RENAL DAMAGE FOLLOWING THE INGESTION OF A DIET CONTAINING AN EXCESS OF INORGANIC PHOSPHATE

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Plates 12 to 14

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The addition of an excess of acid or basic sodium phosphate to the food of young albino rats is followed (1) by a remarkable increase in the size and weight of the kidneys. The gross appearance of these organs is not entirely normal and histological examination discloses extensive pathological changes which have resulted from the administration of inorganic phosphate (2). A description of this renal lesion and a series of experiments which demonstrate that it is due to a specific effect of the phosphate ion form the subject of the present communication.

Methods

The general experimental procedure has been described in detail elsewhere (3). Female albino rats were used as the experimental animal. In each case they were removed from the mother and placed upon the experimental diet when exactly 26 days of age. 44 days later, that is, when the rats were 70 days old, they were etherized and killed. Anatomical measurements were then made in the manner which has been described. Although changes in renal weight were the main interest, the weights of the heart and liver were also recorded. The kidneys and pieces of the heart and liver were preserved in Orth's fluid for histological examination.

Throughout each experiment every rat was weighed daily. If there was a loss of weight for several days the rat was removed from the experiment for it then became questionable whether or not its food intake, and hence the quantity of ingested phosphate, was comparable with that of others of the group. The daily food intake per rat was determined by measuring the amount of food consumed by groups of 4 to 6 rats over 2 day periods.

Experimental Diets

Experiments were carried out with nine different diets containing inorganic phosphate in five different forms. All of the diets were identical in so far as their protein, fat, carbohydrate, basic mineral and vitamin-containing food content were concerned. Their caloric value was also identical. They differed only in the amount and type of inorganic phosphate which they contained. 90 per cent of these diets was composed of the mixture described in Table I. The remaining

TABLE I

Control and Basal Diet

	per cent
Corn-starch	41.0
Casein	15.0
Lard	15.0
Cod liver oil	9.0
Salt mixture (Osborne and Mendel)	4.0
Dried yeast	4.0
Wheat germ	10.0
Agar-agar	2.0

1 gm.—4.8 calories

Element	Per cent of diet	Per cent of calories
Protein	17.2	14.8
Fat	25.1	48.6
Carbohydrate	42.7	36.6
Water	6.3	0.0
Roughage	3.4	0.0
Salts	5.2	0.0

constituents of each of the diets are summarized in Table II. The phosphate content and changes in the sodium and potassium contained in each diet are given in Table III. Diet 2 is strongly acid and acid-producing and Diet 5 strongly alkaline before and after being metabolized. Diet 3 is definitely acid and No. 4 definitely alkaline while the remainder are more nearly neutral. From 18 to 25 rats comprised the group which was fed upon each diet. Since more than 3 years intervened between the first (Nos. 1, 3 and 4) and the remaining phosphate experiments, two control experiments were carried out

on Diet 1, one (No. 1) with the original group and a second (No. 1 *a*) 3 years later. They gave essentially the same results and are evidence of the constancy of the experimental conditions.

TABLE II

Experiment No.	Agar-agar	H_3PO_4	NaH_2PO_4	Na_2HPO_4	Na_3PO_4	KH_2PO_4	K_2HPO_4
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
1	10.00						
2	6.54*	2.94					
3	4.50		5.50				
4	3.50			6.53			
5	1.70*				4.92		
6	6.07		1.80	2.13			
7	4.10		2.71	3.19			
8	2.14		3.60	4.26			
9	5.35					2.04	2.61

* These ingredients do not total 10 per cent because of water in the phosphate compound which made up the difference.

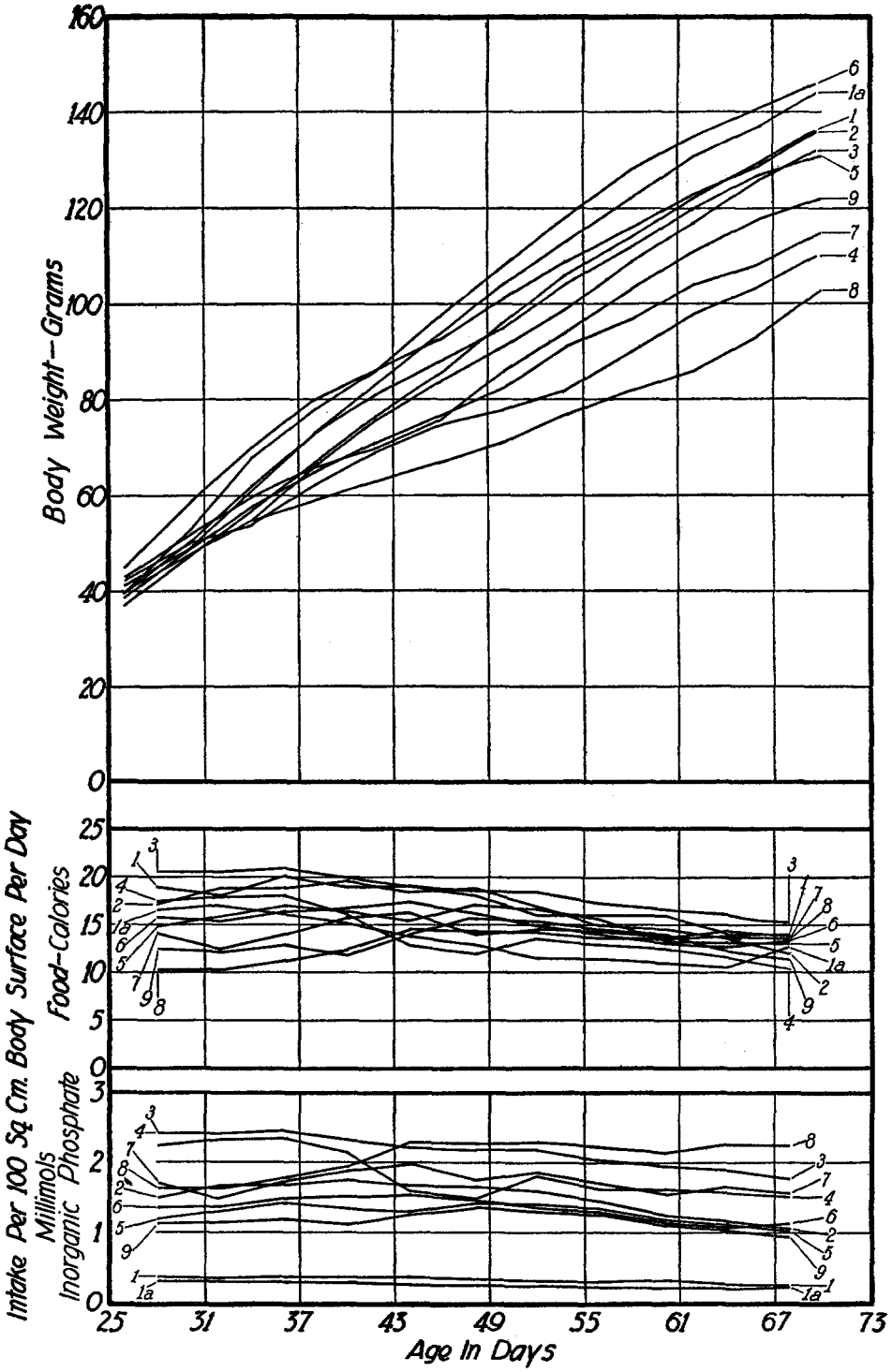
TABLE III

Experiment No.	Form of added phosphate	Added phosphate	Total phosphate	Added sodium	Total sodium	Added potassium	Total potassium
		Per 100 gm. food					
		*m.-eq.**	*m.-eq.*	*m.-eq.*	*m.-eq.*	*m.-eq.*	*m.-eq.*
1			20.0		5.3		12.9
2	H_3PO_4	90.0	110.0		5.3		12.9
3	NaH_2PO_4	138.0	158.0	46.0	51.3		12.9
4	Na_2HPO_4	138.0	158.0	92.0	97.3		12.9
5	Na_3PO_4	90.0	110.0	90.0	95.3		12.9
6	NaH_2PO_4(45) +Na_2HPO_4(45)	90.0	110.0	45.0	50.0		12.9
7	NaH_2PO_4(67.5) +Na_2HPO_4(67.5)	135.0	155.0	67.5	72.8		12.9
8	NaH_2PO_4(90) +Na_2HPO_4(90)	180.0	200.0	90.0	95.3		12.9
9	KH_2PO_4(45) +K_2HPO_4(45)	90.0	110.0		5.3	45.0	57.9

* M.-eq. = milli-equivalents; phosphorus assumed to be trivalent.

RESULTS

In Text-fig. 1 have been charted for each of the ten groups, growth in terms of the mean daily body weight, and food intake on the basis


Body Weight—Grams
160
140
120
100
80
60
40
20
0
6
1a
1
2
3
5
9
7
4
8
Intake Per 100 Sq. Cm. Body Surface Per Day
Food-Calories
25
20
15
10
5
0
Millimols Inorganic Phosphate
3
2
1
0
25
31
37
43
49
55
61
67
73
Age In Days

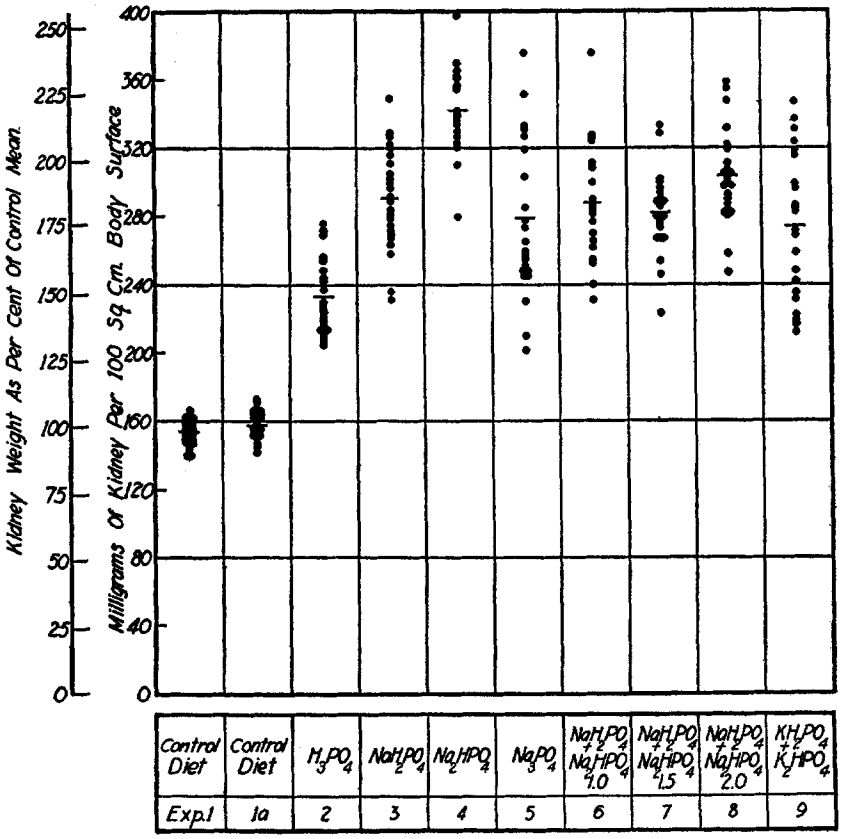
TEXT-FIG. 1

TABLE IV

Group Means of Anatomical Measurements Made at Death

Experiment No.	1	1a	2	3	4	5	6	7	8	9
Nature of experiment	Control	Control	H_3PO_4	NaH_2PO_4	Na_2HPO_4	Na_3PO_4	NaH_2PO_4 + Na_2HPO_4	Same × 1.5	Same × 2.0	KH_2PO_4 + K_2HPO_4
No. of rats in experiment	25	22	22	24	18	22	19	22	22	22
Body weight (gross), *gm.*	135	143	135	132	111	130	137	115	97	122
Body weight (corrected), *gm.*	133	140	127	125	103	126	133	110	93	115
Body surface, *sq. cm.*	290	313	287	284	261	285	295	259	231	267
Body length, *mm.*	177	180	175	176	167	175	180	168	157	172
Heart weight (actual), *mg.*	501	503	476	516	446	493	512	452	380	464
Heart weight per 100 sq. cm. body surface, *mg.*	173	165	166	182	178	173	174	175	164	173
Liver weight (actual), *gm.*	5.02	5.67	5.71	6.10	5.64	5.06	5.86	4.81	4.62	
Liver weight per 100 sq. cm. body surface, *gm.*	2.11	1.86	1.99	2.23	2.26	1.77	1.98	1.85	2.00	
Kidney weight—left, *mg.*	441	474	653	835	848	774	821	723	689	732
Kidney weight—right, *mg.*	457	502	676	860	868	814	859	749	719	747
Kidney weight—total, *mg.*	898	975	1328	1695	1716	1588	1680	1472	1408	1479
Kidney weight—average, *mg.*	449	488	664	848	858	794	840	738	704	739
Kidney weight per 100 gm. body weight, *mg.*	337	348	523	678	834	631	631	670	757	642
Kidney weight per 100 mm. body length, *mg.*	254	271	379	482	514	452	467	439	448	430
Kidney weight per 100 sq. cm. body surface, *mg.*	154	158	233	291	342	278	288	282	303	274
Kidney weight per 100 mg. heart, *mg.*	90	97	142	165	193	169	164	162	186	159

of the mean daily caloric intake, and phosphate consumption in relation to the calculated body surface, during the period of the experiment. Although the effect varies all of the phosphate diets had a deleterious effect upon the growth of the animals.



TEXT-FIG. 2

The mean results of the anatomical measurements made at death comprise Table IV. From these it is evident that the addition of an excess of inorganic phosphate in any form to the diet leads to a tremendous increase in the weight of the kidneys. In Text-fig. 2 this is shown graphically for the individual rats of each group. They are likewise much larger in size than the controls (Fig. 1). The variation in the

phosphate intake had no constant effect (Table IV) upon the weight of the heart or the liver.

From the results summarized in Table V it is seen that there is no constant relationship between the phosphate intake and the increase in renal weight. Neither is there a consistent difference in the effect of various types of phosphate. It is evident, however, from Text-fig. 3 that there is a general tendency for the increase in the weight of the kidneys to keep pace with the increasing phosphate intake. That this is not constant in the same manner as that with which the renal weight

TABLE V

Food Intake and Kidney Weight, Group Averages

Experiment No.	Nature of experiment	Intake per 100 sq. cm. body surface per day*		Kidney per 100 sq. cm. body surface		Phosphate above control	Ratio† Phosphate: Kidney weight
		Food	Phosphate	Total	Above control		
		gm.	*m.-eq.*	*mg.*	*mg.*		
1	Control	3.06	0.61	154			
1*a*	Control	2.88	0.58	158			
2	H_3PO_4	3.13	3.44	233	77	2.85	27
3	NaH_2PO_4	3.54	5.60	291	135	5.01	27
4	Na_2HPO_4	2.83	4.47	342	186	3.88	48
5	Na_3PO_4	3.17	3.49	278	122	2.90	42
6	$NaH_2PO_4 + Na_2HPO_4$	2.91	3.20	288	132	2.61	51
7	Same as No. 6 × 1.5	3.36	5.21	282	126	4.62	27
8	Same as No. 6 × 2.0	3.30	6.60	303	147	6.01	24
9	$KH_2PO_4 + K_2HPO_4$	2.91	3.20	274	118	2.61	45

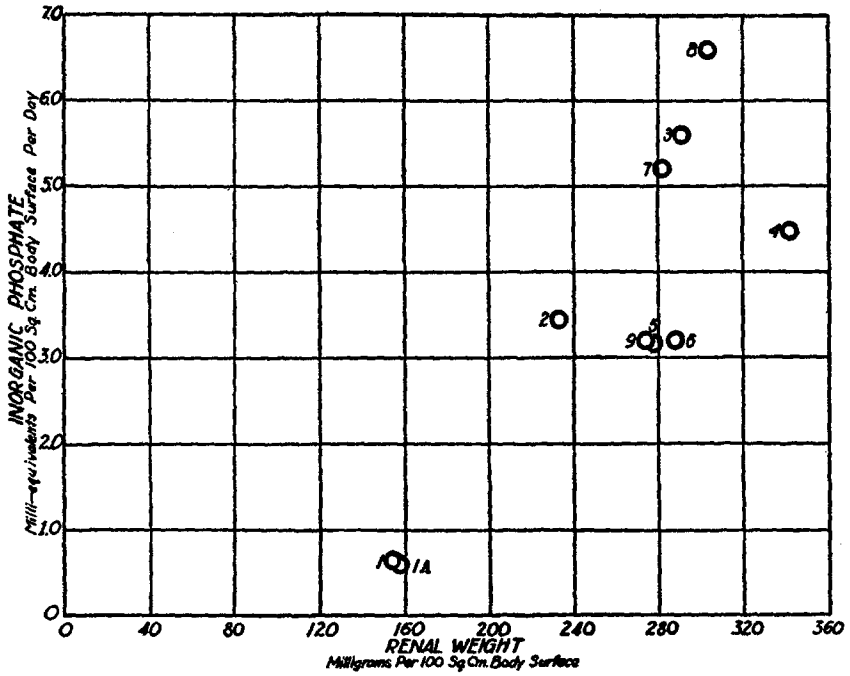
* Average of last 10 days of each experiment.

† Ratio = increased phosphate intake ÷ increase in kidney weight.

follows the protein intake (4) is hardly surprising, since a lesion is produced in this instance while the renal hypertrophy produced in increasing the protein intake is, as far as we know, physiological in nature.

The gross appearance of all of the phosphate kidneys was unusual. Their capsules always stripped readily and the color was then ordinarily more of a greyish white than the normal red-brown, particularly after the blood had been drained from the organ. In some of the experiments most of the kidneys had a smooth but mottled surface while in

others the majority were coarsely granular or even pebbled in appearance (Fig. 1). The cortical surfaces were most granular in Experiment 4 but also very noticeably so in Experiments 3, 7, and 8, less so in Nos. 5 and 9 and only occasionally in Nos. 2 and 6. The kidneys from all of the phosphate-fed animals felt very much firmer than normal and on section the cortex and medulla stood out clearly, particularly the outer stripe of the outer zone of the medulla.



TEXT-FIG. 3

The Histological Lesion

Microscopical examination showed essentially the same lesion in all the kidneys, irrespective of the nature of the phosphate used in the experiment. No abnormalities were found in sections of the heart or liver. The kidneys of the control animals of all the experiments were entirely normal.

The lesion consists of a complete disorganization of the outer stripe of the outer zone of the medulla. In a section of the normal rat kidney this is that clearly delimited band of tissue, lying immediately beneath the cortex which contains as its characteristic component, the terminal divisions of the proximal convoluted tubule. In the kidneys of the phosphate-fed animals it is transformed into a poorly outlined zone of distorted tubules that have lost all their normal characteristics. They are lined by a regenerated epithelium of markedly atypical appearance in which hyperplasia of the component cells is so extreme that giant cell-like masses may occlude the lumen. If an irregular lumen persists it is commonly filled with debris and masses of calcareous material. Other tubules are greatly dilated and they too may be packed with calcium deposits. About the distorted cross-sections of the tubules may be seen round cell infiltration and some fibrosis (Fig. 2).

The cortex is also involved to a greater or less degree in all the kidneys. The lesion in this part of the kidney appears to be an extension upward from the more severely involved outer stripe of the medulla and consists of either cystic dilatation of tubules or collapse of them associated with more or less round cell infiltration in the interstitial tissue. If such areas reach the free surface of the organ a retracted scar results.

The medulla, except for its above described outer stripe, is essentially normal. Occasional collecting tubules contain casts, and many of these are impregnated with calcareous substance.

The Histogenesis of the Lesion

For a study of the origin and early stages of the lesion rats were fed various mixtures of phosphate and killed on succeeding days. The earliest lesion found was observed in the kidneys of those that had been on a diet of 10 per cent Na_2HPO_4 for 1 day. The majority of the kidneys of animals of this early group show little evidence of damage, but in some the initial lesion is clearly evident and consists of a definite necrosis of the terminal portion of the proximal convolution (Fig. 3). The tubule presents a very definite localization of this damage, since it is only its termination that is involved at this early period, just at the point where the broad proximal tubule abruptly decreases in diameter to form the narrow limb of Henle's loop. The more proximal portions that extend down from the cortex are still entirely normal.

At the end of the 2nd day of feeding, similar lesions are found in the same portion of the tubule with increasing frequency. The limitation of the lesion to the termination of the tubule is, however, still observed.

During the 3rd day a rapid extension of the necrosis throughout all that part of the proximal convolution that is contained in the outer stripe of the outer zone of the medulla is regularly found in all animals. Two further complications are now present; namely, regeneration of an abnormal epithelium and the deposition of calcium salts in the necrotic debris that fills the involved tubules.

The regeneration is the most atypical that we have ever seen in the kidney. The exuberance of the process is extreme; masses of epithelial cells of varying shape and size, with large oval and vesicular nuclei heaping up on each other or fusing to form giant cells of relatively enormous dimensions replace the normal regular pattern of the outer stripe. The giant cells in many instances evidently represent the cross-section through a tubule occluded by epithelial proliferation and its center, a remnant of the lumen, may contain masses of calcareous material so that the similarity of the appearance to a typical foreign body giant cell is striking (Fig. 4).

Throughout all the damaged tubules similar calcareous deposits are found in great number (Fig. 2). They consist of scattered isolated granules and conglomerates or large spherical masses that lie either free or in necrotic debris surrounded and even infiltrated by the exuberantly regenerated atypical epithelial cells.

The further progress of the lesion can be followed through the succeeding days by the extension of the processes of necrosis, calcification and atypical regeneration throughout the entire breadth of the outer stripe of the outer zone of the medulla. Although variation is noted in the rate of development of the lesion in different experiments its general course can be described as follows:

By the 6th day the outer stripe of the outer zone is involved throughout its entire extent. Its spread towards the medulla is limited, however, and only rarely is there any extension past the sharp line which separates the inner from the outer stripe. The reason for this striking arrest of the process is evident when one remembers that the terminal portions of the proximal convolution, which are the segments of the tubule involved by the necrotizing process, stop sharply at this line of demarcation and the limitation of the lesion at this line is therefore conclusive proof that the broad ascending limbs of Henle's loop are not affected, for these extend downward through the entire

depth of the inner stripe of the outer zone of the medulla. In fact isolated ascending broad limbs lying between the degenerated and distorted proximal convolutions can still be seen in the outer zone as they ascend to enter the cortex.

By the 15th day the entire outer stripe is transformed into a zone of calcified distorted structures that bear little resemblance to tubules. Furthermore there has now developed about the distorted epithelial elements a definite increase in the interstitial connective tissue and scattered focal areas of round cell infiltration are present. Although the limitation of the spread downward through the medulla is still maintained, an involvement in the cortex becomes apparent. Necrosis and calcification along with atypical regeneration of epithelial cells has extended up the proximal convolution so that the distinctive pattern of the contiguous cortex is destroyed and blends with the abnormal tissues of the outer zone of the medulla. There results an apparent thinning of the cortex, though the cortical nature of the tissue may still be recognized by the persistence of glomeruli, still fairly well preserved, each surrounded by an island of easily recognizable proximal convolution.

Though the ascending limbs of Henle's loop never show any direct damage in the earlier stages of the lesion, it is plain that as the lesion develops they could hardly preserve their normal condition while passing through a wide band of disorganized tissue. This becomes especially true when connective tissue and round cell infiltration begins to develop in this region about the distorted tubules. The effect on the hitherto normal ascending limbs in the area of damage, *i.e.* in the outer stripe of the medulla, is collapse and their resulting disappearance as tubular structures. An even more striking effect is noted, however, at a distance from the immediate zone of damage, namely in the outer levels of the cortex, for here the distal convolution collapses as a result of the obliteration of its more proximal ascending limb of the loop. About these collapsed distal convolutions, that lie in the region of glomeruli, there occurs a proliferation of interstitial tissue and accumulation of round cells and fibroblasts and if near the surface a retracted pitting scar is thus produced (Fig. 5). Even in later stages the glomeruli persist, relatively little changed, except perhaps for occasional cystic dilatation of Bowman's space, and about

each one lies the periglomerular cluster of the attached proximal convolution also still fairly well preserved.

The final picture is therefore that of a kidney with a narrow cortex throughout which are scattered focal areas of tubular collapse and cellular infiltration and scarring. This cortex is separated by a zone of disorganized tissue, in which atypical regeneration, calcification and fibrosis are extreme, from a medulla that, except for the presence of occasional casts in the collecting tubules, is essentially normal. This destruction of the architecture of the organ is apparently a permanent one, as animals after 20 days of phosphate feeding were placed on a normal control diet with no excess of phosphate and killed after 30 days. Their kidneys still showed the lesion in a marked form.

DISCUSSION

There can be no doubt but that the renal lesion with which we are concerned is due solely to the excess of phosphate ion in the food. The changes occur in the kidney whether the phosphate is administered as the free acid, in combination with an excess of alkali (trisodium phosphate), as the acid salt (monosodium phosphate), as the alkaline salt (disodium phosphate), as a neutral mixture of these salts or whether the cation in combination with the phosphate is sodium or potassium.

Numerous cations, particularly the heavy metals, have long been known to cause varying degrees of renal damage. There is some evidence (5) that a general excess of acid radicles may result in a mild degree of renal irritation. In 1878 Kobert (6) found that strong phosphoric acid given either intravenously or *per os* resulted in an acute renal irritation, but gives no evidence nor suggests that the effect was due to the fact that not only acid but phosphate had been given. Hirsch (7) describes acute changes in the convoluted tubules following the intravenous injection of sodium acid phosphate solutions which resemble very closely the renal damage which Seegal (5) found to follow a severe experimental acidosis. These changes apparently have nothing in common with the lesion with which we are concerned here.

Cramer has recently reported (8) renal lesions not unlike those with which we are dealing produced in rats fed on a diet deficient in magnesium. However the salt mixture which he used in his diet contained sufficient phosphate to produce damage and he notes that there were also many changes in the kidneys of his controls. We have been unable to produce the lesion solely through a low magnesium diet and Gough, Duguid and Davies (9) have reported a similar experience. These

investigators in a way have confirmed our report (2) of phosphate damage to the kidneys, for in studying the renal lesions of hypervitaminosis D they found that the damage was greatly intensified when large amounts of sodium phosphate were added to the diet. The kidneys from these rats showed lesions very similar to our findings.

Our experiments give no evidence concerning the mechanism by which the renal lesion is produced in the administration of phosphate. A direct effect of an excess of phosphate ions on the renal cells seems the most likely mechanism, although we have been able to produce only a transient swelling of the tubular epithelium through daily intraperitoneal injections of a neutral sodium phosphate solution in a quantity equal to that which produces marked renal damage when given *per os*. The deposition of calcium salts seems definitely to follow cell destruction, a point that has given rise to speculation in the rather similar lesions produced by parathyroid extract (10, 11) and toxic doses of viosterol (12, 13). The calcification would seem therefore to be analogous, though much more excessive, to the commonly observed deposition of calcium in the necrotic tubular debris that results from damage by many renal poisons. Even the degree observed in our experiments, however, may be equalled in the lesion caused by toxic effects of such a different substance as arsphenamine (14).

The anatomical aspects of the lesion are interesting, chiefly from two standpoints. First, in the very definite localization of the damage to a certain region of the kidney. The lesion begins in and, except for certain secondary effects, remains localized to the outer stripe of the outer zone of the medulla. This localization depends in turn on the fact that it is only the terminal segment of the proximal convoluted tubule that is directly affected by the toxic agent. Selective action of renal poisons on various parts of the proximal convolutions are well known but in no case, not even after uranium poisoning (15) do the late changes in the architecture of the kidney remain so localized. The second point of interest is the speed with which the lesion develops. By the end of the 3rd day, the outer stripe of the outer zone of the medulla is completely transformed, not only by the regressive processes of degeneration and necrosis but also by the proliferative changes of regeneration and hyperplasia.

SUMMARY

The addition of an excess of inorganic phosphate in the form of orthophosphoric acid, acid, basic or neutral sodium or potassium phosphate to the diet of albino rats results in the development of an interesting and permanent renal lesion.

The phosphate renal lesion is characterized by a necrosis of the cells of the convoluted tubules commencing at the terminal end, followed by a regeneration of atypical epithelium and calcification of the necrotic debris that fills the tubules.

The entire outer stripe of the outer zone of the medulla is transformed into a zone of distorted structures and there is an increase in the interstitial connective tissue. The adjoining cortex is also involved with cystic dilatation of tubules and collapse. Such areas may reach the free surface of the organ and produce a retracted scar.

In the gross the kidneys are enlarged and firm on section with a pebbled surface produced by numerous scars.

The maximum changes in the kidney structure are reached after some 15 days although necrosis of the convoluted tubule cells is evident after a single day of phosphate feeding.

The renal structure is not restored to its normal form when the excess of phosphate is removed from the diet.

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EXPLANATION OF PLATES

PLATE 12

FIG. 1. The kidneys from experiment described in Table IV in which phosphate in various forms was fed for 44 days. The upper row is of the control animals (Experiment 1*a*); from above down each row shows the effect of H_3PO_4 (Experiment 2); Na_3PO_4 (Experiment 5); NaH_2PO_4 + Na_2HPO_4 (Experiment 6); same mixture × 1.5 (Experiment 7); same mixture × 2.0 (Experiment 8); and KH_2PO_4 + K_2HPO_4 (Experiment 9).

PLATE 13

FIG. 2. The typical lesion after 6 days of a diet containing a mixture of 3.19 per cent Na_2HPO_4 and 2.7 per cent NaH_2PO_4. Above, the cortex with its convoluted tubules and glomeruli is unaffected. The lower two-thirds of the figure is occupied by the outer stripe of the outer zone. The pattern of the tubules is completely disorganized by the necrosis, atypical regeneration and calcification. Hematoxylin and eosin stain. × 150.

FIG. 3. The initial lesion from the kidney of a rat fed 48 hours on a diet containing 10 per cent Na_2HPO_4. The outer stripe of the outer zone of the medulla. Most of the terminal portions of the proximal convoluted tubule are normal, but extending down through the center of the figure is the end-piece of one whose epithelium is entirely necrotic. Hematoxylin and eosin stain. × 350.

PLATE 14

FIG. 4. The outer stripe of the outer zone of the medulla from the kidney of a rat fed 15 days on a diet containing 10 per cent Na_2HPO_4. Exuberant and atypical regeneration of the tubular epithelium distorts the tubule pattern. Many are transformed to solid structures. Giant cell-like masses are seen in several places. The two open areas on each side of the figure are spaces that were filled with calcareous material which has broken out of the tissue in sectioning. Hematoxylin and eosin stain. × 350.

FIG. 5. The cortex from a kidney of a rat fed 44 days on a diet containing $Na_2H_2PO_4$ and Na_2HPO_4, (Experiment 6 of Table IV and Fig. 1). Above the glomeruli and periglomerular proximal convolutions are fairly well preserved. Below and to the right fibrosis and round cell infiltration about collapsed distal convolutions are seen. Hematoxylin and eosin stain. × 150.

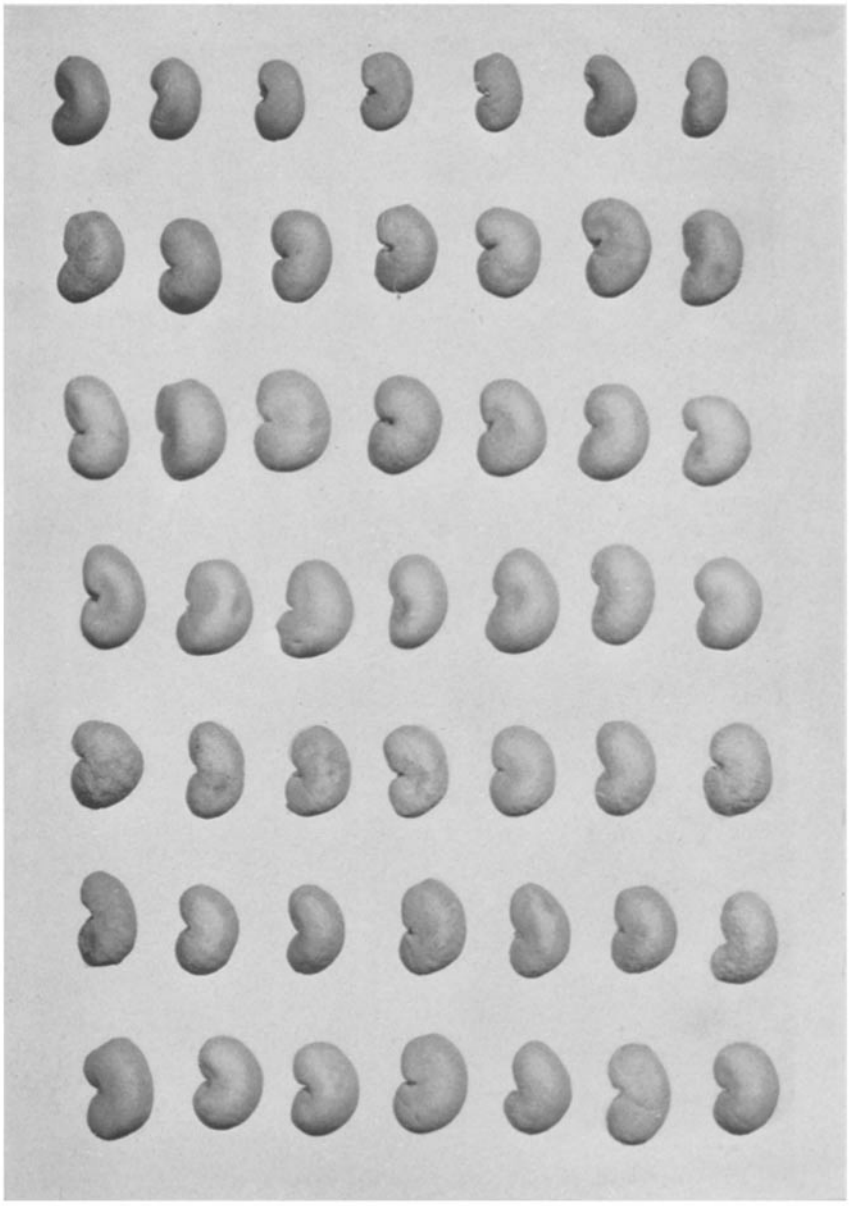

FIG. 1

(MacKay and Oliver: Renal damage after excess of phosphate)

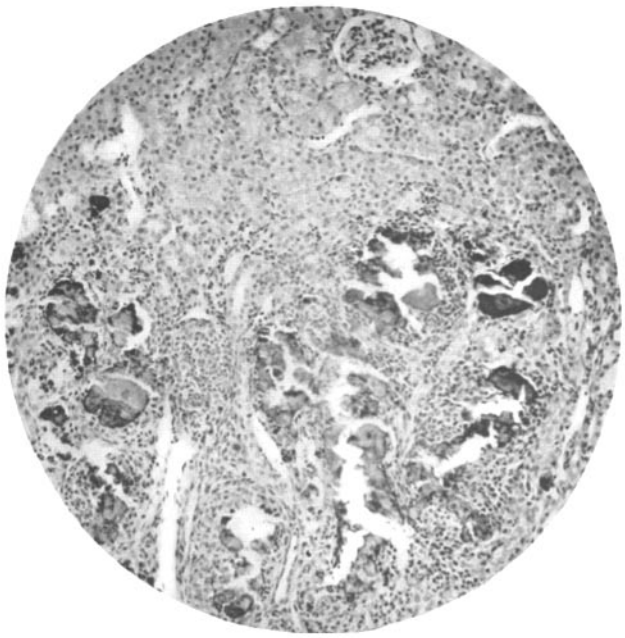

FIG. 2

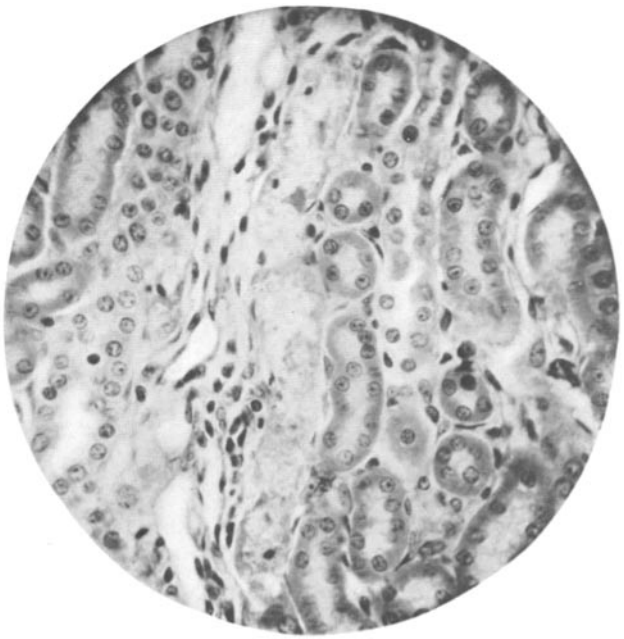

FIG. 3

(MacKay and Oliver: Renal damage after excess of phosphate)

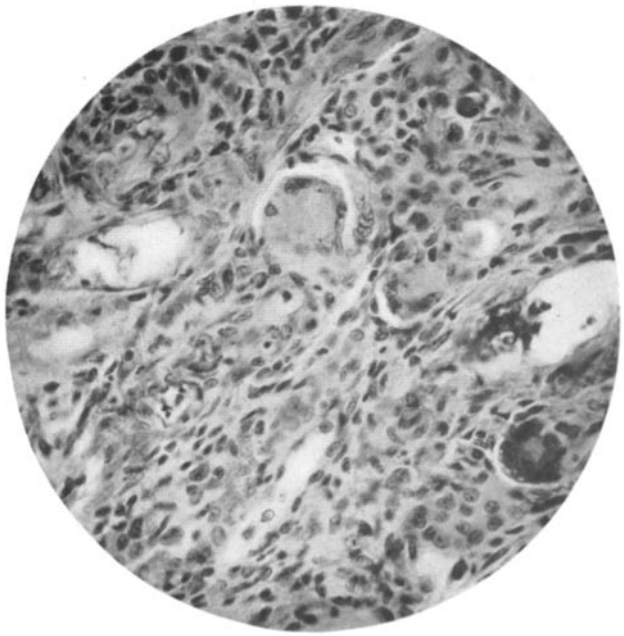

FIG. 4

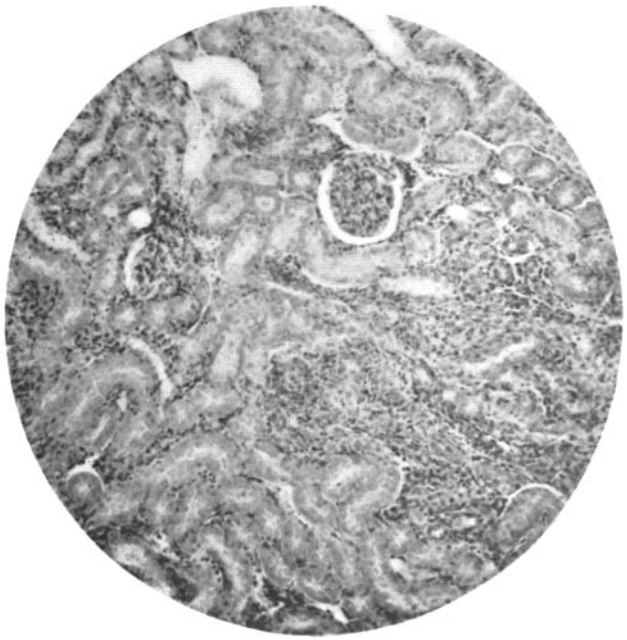

FIG. 5

(MacKay and Oliver: Renal damage after excess of phosphate)