CXLVIII. KIDNEY PHOSPHATASE.
II. THE ENZYME IN DISEASE.

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In an investigation recently described by one of us in this *Journal* [Kay, 1926] data were quoted which strongly suggested a correlation between the phosphatase content of the kidney and the functional activity of this organ.

Further support for this suggestion has now been obtained from a study of the phosphatase content of (*a*) human kidneys, obtained *post mortem* from individuals dying from various causes, including kidney disease, (*b*) kidneys of rabbits with acute experimental nephritis.

Method.

The method used for determining the phosphatase content of a given kidney is that described on pp. 795 and 797 of the communication just mentioned. The activity of the phosphatase of rabbit's, rat's and pig's kidney has been previously shown to have a fairly broad optimum between p_H 8·8 and 9·2. This is true also for human kidney phosphatase. The optimum reaction becomes somewhat less alkaline as the period over which the activity of the enzyme is determined increases. In the great majority of the determinations which are given in the present paper, the activity of each kidney extract has been ascertained at a series of p_H values from 8·25 to 10·0. For two hours' activity the optimum is invariably between p_H 8·8 and 9·2. The unit of kidney phosphatase we define as the amount of enzyme which, at 38°, and in Sørensen's glycine-NaOH buffer solution at p_H 8·9, is required to liberate 1 mg. phosphorus as inorganic phosphate from excess of sodium β-glycerophosphate solution in 2 hours. The phosphatase activity of a tissue we express in units per g. (wet weight). Provided care is exercised in the sampling of the tissue (which should be obtained with as little delay as possible *post mortem*), analyses by different observers on the same kidney give reasonably concordant results (Table I).

Table I. *Kidney phosphatase in units per g. tissue (wet weight).*

	Observer			
No. of expt.	R. T. B.	H. D. K.	R. H. R.	Remarks
1	2·6	2·7	—	Normal
31	0·5	0·4	—	Nephritic
A 241	—	4·7	4·9	Normal
A 192	2·6	2·8	—	Cardiac failure "back pressure" kidney

If a portion of a rabbit's kidney is kept for 24 hours at room temperature before making the determination, there is usually a slight fall (about 10 %)

in the phosphatase activity. The human kidneys used in this series were obtained at the routine *post mortem* examination, usually within 24 hours of death, during which time the cadavers were kept in a cold chamber. With human kidney a further period of 24 hours in the cold box in addition to the usual time between death and *post mortem* examination has no appreciable effect on phosphatase activity. It is therefore unlikely that variations in the phosphatase content of the kidneys, due to *post mortem* changes, exceed 10 % in any of our determinations.

A. Human Kidneys.

Results of determinations carried out on portions of kidney obtained *post mortem* from cases of disease and of accidental death are shown in Tables II, III, IV, and V.

Table II. *Cases without definite clinical or* post mortem *evidence of renal disease or abnormality other than slight parenchymatous degeneration.*

No. of expt.	Age of individual	Cause of death	Report on kidneys *p. m.*	Phosphatase units per g.
A 67	6½ months foetus	Foetus quite healthy. Premature delivery	Normal	1·0
A 80	2 full term foetuses	Delivery	,,	1·8 2·4
A 180	5 hours	—	,,	0·8
17	2 days	Haemorrhage	Anaemia*	1·9
1	6 years	Fractured skull	Normal	2·7
A 241	6 ,,	Injuries	,,	4·7
5	10 ,,	Abscess of brain	,,	4·6
6	Adult	Heart disease	,,	5·4
10	52 years	Injuries	One kidney lacerated, other normal (latter used)	6·2
9	60 ,,	Cerebral tumour	Parenchy. degeneration	3·3
A 11	10 ,,	Injuries	To naked eye, normal	5·8
24	3 months	Diarrhoea and vomiting	Parenchy. degeneration	5·8
25	18 years	Injuries	Anaemia*	6·2
32	35 ,,	Haemorrhage from gastric ulcer	,, *	5·1
A 202	46 ,,	Cerebral tumour	Normal	4·8

* Due to pre-mortal haemorrhage.

Table III. *Cases in which death was due to nephritis.*

No. of expt.	Age of individual	Cause of death	Report on kidneys	Phosphatase activity
2	50	Uraemia	Slightly narrowed cortex	1·6
3	18	,,	Considerable reduction of patternless oedematous cortex	0·4
8	23	,,	Considerable reduction in cortex, pattern moderately clear	0·75
14	48	,,	Broad cortex with indistinct pattern	1·1
23	18	,,	Great reduction in completely patternless cortex	0·7
27	53	.	Great dilatation of pelvis with thinning of renal substance	0·85
29	20	,,	Marked narrowing of cortex. Amyloid infiltration	0·5
31	53	,,	Considerable reduction in width of cortex and greatly blurred pattern	0·45
A 257	46	,,	Typical red granular kidney. Moderate reduction in cortex. Granular distorted pattern	1·0

Table IV. *Cases in which death was due to causes other than nephritis, but in which renal abnormalities were found on* post mortem *examination.*

No. of expt.	Age of individual	Cause of death	Report on kidneys	Phosphatase activity
4	75	Broncho-pneumonia	Atrophied kidneys with a few cysts in cortex	2·2
21	53	Cerebral tumour	Bilateral cystic kidney with cysts throughout cortex and medulla	1·0
7	25	Heart failure	A few cysts and small areas of infarction in cortex beneath the capsule	2·9
30	63	Strangulated hernia. General peritonitis	Slight sub-capsular fibrosis and a few cysts	1·4

Table V. *Cases in which a severe infection was present before death.*

No. of expt.	Age of individual	Description of case	Report on kidneys	Phosphatase activity
11	43	Post-operative broncho-pneumonia	Severe parenchy. degeneration and oedema	4·6
13	50	Pericarditis. Heart failure	Congestion	4·7
15	22	Broncho-pneumonia	Parenchy. degeneration and oedema	2·8
19	14	Lobar pneumonia	Severe parenchy. degeneration	5·7
16	51	Pernicious anaemia. Tuberculosis	Anaemia, parenchy. degeneration and miliary tubercles	3·4
22	41	Broncho-pneumonia. Peritonitis	Anaemia, parenchy. degeneration	2·8
12	46	Hydatid disease of the liver. General peritonitis	Fatty or lipoid degeneration	2·25

Table VI. *Average values.*

Description of cases	Ages	No. of cases	Average value for kidney phosphatase
Normal	2 days and under	5	1·6
Normal, or no evidence of renal disease	3 mths. to 60 yrs.	11	4·8
Chronic nephritics	18 yrs. to 53 yrs	9	0·8
Not nephritic but other renal abnormality	25 yrs. to 75 yrs.	4	1·9
Severe infective conditions	14 yrs. to 51 yrs.	7	3·7

Table VI summarises the first series of findings:

(*a*) Foetal and very young kidney tissue is considerably less active than older tissue.

(*b*) In patients with chronic nephritis dying from uraemia, the phosphatase content of the kidney is markedly diminished, being reduced, on the average, to about one-sixth of the normal adult value.

(*c*) In cases in which death was not due to nephritis, but in which degenerative conditions were found in the kidneys *post mortem*, the phosphatase content of the kidney is also much reduced.

(*d*) The kidneys from cases in which a severe infective process was present before death, show some diminution in phosphatase content which is, however, much less marked than in (*b*) or (*c*) above.

B. KIDNEYS OF RABBITS WITH ACUTE EXPERIMENTAL NEPHRITIS.

Acute experimental nephritis was induced in rabbits by subcutaneous or intravenous injection of lethal doses (from 1·3 to 4 mg. U per kg.) of uranyl nitrate [cf. MacNider, 1920]. Death usually ensued from 4 to 7 days after the injection, and the kidneys were examined as soon as possible *post mortem*. Together with cardiac dilatation, there was invariably severe generalised oedema with large exudates of clear fluid into the peritoneal and pleural cavities. The kidneys were swollen and oedematous, but there was little if any change in the relative breadth of the cortex to that of the medulla.

In addition to the phosphatase content, the ratio dry weight to wet weight was determined in a number of cases, in order that the numerical correction of the phosphatase content for the "dilution" of the kidney tissue with oedema fluid might be ascertained.

The results are shown in Table VII.

Table VII.

Kidneys of control rabbits			Kidneys of animals with experimental nephritis				
No. of expt.	% dry wt.	Phosphatase activity	No. of expt.		% dry wt.	Phosphatase activity	Summary of histological report on kidneys*
219 (1 animal)	—	8·1	219 (2 animals)	A	—	2·9 L.	In all cases a severe degeneration of the tubules, and to a less extent of the glomeruli was found. In 219 B glomerular damage was relatively trivial. The order of severity of damage in these four animals based on histological examination was as follows: (1) 221 A (R) (2) 221 B (R) (3) 219 A (R) (4) 219 B (R)
					—	3·1 R.	
				B	—	3·3 L.	
					—	3·7 R.	
221 (2 animals)	23·9	10·9 L.	221 (2 animals)	A	17·5	2·4 R.	
	22·9	12·5 R.			17·6	2·3 L.	
	24·0	12·6 L.		B	16·1	2·5 R.	
					15·6	2·2 L.	
228 (1 animal)	23·8	10·7 L.	228 (1 animal)		15·7	2·8 L.	Severe degeneration and necrosis of the tubules
	22·4	— R.			16·0	3·3 R.	
238 (1 animal)	—	12·6	238 (1 animal)		—	3·4 L.	Not examined
					—	3·4 R.	

L. = left kidney; R. = right kidney.

* We are much indebted to Dr D. S. Russell for her kindness in making a histological examination of these kidneys.

From Tables VI and VII it will be seen that severe kidney damage, whether brought about by a protracted process of disease or induced rapidly by a toxic agent, is associated with a very large fall in the phosphatase content of the tissue. The observed diminution far outweighs any decrease which the "dilution" of the tissue by oedema fluid might bring about. Thus taking Exp. 221, Table VII, the average dry weight of the normal kidney was 23·6 % of the wet weight, giving an average phosphatase content of 50·5 units per g. dry weight. For the nephritic kidneys, with an average dry weight of 16·7 % of the wet weight, the phosphatase content per g. dry weight is only 23·5 units.

From Table VII it will also be seen that the order of increasing severity of damage, as determined histologically by a second observer, agrees with the order of decreasing phosphatase content per g. of tissue.

In the previous communication, already cited, we have shown that in the developing animal the phosphatase content of kidney tissue increases with increasing functional activity of this organ. Also, the renal cortex, which contains the essential secretory elements of the kidney, was shown to contain more phosphatase than the medulla. In the present paper, a diminished phosphatase content of the tissue is shown to be associated with diminishing functional capacity resultant from disease. These results suggest that the enzyme phosphatase plays an intimate part in renal activity, either cellular or secretory, and that its presence in amounts greater than a certain minimum is essential for the proper functioning of the organ.

It is admitted that the evidence is circumstantial and indirect, and that we may be dealing here merely with an associated failure of actually independent variables. Thus (*a*) in chronic nephritis the observed diminution in phosphatase activity may be due to the progressive decrease in the number of secretory units and their replacement by scar tissue, leading to a relative and absolute diminution in the amount of the more active cortical tissue; (*b*) in acute experimental nephritis, the poisoning and subsequent destruction of the glomerular and tubule cells would naturally result in the loss of many activities associated with the healthy cells (*e.g.* oxygen uptake, lipase and ereptase activity, glycolytic power), without there being of necessity any direct connection between the activities concerned—in this case between phosphatase activity and secretory ability. Nevertheless, the considerable circumstantial evidence in favour of a more direct relationship between the last two activities is at least not weakened by the results just described.

Summary.

Both in chronic nephritis in man and in acute experimental nephritis in rabbits, the phosphatase activity of the renal tissue is markedly reduced.

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MacNider (1920). *Arch. Int. Med.* **26**, 1.