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Prostatic acid phosphatase in carcinoma of the prostate gland

R Paul Hoff
University of Nebraska Medical Center

PROSTATIC ACID PHOSPHATASE IN CARCINOMA OF THE PROSTATE GLAND

R. Paul Hoff

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GENERAL CONCEPTS AND CONSIDERATIONS

Acid phosphatase is defined as that enzyme present in serum capable of hydrolyzing monophosphate esters at pH 5. [18] It is found in the liver, spleen, bone and kidney, which are probably the sources of the relatively small amount of enzyme appearing in the serum. However, the acinar epithelium of the prostate of mature males is a rich source of this enzyme and contains from one-hundred to five-hundred times as much acid phosphatase per gram of tissue as all the other organs. [18] Under normal conditions, the acid phosphatase of the prostate does not enter the blood stream and, therefore, this gland does not add to the contribution of circulating enzyme. [18] The role acid phosphatase plays in the bodily processes is not known.

For seventeen years the determination of serum acid phosphatase has been used for detection of carcinoma of the prostate. Elevated values have been correlated with advanced carcinoma of the prostate with spread to bones or distant metastasis. As a consequence, the finding of an abnormal serum acid phosphatase in a patient with clinical evidence of carcinoma of the prostate with or without x-ray evidence of bony involvement, the management has been solely palliative.

Fishman and others, found in their studies [9] of metastatic carcinoma of the prostate, a positive correlation with high serum acid phosphatase in only fifty per cent.

Clearly was there a need for improvement in detection, evaluation and management of these cases. Marked improvement in detection had to come before the latter two could be accomplished. Not only was there need for more acurate detection, but, even more, a need for much earlier detection, so as to bring the patient with carcinoma of the prostate to the attention of his physician in a perhaps, curable stage of his disease.

In 1953, it was found that L-tartrate is a potent inhibitor of acid phosphatase as well as liver, spleen and kidney.[7] Therefore, it was felt that if, in early carcinoma of the prostate, the level of acid phosphatase did rise even slightly, a test could be devised to estimate that produced by the prostate gland (the liver, spleen and kidney portions being almost negligible) and, thereby, curative treatment could be employed.

Such a test was developed by Fishman and Lerner in 1953,[7] with alterations being made in 1958[9] to simplify the procedure. The method of this test will be explained in detail in another part of the paper.

Through the years a level of 2.5 K. A. units of acid phosphatase has been considered the normal average, with a level over 5 K. A. units being indicative of metastatic disease of the prostate.[18]

There exists a category of acid phosphatase levels intermediate between the average of 2.5 K. A. units and those levels

over 5 K. A. units with probable carcinoma of the prostate. Two factors have mainly been responsible for this category. One is the phenomenum of hemolysis which, however slight it may be, enriches the serum with erythrocyte acid phosphatase. [7, 2] The other is the failure to correct for a certain degree of spontaneous hydrolysis, which the substrate, phenyl phosphate, depending on its purity, may undergo during the incubation of the serum digest. [7] In the past, these difficulties have been overcome separately by the formaldehyde inhibition of erythrocyte acid phosphatase [1] and by the use of suitable substrate controls in the assay procedure.

The view that, the serum acid phosphatase inhibited by the L-tartrate is most probably of prostatic origin is based on the following observations:

1. Solutions of purified human prostatic acid phosphatase were almost completely inhibited by 0.02 M L-tartrate. [2]

2. All patients with active carcinoma of the prostate showed a high proportion of prostatic acid phosphatase in their sera. [7,8,9, 21, 10]

3. L-tartrate invariably inhibited prostatic acid phosphatase of patients sera as well as added purified prostatic acid phosphatase. [7, 2]

4. In patients in which the disease had become activated, the prostatic acid phosphatase component of the sera increased progressively to high levels, forming an increasingly greater pro-

portion of the serum acid phosphatase. [7,8,21]

With these findings in mind it would, therefore, seem reasonable to assume that an elevated serum prostatic acid phosphatase in male patients is of prostatic origin.

The Determination of Prostatic Acid Phosphatase.

In 1953, Fishman and Lerner described a method for measuring the tartrate-sensitive fraction of serum acid phosphatase that reflected the enzyme of prostatic origin. This method, in their hands, proved to be more accurate in the detection of carcinoma of the prostate gland, [7,8,11,9] Other investigators, however, had trouble obtaining the same good results. [6,12,19] As will be pointed out later, Fishman suggested that because certain steps were tedious and time consuming, all calorimeter readings had to be made at certain times, some men have been "short cutting" the procedure and thus, not obtaining true values. [10]

It was clear, however, that any modification which would simplify the procedure without sacrificing accuracy, would be welcomed and lead to more widespread use of the test.

The "Diazo" method developed by Stolbach and others in 1958, seems to fulfill this requirement.

In the old procedure, the measurement of phenol liberated from the substrate, phenyl phosphate, involves precipitation of the serum proteins. As stated before, this is tedious and time consuming. Two reactions for eliminating the precipitation of

protein but retaining phenyl phosphate as the substrate have been suggested. One is based on the use of the amino-antipyrene condensation reaction for development of color with phenol;[15,20] in the other ("Diazo" method), a diotized coupling agent is used to form a phenol dye.[14]

The "Diazo" method seemed to be preferred because of final color stability, in addition to precipitation of protein not being required.

METHOD[21,7]

I. REAGENTS

SUBSTRATE: A one percent solution of disodium phenyl phosphate (Paul Lewis Laboratories, Milwaukee, Wisconsin) is freshly prepared every two weeks. It is discarded if incubation blanks manifest a sudden increase from the usual daily values or when blank contains more than 0.015 mg of phenol.

CITRATE BUFFER: pH 4.9. Dissolve 18.9 gm of citric acid in 500 ml of H_2O and 180 ml of 1 N NaOH, and then 100 ml of 0.1 N HCl are added. Make up to one liter with distilled water. Check pH of buffer and adjust to pH of 4.9 with N NaOH or 0.1 N HCl as needed. Store in refrigerator in a glass stoppered bottle.

0.2 M L-TARTRATE: 3.002 gms. of tartaric acid are dissolved in 50 cc. of H_2O. Approximately 35 cc. of N NaOH are added, the pH of the solution is checked and again adjusted to 4.9 with 1 N NaOH or 0.1 N HCl. The volume is made up to 100 ml and the

solution is stored in refrigerator in a glass stoppered bottle.

CITRATE-TARTRATE MIXTURE: This reagent is used for incubation and is prepared by combining 8 parts of citrate buffer (pH 4.9) with one part of 0.2 M. tartrate (pH 4.9), and the solution again stored in a refrigerator.

SATURATED ALCOHOL SOLUTION OF BORATE: To 300 ml of 95 per cent ethyl alcohol and 1700 ml of H_2O, 70 gm of sodium borate ($Na_2B_4O_7 \cdot 10\ H_2O$) are added. The solution is shaken well and left in contact with the undissolved material that settles to the bottom.

SATURATED SOLUTION OF SODIUM FLUORIDE: Stir 60 gm of sodium fluoride into 1000 ml of H_2O and filter.

DIAZO REAGENT: One gram of Red B salt (available commercially)* is dissolved in 200 ml of H_2O previously cooled to less than 5° C. in an ice bath. (It is essential that the temperature be less than 5° C.) The mixture is thoroughly shaken and the temperature is maintained below 5° C. The solution is then filtered rapidly, using a fluted filter paper and a wide stemmed funnel. Two milliliters of approximately 1.8 N H_2SO_4 (5 ml of concentrated H_2SO_4 diluted to 100 ml) are added, and the "Diazo" solution is then stored in the refrigerator. Only an amount required for each days use is removed at one time. If the solution turns orange, or if a precipitate begins to form, it must be discarded.

*National Aniline Division, Allied Chemical & Dye Corporation, Yew York, Catalog No. 682.

STANDARD AQUEOUS SOLUTION OF PHENOL, 0.01 mg of phenol per ml: Prepare a solution of phenol in 0.1 N NCl which contains approximately 1 mg per cc. of "crystallized phenol". Transfer 25 cc. of this solution to a 250 cc. Erlenmeyer flask, add 50 cc. of 0.1 N NaOH and heat to 65° on a hot plate. To the hot solution, add 25 cc. of 0.1 N iodine solution. Stopper the flask and let stand at room temperature for 30-40 minutes. Add 5 cc. of concentrated HCl and titrate the excess iodine with 0.1 N thio sulfate solution. Each cc. of 0.1 N iodine (cc. of iodine minus cc. of thiosulfate used in titration) corresponds to 1.567 mg of phenol. On the basis of the titration data , the solution of phenol is diluted with citrate buffer (pH 4.9) so that 1 cc. contains 0.01 mg of phenol.

CALIBRATION CURVE: One tenth, 0.2, 0.5, 1.0 and 1.5 ml of standard aqueous solution of phenol are pipetted into a series of Evelyn tubes. The contents of each of the calorimeter tubes are made up to 1.8 ml with citrate buffer. Pooled serum, 0.1 ml, is added to each tube and mixed well. Two tenths of a milliliter of H_2O and 2 ml of saturated solution of Na F are added. Color is developed as directed in the next section. The reagent blank contains 1.8 ml of citrate buffer, 0.1 ml of serum, 0.2 ml of water, 2 ml of Na F, 4 ml of alcoholic solution of Borate, and 0.5 ml of "Diazo" reagent. All of the tubes are read at 490 m u. The curve should pass through zero concentration at 100 per cent trans-

mittance.

II. Procedure: Separate the serum within a few hours of collection and make determinations within 24 hours. After this time, as much as 50 per cent of the tartrate-sensitive fraction may be absent. It is important that the blood be refrigerated at all times before use.

Each test consists of five incubated digests: duplicate tubes that lack(C-tubes)or contain(D-tubes)L-tartrate, and one serum blank. Incubation and the development of color may be performed in calorimeter tubes since no deproteinization or transfers are required.

Citrate buffer, 1.8 ml, is pipetted into 3 tubes (2 C-tubes, 1 A-tube), and 1.8 ml of citrate-tartrate mixture (8 parts of citrate buffer, pH 4.9, and one part of 0.2 M tartrate) are pipetted into the other 2 tubes, (D). Serum, 0.1 ml., is added to each of the tubes, using a 0.1 ml "blow out" pipett, and the controls are mixed well. Substrate, 0.2 ml, is added to all but one of the citrate tubes. (The latter tube is the serum blank to which substrate is added after the addition of the solution of Na F). The digests are incubated for three hours at 37° C. All of the reactions are stopped by means of adding 2 ml. of the solution of Na F, after which 0.2 ml. of substrate are added to each of the serum blanks. Saturated alcoholic solution of borate, 4 ml., is then added to each of the tubes, and then 0.5 ml. of "Diazo" reagent. The "Di-

azo" reagent should be delivered by means of a 0.5 ml. "blow out" pipett. Each of the tubes is shaken immediately after adding the "Diazo" reagent.

Because there is some spontaneous decomposition of substrate during incubation at 37° C. for three hours, two substrate-incubation blanks are also made (C, to control C and D, to control D); one lacks tartrate, the other contains tartrate. The composition of the digest for each determination on serum and for the substrate blank (C & D) standard (S), and Reagent (R) blanks is indicated in TABLE I. The standard blank (S) is seen daily on 1 ml of phenol standard (102 per ml).

TABLE I

COMPOSITION OF DIGESTS FOR ANALYSIS OF SERA, AND FOR THE SUBSTRATE AND REAGENT BLANKS

Tube	Serum	Water	Citrate	Citr.-Tart. mixture	Substrate	Time of incubation
	ml	ml	ml	ml	ml	hrs.
A (Serum Blank)	0.1	0	1.8	0	0.2*	3
C (Total) ‡	0.1	0	1.8	0	0.2	3
D (Tartrate inhibited) ‡	0.1	0	0	1.8	0.2	3
C_1	0	0.1	1.8	0	0.2	3
D_1	0	0.1	0	1.8	0.2	3
R (reagent blank)	0	0.1	1.8	0	0.2*	3
S (Standard 102 phenol)	0	0	1.9	0	0.2*	3

* Added after sodium fluoride. ‡ Performed in duplicate.

After ten minutes, for full development of color, the tubes are read in a calorimeter, using a 490-m u filter. C_1 and D_1 tubes are read with the R. tube (reagent blank) adjusted to 100 per cent transmittance; C and D tubes are observed with the corresponding A tube adjusted to 100 per cent transmittance.

Calorimeter readings are transmitted into mg. of phenol by means of using the standard curve. The value of C_1 is subtracted from the average of the two values for C tubes, and the figure for D_1 from the average of the 2 D values.

III. Computation of Results: The results are expressed in terms of the conventional King-Armstrong units, which are defined as the number of mg. of phenol liberated by 100 ml of serum in one hour, from phenyl phosphate under standard conditions.[18,21]

Therefore: $$\frac{\text{mg of phenol} \times 100}{\text{ml of serum} \times \text{hours of incubation}}$$

or:
$$\frac{(C - C_1) \times 100}{0.1 \times 3} = \text{T units per 100 ml of serum}$$

$$\frac{(D - D_1) \times 100}{0.1 \times 3} = \text{U units per 100 ml of serum}$$

Then T - U = units of prostatic acid phosphatase per 100 ml of serum. If reading of C_1 or D_1 are appreciably greater than the optical density of freshly prepared solutions, one should suspect deterioration of one or more of the reactants such as the

substrate or the solution of tartrate or citrate.

The results obtained by Stolbach and others, [21] when both, the "Diazo" method and the Fishman - Lerner method were used simultaneously on 42 consecutively collected specimens of serum of patients without carcinoma of the prostate, were generally in agreement. However, the values for total tended to be less with the "Diazo" method. These investigators stressed the importance of accuracy in technique and particularly the time of incubation. The limits of normal have been set on the basis of three hours incubation and shorter time would give higher values due to decreasing enzymatic action with longer incubation periods.

Once the final color has been achieved, one may read the tubes as long as 24 hours later.

Results of Studies of Patients without Carcinoma of the Prostate*

NORMAL VALUES

When this laboratory test was first described in 1953,[7] it was found that the level for the "normale Male" was below .5 Fishman - Lerner units. Since that time, further studies have lead the original investigators to boost this upper level of normal to .6 K. A. units.

In 1956, Mathes inferred that 0.8 units should be the upper limits of normal for prostatic acid phosphatase. He reported results of determination of acid phosphatase levels in 234 women and 160 men with no prostatic disease, or a total of 394 controls. Of

* See bottom page 12

the 234 women, 16 gave values above 0.5 units for prostatic acid phosphatase and only 2 were above .8 units. Of the 160 men examined without known prostatic disease, 160 men examined without known prostatic disease, 16 had prostatic acid phosphatase levels above 0.5 units while only 6 had levels above 0.8 units. The total results showing that only 8 of 394 control patients, two per cent (2%) had prostatic acid phosphatase levels above 0.8 units, whereas, 32 or eight per cent (8%) were above 0.5 units.

Further convinging evidence was presented in the report of 70 cases of Benign prostatic hypertrophy proven by surgery. Total acid phosphatase levels ranged from 0.50 to 3.10 K. A. units, all within normal range. The prostatic phosphatase levels ranged from 0.10 to 0.80 units. Thirteen of the seventy had prostatic acid phosphatase levels over 0.5 units but none above 0.8 units.

Although these are convincing figures, one must not be too quick to assume that this is proof. Apparently only one determination was done on these patients, as will be pointed out later. Far more determinations are preferred. Also, there is no way of knowing the state of the patient, that is, whether he had just undergone one or more rectal examinations, or just prior to the determination had received an enema. No repeat determinations were done on the patients showing the abnormal levels. How many patients

*All investigations prior to April 1958 [21] were studied, using the Fishman-Lerner technique,[7] unless otherwise stated.

had levels over the newly fixed mark of 0.6 F. L. [9] units, was not reported. For the purpose of the paper, 0.6 F. L. units will be usedas the upper limit of normal. This value represents the mean plus somewhat more than the two standard deviations based on all the patients investigated by Fishman and others for over a three year period.

An upper limit of 5 K. A. units has been established as normal which seems to agree with the findings of most workers.

EFFECT OF PROSTATIC MASSAGE

Occasionally investigators found elevations of prostatic acid phosphatase in patients with no clinical evidence of prostatic carcinoma and later, an autopsy examination found no pathological evidence of the disease. This led the workers to wonder if physical massage or even one rectal examination, as is usually performed in hospitals, could account for this elevation.

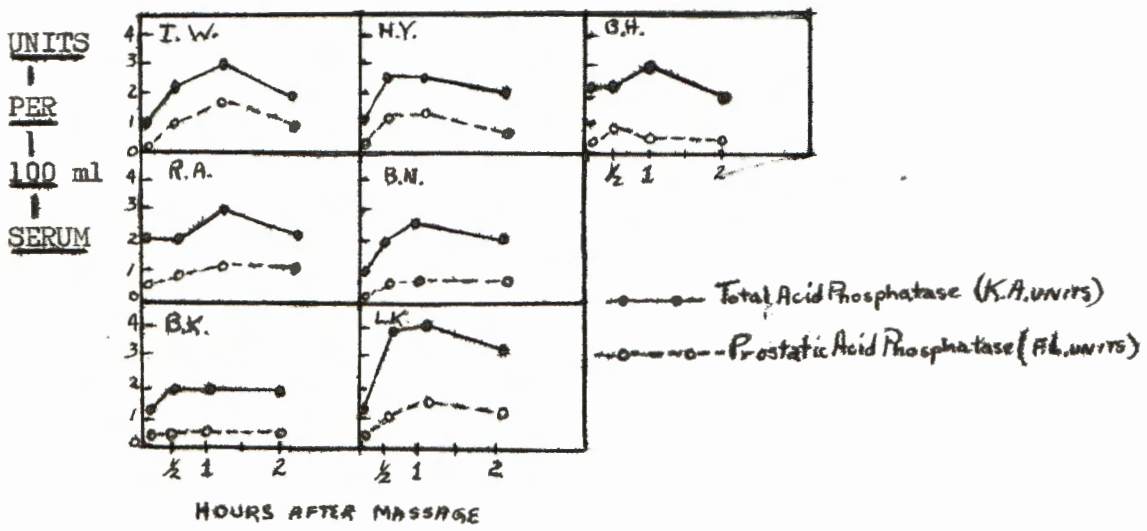
Bonner and others [4] found definite elevations in some patients in the following study. They drew initial venous blood, then massaged the prostate for a short time (approximately, one minute). Blood samples were then drawn at half hour, one hour and two hour intervals. Samples were also drawn on four patients before and after warm enemas. No abnormal elevation of the enzyme were found in five patients previously prostatectomized; in 10 of the 22 patients with non malignant prostate glands, and four patients studied after warm enemas. However, there was an elevation of the pre-

static fraction into the abnormal range in 12 of 22 patients with non malignant prostate. Only one of these showed an increase in the total acid phosphatase.

Fishman and others [7,4] found early, that prostatic massage definitely had a bearing on the values of prostatic acid phosphatase. As seen in Table II, there was a definite elevation of both, total and prostatic enzyme, 5 out of 7 patients, and a slight rise in one. Though the total never rose so high as to be considered abnormal, the prostatic portion was above the "normal" line in 5 of 7 patients, and borderline, in one. The obvious conclusion is that the blood should either be drawn on these patients before rectal examination, or the procedure postponed for at least thirty-six to forty-eight hours.

TABLE II

EFFECT OF PROSTATIC MASSAGE ON SERUM TOTAL AND "PROSTATIC" ACID PHOSPHATASES. B.H. & I.W. FOR 5 MINUTES, OTHERS FOR 2 MINUTES.



RESULTS OF STUDIES OF PATIENTS WITH CARCINOMA OF THE PROSTATE

CARCINOMA WITH METASTASIS

The first consideration in relation to prostatic acid phosphatase and that of carcinoma of the prostate, was to find if, with proven, advanced prostatic carcinoma, there was a definite increase above normal. Fishman [7] made a comparison of total and prostatic serum acid phosphatase levels in eight patients with known advanced carcinoma of the prostate, proven either radiographically or pathologically. As is shown in Table III, there is definitely a relative increase in the prostatic acid phosphatase along with the increase in total, both being raised into the abonormal.

TABLE III

TO SHOW THE RELATIVE INCREASE IN THE "PROSTATIC" PORTION OF SERUM ACID PHOSPHATASE IN METASTATIC PROSTATIC CARCINOMA

Patient	Total	"Prostatic"
A.W.	11.6	10.2
G.H.	20.6	18.2
AC.	6.8	4.0
C.E.	5.1	2.5
J.H.	32.2	27.9
C.F.	46.1	42.2
D.P.	8.8	7.1
C	16.8	15.0

Mathes[16] found that of 17 patients who were not on hormonal therapy, and have had proven rpostatic acid phosphatase while only 9 had abnormal total. He had a total of 50 cases of known carcino-

noma of the prostate, 33 being on hormonal therapy . In the total group, the prostatic acid phosphatase was elevated in 29 (58%) of the 50 cases while only 11 (34%) had elevated total acid phosphatase. (The effects of hormonal therapy are discussed later in this paper). In a comparison of prostatic acid phosphatase versus total acid phosphatase, the prostatic portion was significantly elevated in 30% more cases than the total acid phosphatase. Bonner and others [5] found that out of a total of 113 patients with proven carcinoma of the prostate, 54 had abnormal levels of prostatic acid phosphatase, but normal acid phosphatase. To further relate his findings, the prostatic portion of the enzyme was elevated in eleven of twelve patients with soft tissue metastasis, while the total value was abnormal in only two cases. In the group with both, soft tissue and bony metastasis, (Many of these on estrogen therapy), the prostatic serum acid phosphatase level was abnormal in 45 of 53 instances as compared to only 24 high total acid phosphatase values.

Noble and others [19] agree that there is a definite rise of the prostatic portion with metastasis, but did not find elevations of this portion without a concommitant rise in the total value. They went further to say that they found no cases in which the prostatic portion was elevated without this similar total response whether metastasis had occurred or not.

In 1956, Fishman and others reported the following studies.

Ninety-one patients were divided into three categories; first, those with bony metastasis; second, those with soft tissue metastasis; third, those with no metastasis. In patients with soft tissue metastasis, the serum prostatic fraction was abnormal in 84%, whereas, the total, total acid phosphatase was abnormal in 17%. In patients with bony metastasis, there was some improvement in correlation of the conventional acid phosphatase procedure with the prostatic fraction. The latter being elevated in 90% of the cases, while the former was only 50%.

As is evident by these studies, most investigators agree that in advanced carcinoma of the prostate, the prostatic acid phosphatase fraction will be elevated in a significantly larger percentage than will the total acid phosphatase.

CARCINOMA WITHOUT METASTASIS

Although large series are not as yet available, results in early prostatic carcinoma appear to follow the pattern found with advanced disease; the prostatic portion being elevated in a significantly larger percentage than is the total.

In 1953, Fishman and others [8] reported that in four of five patients with untreated cancer of the prostate, without demonstrable metastasis, abnormal values for prostatic acid phosphatase were found in the presence of normal total serum acid phosphatase. The fifth patient had both normal total and prostatic portion.

By 1956, [9] their series had risen to 26 patients, with lo-

calized carcinoma of the prostate. In this study, twenty-one of the twenty-six showed abnormal prostatic fractions, whereas only four of the twenty-six were found to have abnormal total values.

Noble, [19] in his report in 1957 did not concur. He states that of 17 localized prostatic cancers only one patient had abnormal prostatic acid phosphatase, while all 17 had normal total values. In explanation of this discrepancy, Fishman suggested the complexity and lack of standardization of the determinations.[10,21]

The Holy Ghost Hospital in Cambridge, Massachusetts, routinely performs prostatic acid phosphatase determination on all male patients when admitted. During the years 1954-1955, two hundred thirty three males with a variety of chronic diseases were admitted. Twelve were known to have cancer of the prostate. Among the remaining 221, five unsuspected carcinomas of the prostate, later proven, were detected. All had initial nornal total serum acid phosphatase with abnormal prostatic portions. [5] This is 2.26 per cent of the 221 male patients admitted.

TESTOSTERONE STIMULATION

In 1954 Bonner [4] showed that 100 mg. of Testosterone given daily to patients without malignant disease of the prostate, would not cause significant elevation in the prostatic serum acid phosphatase. He, therefore, gave 50 mg. of Testosterone three times a week to patients with questionable prostatic carcinoma, in the hope that these would result a limited stimulation of tumor growth

and a consequent of the increase of the prostatic serum acid phosphatase levels. In two of the three patients who had normal total and prostatic acid phosphatase levels, the administration of Testosterone resulted in slow, but persistent rise in the prostatic portion. The third patient had only one determination above normal. None of these patients had an abonormal total acid phosphatase level, for at least three months after the prostatic portion was elevated.

Single doses of Testosterone were found to have no effect on three patients with benign hypertrophy, which would seem to indicate, that the Testosterone itself, has no direct effect in creating increased prostatic acid phosphatase.

ESTROGEN THERAPY

In some patients with proven cancer of the prostate, the values of both, prostatic and total acid phosphatase fell to almost zero.[9]

To determine if Estrogen in the serum of patients receiving hormonal therapy had any direct inhibitive effect upon the serum prostatic and total acid phosphatase, Mathes[16] added one mg. of Estrogen to the substrate in 6 patients not receiving Stilbesterol. Instead of a decrease, a slight increase occurred in the six cases checked, suggesting that there is no direct inhibiting from Estrogens.

Among Fishman's patients receiving estrogenic treatment, twenty of fifty-two were found to have abnormal total acid phosphatase

levels, while forty-two of the fifty-two gave positive results for the prostatic enzyme.

Mathes [16] found that in a group of thirty-three patients on hormonal therapy, fourteen, (45%) gave positive prostatic acid phosphatase levels, while only nine, (27%) had positive total values.

In the overall long term studies of hormonal therapy of carcinoma of the prostate gland, there is a close parallel behavior of both, total and prostatic serum acid phosphatase. "The abnormal prostatic portions seem to precede and succeed the appearance and subsequent disappearance of pathological levels of the total acid phosphatase.

SUMMARY

For many years, total serum acid phosphatase has been used for detection of carcinoma of the prostate. Most men considered an elevated acid phosphatase as indicative of a late or metastatic carcinoma, and, therefore, only palliative treatment was employed.

Studies indicated that there is only a fifty per cent correlation between abnormal acid phosphatase levels and metastatic carcinoma.

In 1953, Fishman and Lerner devised a laboratory test using L-Tartrate which inhibited that portion of acid phosphatase liberated by the prostate. Normal values were found to range from zero to 0.6 Fishman-Lerner units, with an average of about 0.3 F. L. units. Although the test was accurate for their studies, other investigators had difficulty duplicating their results because of the very sensitive and involved procedures. In 1958, Stolbach and others, simplified the technique without changing the accuracy of the test. Today most laboratories should have no difficulty in obtaining accurate determination.

It is shown that the re is a definite increase in values of the prostatic fraction after prostatic massage. Because of this, most investigators suggest that all determinations be run before rectal exam or 36 to 48 hours after the rectal.

In comparing the two methods and their correlation with me-

tastatic disease of the prostate, it was found, that the prostatic fraction of the serum acid phophatase was elevated in a significantly larger percentage than the total acid phosphatase.

Large series of patients with carinima confined to the prostate gland have not yet been accumulated. Those that have been studied, often times have been found to have increased prostatic acid phosphatase in the face of normal total acid phosphatase.

Holy Ghost Hospital in Cambridge, Massachusetts, routinely performs prostatic acid phosphatase determinations on all male patients. They found five patients with unsuspected carcinoma of the prostate out of 221 tested. (2.26%)

Some reporters do not give concurring results. Noble states that he found only one case in which the prostatic portion was abnormal in the face of a normal total value. Advocators of the new test suggest, however, that this discrepancy in results may stem from "short cuts" in laboratory procedure.

After showing that a daily 100 mg. dosage of Testosterone given, patients without prostatic malignancy showed no significant elevation in the prostatic acid phosphatase . Bonner administered 50 mg. three time a week to those with questionable carcinoma, later proven. There resulted a slow, but steady, rise in the prostatic portion into the abnormal. The total value did not become abnormal for many months following. Single doses of Testosterone had no effect on either value.

In patients receiving Estrogen therapy, abnormal prostatic acid phosphatase levels preceded and succeeded the appearance and subsequent disappearance of abnormal total acid phosphatase.

CONCLUSIONS

Abnormal prostatic acid phosphatase levels appear to correlate with metastatic carcinoma of the prostate in a higher percentage than total serum acid phosphatase.

It appears that this laboratory test will also be helpful in detection of carcinoma confined to the prostate gland. This being the case, screening tests could be used much like the cervical smears now used in women for detection of early malignancy of the cervix. Early detection would mean earlier, and often, curative treatment.

It is advised, when doing the laboratory determinations, that strict attention be given to the directions, especially those concerning the incubation time. The standard group of values is based on strict procedure. If variations of this procedure are used, the test is no longer standard and the results cannot be compared to those using the standardized form.

False positive values may occur when the patient has had rectal digital examination within 36 hours of determination, false negatives, when he is on Estrogen therapy.

Although there is some disagreement as to the value of this test, as an indication of early prostatic carcinoma, investigators have obtained results no worse than when using the conventional total acid phosphatase level. It is, therefore, concluded that whenever possible, this determination should be

substituted for the total serum acid phosphatase.

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