URINARY EXCRETION OF ACID PHOSPHATASE

BY

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Marked elevation of serum acid phosphatase due to carcinoma of the prostate is often associated with evidence of impaired renal function, thus suggesting the possibility that the kidneys may excrete this substance, and that serum levels represent the balance between the rate of production and that of excretion of acid phosphatase (Daniel, 1952). It has long been known that urine is rich in acid phosphatase (Demuth, 1925), and Scott and Huggins (1942) have shown that, although most of this is added direct in the form of prostatic secretion, part is excreted by the kidneys.

The investigation reported here was undertaken with the object of discovering whether carcinoma of the prostate produced a change in the rate of urinary excretion of the prostatic (formol-stable) acid phosphatase, but the results show that there is no such change even when the serum formol-stable acid phosphatase is raised

and the kidney function normal. A series of estimations was also carried out on female patients with carcinoma of the breast.

Materials and Methods

All estimations carried out were of the prostatic formol-stable acid phosphatase (Abul-Fadl and King, 1948), but for convenience' sake they will be referred to as "acid phosphatase" throughout this paper.

The total daily excretion of urinary acid phosphatase was estimated on one or more occasions on four healthy young adult males, ten patients with benign prostatic hypertrophy, seven patients with carcinoma of the prostate, nine healthy women, and 13 women with carcinoma of the breast, of whom five had bone metastases.

Males who could micturate normally were instructed to void in three parts, and the volume and acid phosphatase content of each specimen were measured separately after each micturition performed during the 24-hour test period. It was assumed that the acid phosphatase in the mid-stream specimen had been excreted by the kidneys, and that the larger amounts found in the first and last parts were derived partly from kidney excretion and partly from prostatic secretion. Patients with catheter bladder drainage passed their urine into bedside bottles, and the volume and acid phosphatase content of this were measured for 24-hour periods. It was assumed that there was no regurgitation of prostatic secretion into the bladder and that all the urinary acid phosphatase was excreted by the

TABLE I.—Daily Excretion of Urinary Acid Phosphatase

Name	Age	Method of Collection of Urine	Total Excretion of Urinary Acid Phosphatase (Units/24 hrs.)	Renal Excretion of Acid Phosphatase (Units/24 hrs.)	Prostatic Excretion of Acid Phosphatase (Units/24 hrs.)	Serum Acid Phosphatase (Units/100 ml.)	Renal Clearance of Acid Phosphatase (ml. Plasma Cleared/Min.)	Renal Function	Clinical Features
<i>A. Apparently Healthy Men (4)</i>									
D. A. L. ..	35	In 3 parts	{ 1,876 1,534 1,583	{ 1,567 1,220 953	{ 309 304 630	{ 1.2 1.1 1.0	{ 58 48 41	Normal	
W. I. S. ..	30	" " "	—	503	—	0.8	41	"	
J. A. D. ..	24	" " "	—	1,605	—	1.0	108	"	
F. R. A. ..	34	" " "	864	598	266	2.1	12.2	"	
Average:	31		1,462	1,074	377	1.2	53		
<i>B. Patients with Benign Prostatic Hypertrophy (10)</i>									
R. I. C. ..	72	Suprapubic catheter	—	66	—	2.0	2.3	Normal	Small fibrous prostate
M. A. R. ..	65	"	—	251	—	1.5	7.0	"	"
T. I. S. ..	82	"	—	198	—	2.6	9.1	"	Large fibro-adenomatous prostate
D. E. N. ..	68	"	—	84	—	1.6	3.6	"	"
D. A. C. ..	70	"	—	254	—	1.5	7.0	"	"
S. W. A. ..	65	"	—	378	—	0.9	28.0	"	"
M. A. D. ..	74	"	—	272	—	1.1	—	"	"
V. E. N. ..	77	"	—	400	—	1.2	—	"	"
P. O. L. ..	70	In 3 parts	234	212	22	2.0	—	"	"
P. V. C. ..	72	" " "	290	222	68	0.4	8.4	"	"
Average:	71		262	234	45	1.5	9.3	"	
<i>C. Patients with Carcinoma of Prostate (7)</i>									
T. E. R. ..	72	Suprapubic catheter	{ — — —	{ 96 80 39	{ — — —	{ 6.5 10.8 14.6	{ 0.2 0.4 0.2	Normal	Histological diagnosis
H. O. B. ..	90	"	{ — — —	{ 290 360 —	{ — — —	{ 144 144 —	{ 0.14 0.17 —	"	Before stilboestrol therapy
R. E. D. ..	56	"	{ — — —	{ 254 87 72	{ — — —	{ 2.5 10.7 73.0	{ 7.0 — 0.06	"	After stilboestrol therapy
V. E. S. ..	76	"	—	49	—	1.2	2.9	Very poor	Blood urea 60
I. O. O. ..	73	In 3 parts	82	158	33	—	—	Poor	" " 100
L. O. T. ..	62	"	158	—	—	2.5	—	Normal	" " 80
B. U. M. ..	80	Suprapubic catheter	—	12	—	2.1	0.39	Very poor	Clinical diagnosis
Average:				128		37.5	1.3		Total prostatectomy for carcinoma On stilboestrol therapy Blood urea 90

kidneys. The healthy women were instructed to measure the volume of urine passed at each micturition during the test period, and to save a part of each specimen for acid phosphatase estimation. In the case of the other women, complete 24-hour collections of urine were estimated.

Estimation of Urinary Acid Phosphatase

Twenty ml. of each sample of urine was dialysed overnight in parchment shells against cold running tap-water, the volume measured after dialysis, and any change accounted for in the final calculation. The dialysed urine was diluted, usually four times, and the enzyme content estimated by a slightly modified King-Armstrong method. 0.5 ml. of urine was added to a substrate buffer mixture consisting of 1 ml. of 0.02 M disodium phenyl phosphate, 2 ml. sodium citrate/citric acid buffer, pH 4.9, and 1 ml. 5% neutral formalin, and incubated at 37° C. After one hour 1.5 ml. of dilute (1 in 3) Folin and Ciocalteu reagent and 3 ml. of 15% sodium carbonate were added, and after further incubation for 15 minutes at 37° C. the colour was measured in a photoelectric colorimeter with an Ilford 608 red light filter (cf. Delory and Hetherington, 1952).

Results

Four apparently healthy males whose ages ranged from 24 to 35 years excreted in the urines a daily average of 1,462 units of acid phosphatase. Of this amount 1,074 units were calculated, on the basis of mid-stream determination, to have been excreted by the kidneys and the remaining 377 units to have been added in the form of prostatic secretion. The average serum acid phosphatase of this group was 1.2 King-Armstrong units per 100 ml., and the renal clearance of acid phosphatase, as calculated from the formula $\frac{UV}{P}$, was 53 ml. of plasma cleared of phosphatase per minute (Table I, A).

Comparison of the acid phosphatase content of the urines collected in three parts shows that the lowest values were constantly found in the mid-stream specimens (Table II),

TABLE II.—*Acid Phosphatase Content of Urine Collected in Three Parts (Units/100 ml.)*

First Part	Mid-stream Part	Final Part
149	117	720
238	134	790
260	165	630
105	91	98
127	86	127
44	25	410
9	3	13
25	14	810
99	45	770
65	32	128
41	22	620
83	38	138
Average 104	65	438

and that the last part often contained much more acid phosphatase than either the first or the mid-stream specimen. Urine was withdrawn from the bladder of three of the first group of subjects by means of urethral catheters, and the rate of renal excretion of acid phosphatase found to vary from 0.35 to 2.25 units per minute, as compared with 0.38 to 2.4 units per minute as calculated from mid-stream specimens.

Ten patients with benign prostatic hypertrophy, whose ages ranged from 65 to 85 years, excreted a daily average of 262 units of acid phosphatase from their kidneys. Two of the ten were able to collect their urines by the three-part method, and it was found that their prostates excreted an average of 45 units of acid phosphatase each day (Table I, B). The average serum acid phosphatase of the group was 1.5 units per 100 ml., and the average renal clearance of acid phosphatase 9.3 ml. per minute. Each of the ten patients had normal renal function as shown by blood urea

estimations and intravenous pyelography, and in all of them the nature of the prostatic lesion was confirmed histologically.

Seven patients with carcinoma of the prostate, whose ages ranged from 56 to 90 years, excreted a daily average of 128 units of acid phosphatase from their kidneys (Table I, C). Only one of them could collect his urine by the three-part method, and it was found that his prostate excreted 33 units of acid phosphatase a day into the urethra. The average serum acid phosphatase of this group was 37.5 units per 100 ml., and the mean renal clearance of acid phosphatase 1.3 ml. per minute. The diagnosis of carcinoma of the prostate was based on histological findings in five of the patients and on firm clinical or serological grounds in the other two. Four of the patients had poor renal function as shown by raised blood urea, and their excretion of urinary acid phosphatase averaged 85 units a day as compared with 212 units a day for the three patients who had carcinoma of the prostate and normal renal function. The renal function of two of the patients deteriorated during the course of the investigation, and this deterioration was accompanied by a decrease in the excretion of urinary acid phosphatase. In one (Table I, C; R. E. D.), the serum acid phosphatase increased as the excretion of urinary acid phosphatase decreased; and in the other (Table I, C; H. O. B.) the serum acid phosphatase decreased, probably owing to the regular administration of stilboestrol.

Nine apparently healthy women, whose ages ranged from 23 to 60 years, excreted a daily average of 217 units of urinary acid phosphatase (Table III). Age, within the above limits, did not appear to have any significant effect on the rate of excretion of urinary acid phosphatase. The women with carcinoma of the breast excreted a daily average of 132 units of acid phosphatase (Table III). This was less than that excreted by healthy women. On the other hand, the women who had carcinoma of the breast and bone metastases excreted a daily average of 227 units of acid phosphatase, practically the same as in healthy women. A summary of these results is given in Table IV:

TABLE III

Initials	Age	Urine Acid Phosphatase (Units/24 hrs.)	Serum Acid Phosphatase (Units/100 ml.)	Renal Clearance of Acid Phosphatase $\frac{UV}{P}$ (ml. Plasma Cleared/Min.)
<i>Women with Breast Carcinoma</i>				
A. H. ..	45	93		
B. P. ..	30	85		
L. D. ..	44	102	1.4	5
D. J. ..	56	162	1.4	8.1
P. G. ..	51	118	2.7	3.0
B. L. ..	77	147	1.8	5.7
E. F. ..	48	91	1.6	4.0
N. S. ..	63	257	3.1	5.75
Average:		132	2.0	5.1
<i>Breast Carcinoma with Secondaries in Bone</i>				
P. T. ..	59	207	2.0	7.2
C. L. ..	53	131	2.6	3.5
M. R. ..	51	101	4.5	1.55
E. H. ..	57	230		
		235		
W. H. ..	54	474	1.0	33
Average:		227	2.5	11.6
<i>Healthy Women (9)</i>				
P. E. G.	23	{ 205 206 208		
R. M. H.	31	{ 260 296		
J. E. F. ..	30	{ 292 344		
J. A. L. ..	22	{ 127 128		
H. A. W.	32	{ 418		
A. R. D.	23	{ 137		
H. A. R.	60	{ 93		
S. T. E. ..	35	{ 165	0.5	22.5
S. T. S. ..	60	{ 164	1.0	11.3
Average:		217	0.75	16.9

TABLE IV.—*Summary of Urine and Serum Acid Phosphatase Results*

	Total Excretion of Urinary Acid Phosphatase (Units/24 hrs.)	Renal Excretion of Acid Phosphatase (Units/24 hrs.)	Prostatic Excretion of Acid Phosphatase (Units/24 hrs.)	Serum Acid Phosphatase (Units/100 ml.)	Renal Clearance of Acid Phosphatase $\frac{UV}{P}$ (ml. Plasma Cleared/Min.)
Apparently healthy men, 24-35 yrs.	1,462	1,074	377	1.2	53
Patients with benign prostatic hypertrophy	262	234	45	1.5	9.3
Patients with carcinoma of prostate		128		37.5	1.3
4 with impaired renal function		85			
3 with normal renal function		212			
Apparently healthy women 23-60 yrs.	217	217		0.75	16.9
Women with breast carcinoma	132	132		2.0	5.1
Women with breast carcinoma and bone secondaries	227	227		2.5	11.6

Variation in the Rate of Excretion of Urinary Acid Phosphatase

During the tests on normal men and women a note was kept of the time of each micturition, and the urine of patients with catheter drainage was in many instances collected at six-hourly intervals. Information thus gained shows that the concentration of acid phosphatase excreted by the kidneys was inversely related to the rate of urine formation, and that the rate of excretion of acid phosphatase appears to be independent of the rate of formation of urine.

A slight diurnal variation in the excretion of urinary acid phosphatase was found in all subjects, but this variation did not appear to be cyclical, and in women could not be related to the menstrual cycle.

Discussion

Healthy young adults excrete a considerable amount of acid phosphatase in their urines, and of this between one-third and one-fifth can be attributed to the direct addition of prostatic secretion to the urinary stream. Comparison of the acid phosphatase content of the urines collected in three parts (Table I) suggests that the first part of micturition washes out the prostatic secretion that has accumulated in the urethra, and that straining or some other factor associated with the completion of micturition produces an immediate discharge of more prostatic secretion. The volume of prostatic secretion required to produce these effects is probably small, as the seminal plasma is rich in phosphatase—for example, that of one of the subjects contained 6,000 units of acid phosphatase per ml. The assumption that mid-stream urine is reasonably free of prostatic secretion is supported by the close correspondence between the acid phosphatase content of catheter and mid-stream specimens, although the occasional occurrence of unusually high acid phosphatase levels in mid-stream urine (Table II) can probably be attributed to the added prostatic secretion.

Men in the sixth decade and over, with benign prostatic hypertrophy, excrete approximately one-sixth the urinary acid phosphatase of younger men, and this diminution applies to both the renal and the prostatic excretion of acid phosphatase. The output of acid phosphatase in the urine of old men corresponds closely to that of women aged 20 to 60 years.

Men suffering from carcinoma of the prostate excrete slightly less urinary acid phosphatase than men of a similar age suffering from benign prostatic hypertrophy; and the difference is most pronounced when renal function is poor. There is no evidence that the excretion of urinary acid phosphatase is related in any way to serum acid phosphatase

levels, and it can be concluded that the acid phosphatase put into the serum by carcinoma of the prostate is not eliminated in an active way by the kidneys.

Women suffering from carcinoma of the breast do not appear to excrete an increased amount of acid phosphatase in their urine, even though the plasma level is increased. In the cases of breast carcinoma without bone metastases the average daily excretion is lower than that in healthy women, or women with breast cancer with bone metastases.

No cause has been found for the slight diurnal variation of urinary acid phosphatase observed in all subjects or for the more marked variation in the rate of excretion that takes place throughout the day. The fact that the distribution of the rates of excretion of acid phosphatase by the kidneys of individuals fits the curve of general probability suggests that the rate is determined by many small factors operating at random and that there is no important underlying cause for the change. Calculation of the rate of renal clearance of acid phosphatase does not throw any additional light on the material studied, and merely emphasizes the inability of diseased kidneys to excrete acid phosphatase. The fact that women as well as men excreted a considerable amount of formol-stable acid phosphatase in their urine (217 units per day) shows that there must be some source of such phosphatase other than the prostate.

Summary

The rate of excretion of urinary acid phosphatase has been studied in four healthy young adult males, ten patients with benign prostatic hypertrophy, seven patients with carcinoma of the prostate, nine healthy women, and 13 women with carcinoma of the breast. Young men excrete up to six times more urinary acid phosphatase than elderly men or women of various ages. In both carcinoma of the prostate and carcinoma of the breast there was a decrease in the excretion of urinary acid phosphatase, in spite of a raised serum acid phosphatase.

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The findings of a special survey undertaken after four and a half years' experience of the workings of the National Health Service are included in the annual report for 1952 of the London County Medical Officer and School Medical Officer, Dr. J. A. Scott. These include general comments on administration, co-ordination, and co-operation with other services and separate comments on the individual services. The report also includes a detailed statistical account of the "smog" catastrophe of 1952, which in the space of a week contributed to the year's total death rate an extra 0.5 per thousand population. Further statistics show that cancer is the second leading cause of death among Londoners at 2.30 per thousand and that its incidence is increasing slightly, while cardiac diseases are the first. It is reported that there is a continuing drop in the number of children under 5 years who are being immunized against diphtheria, the total percentage now being only 50. The demands on the Council's Ambulance Service were very great, as were those on the District Nursing Associations, each nurse in the service paying on an average fourteen visits a day. The report also includes a detailed account of the School Health Service. The report is published by the London County Council, and may be purchased (price 2s. 6d., by post 2s. 10d.) from the Information Bureau at County Hall, or from Staples Press, Ltd., Mandeville Place, London, W.1, or direct from any bookseller.