyramids.

Liver.—There is extensive vacuolation of practically all the parenchyma cells, without necrosis or other changes. Sudan III shows this to be diffuse fatty change, somewhat more severe in the peripheries of the lobules.

Rabbit 25.—A well fed rabbit, weighing 2,600 gm., was taken from the stock pen and immediately given by stomach tube 8 gm. of Rochelle salts. Subsequent to the salt administration food was withheld. The rabbit showed no symptoms of any kind and for a period of two days voided normal urine. The volume of urine eliminated during the first day amounted to 140 c.c., while 100 c.c. were excreted on the second day. On this day the animal was killed. Autopsy showed all the organs to be normal in appearance.

Histological Examination. Kidney.—Almost normal; there is a little granular precipitate in some of the tubules, and a little granular change and vacuolation of the epithelium of a few of the convoluted tubules constitute all the changes to be observed. No fat was found with Sudan III.

Liver.—Normal.

Adrenal.—Normal.

Comparison of the effects produced by administration of tartrates *per os* to rabbits in a state of inanition and in a well fed condition shows in each instance the existence of what may be considered the initial stage in the process of renal disintegration. In the former case the pathological change appears to progress to a point considerably beyond the stage reached by the abnormal process in the well fed animal. In other words, even in the animal previously well fed, tartrates given by mouth are capable of initiating pathological changes in the kidney. Nevertheless, these abnormalities are much more in evidence when the animal has been starved previously for a short period. It is apparent, therefore, that the nutritive condition of the animal plays a part in the degree of effect produced by the introduction of tartrates by mouth.

In order to test the correctness of this hypothesis, subcutaneous injections of tartrates have been given to well fed animals. Administration of tartrates in this manner rarely fails to induce marked effects in the fasting rabbit. A procedure like that outlined above should, therefore, decisively answer the question under discussion.

The experiments below are cited as examples bearing upon this point.

Rabbit 26.—A well fed rabbit, weighing 2,000 gm., was taken from the stock pen and immediately given a subcutaneous injection of 1 gm. of Rochelle salts (0.5 gm. per kilo). The animal showed little abnormality during the three days of observation. On the first day 54 c.c. of apparently normal urine were voided; on the second day, 150 c.c. of very pale urine; and on the third day 88 c.c. of urine of the same character. The rabbit was killed at the termination of the third day, and autopsy showed all organs and tissues to be normal in appearance.

Histological Examination. Kidney.—There is considerable vacuolation of the convoluted tubule epithelium, but no necrosis. A few hyaline casts are to be found in the collecting tubules. There is a little blood in some of the collecting tubules, but no source was found for this. Other structures were normal. All the epithelial cells take a diffuse pale yellow stain with Sudan III, not resembling fat droplets in color.

Liver.—Contains much blood. There is slight vacuolation of the liver cells throughout the lobule.

Rabbit 27.—Under the conditions cited for rabbit 26, to a rabbit weighing 2,000 gm. 2 gm. (1 gm. per kilo) of Rochelle salts were introduced subcutaneously. No symptoms were noted except that the urine voided was very pale, being almost colorless. The volume for the first day was 27 c.c., for the second day 130 c.c., and for the third day 100 c.c. On the third day the animal was killed. Autopsy revealed only apparently normal organs.

Histological Examination. Kidney.—A large proportion of the (distal) convoluted tubules show complete necrosis of their epithelium which in some is still granular and in others is fused into hyaline casts. The rest of the convoluted tubules practically all contain either granular debris or hyaline casts, even when their epithelium is intact. The limbs of Henle's loops are usually distended by hyaline casts, while there is some necrosis of the epithelium of the loops themselves. The glomerules and collecting tubules are normal, while the smaller collecting tubules contain many casts. There are some patches of connective tissue proliferation in the medulla at the base of the pyramids. Sudan III shows no trace of fat.

Liver.—Normal.

Adrenal.—Normal.

From these experiments it is evident that the effects produced by tartrates subcutaneously administered to rabbits in an initial well fed condition may be as marked as those evoked during a period of inanition, although from our experience we have gained the impression that the changes induced in well fed animals by the subcutaneous introduction of tartrates are in general somewhat less pronounced than in the starving rabbit. For instance, in a well fed animal larger doses are necessary in order to evoke comparable results, both from the standpoint of urine elimination and the action upon the renal epithelium. Nevertheless, it must be concluded that the nutritive condition has apparently less relation to the subcutaneous introduction of tartrates than to the ingestion of these compounds.

THE INFLUENCE OF ALKALI ADMINISTRATION UPON THE DEVELOPMENT OF TARTRATE NEPHRITIS.

In view of the beneficial action, as alleged by Fischer,⁷ exerted in nephritic conditions by alkali, it appeared of importance to determine to what extent the pathological renal changes induced by tartrates would be affected by an assured sufficiency of alkali in the body. Under normal conditions the urine of the rabbit shows an alkaline reaction. During inanition a change in the balance of acids and bases occurs as evidenced by the markedly acid character of the urine.

According to Fischer's view, an accumulation of acid in the kidney cells is responsible for the production of the nephritic condi-

⁷ Fischer, M. H., *Nephritis*, New York, 1912.

tions in general. It is difficult to understand how a production of acid takes place in the kidney by the subcutaneous injection of a practically neutral (or slightly alkaline) solution of tartrate. An inspection of the protocols presented above will show that in general when solutions of tartrates are given hypodermically the urine assumes a strongly alkaline reaction. On the other hand, it is conceivable that the loss of alkali during inanition may play a part in tartrate nephritis, for instance, by rendering the renal epithelium unusually sensitive to substances like tartrate that are not readily combustible in the organism.

Nevertheless, in spite of these considerations, our observations with tartrates are not in harmony with Fischer's hypothesis, since tartrates, among other salts, are mentioned by him as being of value in the prevention of nephritis. We find, however, that tartrates are capable of provoking a most severe pathological change in the renal epithelium. Fischer probably assumed that tartrates are readily burned to carbonates, in a manner similar to certain other salts of organic acids.

In our experiments concerning the influence of alkali administration upon tartrate nephritis we have taken as an index of alkali sufficiency the maintenance of an alkaline (to litmus) urine. To obtain a permanently alkaline urine in the fasting rabbit two procedures have been followed. In the first place sodium carbonate was employed as the alkali, in other cases sodium acetate and sodium citrate were given, the latter course being pursued with the idea that the greater portion of these salts would only slowly burn to the form of carbonate, and hence might be less rapidly eliminated than when the carbonate was given directly. In order to insure an alkaline urine in the fasting rabbit it is necessary to administer by mouth approximately two grams daily of any of the salts mentioned above. Beyond a slight diarrhea, none of these compounds gave rise to any noticeable symptoms. In control experiments the salts were given on three successive days during inanition, and throughout this period the urine voided exhibited varying degrees of alkalinity. At the end of this time the animals were killed and the kidneys examined histologically. Typical reports concerning specimens thus procured follow.

Sodium Carbonate Administration. Rabbit 37.—There are no distinct pathological changes of any sort beyond a slight precipitate of protein in the convoluted tubules.

Sodium Acetate Administration. Rabbit 38.—There are no pathological changes.

Sodium Citrate Administration. Rabbit 39.—The epithelium of the convoluted tubules is swollen and there is some vacuolation. In the pyramids there are a few foci of acute interstitial inflammation, probably a local infection.

It is evident from these reports that the administration of alkali, such as sodium carbonate, or salts, as sodium acetate, that may form carbonate in large measure, is without significant influence in the production of pathological changes in the renal epithelium. Sodium citrate possibly behaves in an analogous manner, although in the single instance observed a slight action appeared to be exerted upon the convoluted tubules, although this may have been associated with the local infection which produced changes in the interstitial tissue.

With rabbits 40, 41, and 42, in contrast with the earlier protocols, it may be seen that little or no influence upon nitrogen elimination was manifested by the subcutaneous injection of sodium tartrate to fasting rabbits that had received alkali or salts forming alkalies. The dose (0.5 of a gram per kilo) of tartaric acid, however, was relatively small, although it must be granted that this quantity of tartaric acid is usually sufficient to provoke a significant nephritis in the fasting rabbit (rabbit G). The histological report on these kidneys agrees in general with the excretion of nitrogen.

Rabbit 40.—The epithelium of the convoluted tubules is swollen so that practically no lumen remains; this is accompanied by considerable vacuolation, but no definite necrosis and no cast formation. The glomerules and interstitial tissues are normal.

Rabbit 41.—Shows but little change.

Rabbit 42.—There is very slight swelling and vacuolation of the epithelium of the convoluted tubules.

THE INFLUENCE OF ALKALI UPON THE DEVELOPMENT OF TARTRATE
NEPHRITIS. (SMALL DOSES OF TARTRATE.)*Rabbit 40; Weight 2,800 Grams.*

Date (1912).	Water intake in c.c.	Urine.				Remarks.
		Volume in c.c.	Specific gravity.	Reaction to litmus.	Total nitrogen in gm.	
Dec. 5	0	40	1.030	Acid	0.86	2 gm. sodium carbonate by mouth. 0.5 gm. tartaric acid per kilo, neutralized with sodium hydroxide, subcutaneously injected.
6	55	55	1.044	Alkaline	0.90	
7	25	70	1.060	Alkaline	0.83	
8	75	45	1.030	Alkaline	0.88	
9	10	25	1.038	Alkaline	0.71	

Rabbit 41; Weight 2,140 Grams.

Dec. 5	50	35	1.030	Acid	0.52	2 gm. sodium carbonate by mouth. 0.5 gm. tartaric acid per kilo, neutralized with sodium hydroxide, subcutaneously injected.
6	50	85	1.040	Alkaline	1.57	
7	50	95	1.050	Alkaline	1.66	
8	35	53	1.040	Acid	1.65	
9	50	50	1.050	Acid	1.64	

Rabbit 42; Weight 1,720 Grams.

Dec. 5	0	30	1.040	Acid	0.70	2 gm. sodium citrate by mouth. 0.5 gm. tartaric acid per kilo, neutralized with sodium hydroxide, subcutaneously injected.
6	50	40	1.030	Alkaline	0.81	
7	50	95	1.034	Alkaline	0.89	
8	35	43	1.040	Alkaline	0.93	
9	25	35	1.030	Acid	0.84	

It has been shown above that doses of tartaric acid approximating one gram per kilo of body weight given subcutaneously to fasting rabbits invariably produce significant changes both in the elimination of urinary constituents (rabbits H and I), and in the renal epithelium (rabbits C and D).

The tables illustrating the experiments carried out with rabbits 43 and 44 present the results obtained when tartaric acid in doses of one gram per kilo was injected into fasting animals receiving alkali administration similar to those previously discussed. Rabbit 45 shows the influence of the same dosage of tartrate but without treatment with alkali.

Comparison of these figures shows plainly that with the amounts given tartrates are still capable of diminishing the elimination of urinary nitrogen appreciably, even though the urine voided is constantly alkaline. The reduction of urinary nitrogen is less marked under these conditions than it is when no alkali has been administered.

Rabbit 43.—There is considerable precipitate in the convoluted tubules. Some of the epithelial cells here show a slight fusion of the cytoplasm, and in Henle's loops there is considerable necrosis with little cast formation.

Rabbit 44.—There is severe necrosis involving all of the distal and most of the proximal tubules; the same thing occurs in the loops of Henle. Many granular and hyaline casts are present. The glomerules and interstitial tissue are normal.

Rabbit 45.—Most of the distal convoluted tubules have lost their epithelium, not by coagulation necrosis, but apparently by a lysis, which leaves a skeleton of many of the cells. There is practically no coagulation necrosis, except in a few loops of Henle where occasional casts are also found. The glomerules are unchanged.

THE INFLUENCE OF ALKALI UPON THE DEVELOPMENT OF TARTRATE NEPHRITIS. (LARGE DOSES OF TARTRATE.)

Rabbit 43; Weight 1,200 Grams.

Date (1912).	Water intake in c.c.	Urine.				Remarks.
		Volume in c.c.	Specific gravity.	Reaction to litmus.	Total nitrogen in gm.	
Dec. 10	0	59	1.030	Acid	0.87	
11	25	40	1.030	Alkaline	0.96	1.5 gm. sodium carbonate by mouth.
12	125	100	1.030	Alkaline	0.60	2 gm. sodium carbonate by mouth. 1 gm. tartaric acid per kilo, neutralized with sodium carbonate, subcutaneously injected. 2 gm. sodium carbonate by mouth.
13	30	35	1.030	Alkaline	0.25	

Rabbit 44; Weight 1,200 Grams.

Dec. 10	0	45	1.024	Acid	0.56	
11	25	50	1.036	Neutral	0.70	1.5 gm. sodium citrate by mouth.
12	75	44	1.016	Alkaline	0.20	2 gm. sodium citrate by mouth. 1 gm. tartaric acid per kilo, neutralized with sodium carbonate, subcutaneously injected. 2 gm. sodium citrate by mouth.
13	25	155	1.011	Alkaline	0.45	

Rabbit 45; Weight 1,200 Grams.

Dec. 10	0	44	1.014	Acid	0.31	1 gm. tartaric acid per kilo, neutralized with sodium carbonate, subcutaneously injected.
11	35	55	1.020	Acid	0.88	
12	100	18	—	Slightly acid	0.11	
13	0	50	—	Slightly acid	0.14	

Although the number of experiments carried through is too small to permit a final conclusion to be drawn, it is indicated that the administration of alkali may somewhat diminish certain of the effects usually produced by the subcutaneous introduction of tartrates into fasting rabbits. Stated specifically, alkali treatment under the conditions outlined allows a greater elimination of urinary nitrogen than is obtained in animals subjected to analogous conditions, with the exception that alkali was withheld. From a study of the tissues there is evidence that the alkali had a slight beneficial influence upon the pathological manifestation in the renal tissues themselves.

SUMMARY.

Salts of tartaric acid administered subcutaneously to fasting phlorhizinized animals exert a markedly detrimental influence upon the secretory efficiency of the kidney, which is indicated by a greatly lessened output of certain typical urinary constituents. A histological study of the nephritic kidney demonstrates that the salts act specifically upon the epithelium of the convoluted tubules, and to a less extent upon the tubules of the loops of Henle, the glomerules, and interstitial tissue remaining unharmed. In the disintegrative process taking place, vacuolation first occurs, is rapidly followed by necrosis, and finally the dead cells or their debris may entirely fill the lumina of the tubules and form granular and hyaline casts.

There is no strict relation between the dose of tartrate and the extent of damage inflicted. While large doses invariably induce a well marked response small doses may at times produce effects equally significant.

Tartrates introduced into fasting animals call forth symptoms practically identical with those observed in fasting phlorhizinized

animals. It is therefore apparent that in the establishment of the pathological condition under discussion phlorhizin is without significant influence.

Neither the liver nor the adrenal exhibits any detrimental effect from the injection of tartrates.

The introduction of tartrates by way of the mouth to fasting rabbits is not nearly so effective in the production of nephritic symptoms as the administration of much smaller doses subcutaneously. In general, under the former circumstances the initial stages only of epithelial disintegration of the convoluted tubules obtain, which, however, are scarcely sufficient to account for the rapidity with which death usually ensues.

Although in well fed animals distinct pathological changes in the kidney are induced by the introduction of tartrates *per os*, these abnormalities are less in degree, but similar in kind, than those provoked under like conditions in the fasting animal. When tartrates are given subcutaneously to well fed rabbits the effects evoked are somewhat less pronounced than when the salts are injected into fasting animals. From these facts it is evident that the state of nutrition plays a part in the development of tartrate nephritis.

It is indicated that the introduction of a sufficiency of alkali to animals in a state of fasting permits a greater elimination of urinary constituents during tartrate nephritis than obtains under similar circumstances when the alkali is omitted. Histologically there is evidence that the administration of alkali exerts a slight modifying action.

EXPLANATION OF PLATE 20.

FIG. 1. Rabbit C. Section of kidney of rabbit receiving phlorhizin and sodium tartrate. Necrosis of convoluted tubules. The glomerules are normal.

FIG. 2. Rabbit E. Section of kidney of rabbit receiving sodium tartrate only. Necrosis of convoluted tubules. The glomerules are normal.

FIG. 1.

FIG. 2.

(Underhill, Wells, and Goldschmidt: Tartrate Nephritis.)