DETERMINATION OF SERUM "ACID" PHOSPHATASE ACTIVITY IN DIFFERENTIATING SKELETAL METASTASES SECONDARY TO PROSTATIC CARCINOMA FROM PAGET'S DISEASE OF BONE

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Ordinarily, the roentgen criteria for distinguishing between osteitis deformans and osteoplastic skeletal metastases due to prostatic carcinoma (1, 2) permit of reasonable certainty in their differentiation. In early stages of either condition, however, when sclerotic areas are limited to the bony pelvis and spine, it may be difficult or impossible to establish a definite diagnosis roentgenographically. Moreover, as it is in the older age group that clinical examination of the prostate gland for carcinoma is prone to indecisive results, it not infrequently happens that the prognostically significant distinction between a metastasizing carcinoma and Paget's disease is made, if at all, only by biopsy or after protracted observation.

When Kay first discovered (3) the now well substantiated (4) increase in serum phosphatase activity in Paget's disease—the only known abnormality of the blood of consistent occurrence in that condition—it was thought that this observation might prove helpful in the clinical problem under consideration. Since widespread osteoplastic metastases, most commonly secondary to prostate carcinoma, are associated with similarly increased phosphatase values, however (4, 5, 6, 7, 8, 9), it soon became apparent that the determination as ordinarily practised ("alkaline" phosphatase activity) is of no value in differentiating these two conditions (6, 9).

Another approach to the problem now seems possible as the result of observations by Kutscher and co-workers (10, 11, 12), who found that normal prostate tissue is extraordinarily rich in an apparently specific phosphatase with optimum activity at about pH 5. Subsequent study (13, 14) showed this "acid" phosphatase to be present also in carcinomatous prostate tissue, not only in the primary tumor but at the site of skeletal metastases as well. The enzyme was then sought and found in the blood serum of patients having prostate carcinoma with metastases to bone, irrespective of whether the metastases were predominantly osteoplastic or osteolytic (15, 16, 17, 14, 18). Of 44 cases studied to date (19), 37 have shown significantly elevated serum "acid" phosphatase levels, i.e. above 3.0 units per 100 c.c. serum as determined by the modified King and Armstrong method (20) which we have employed (16, 19). The majority of these cases yielded values under 10 units, but many were higher and in two instances values of 260 and 516 units, respectively, per 100 c.c. were obtained (16, 19). Apparently, prostate phos-
<table>
<thead>
<tr>
<th>No.</th>
<th>Age and Sex</th>
<th>Serum Phosphatase Activity</th>
<th>Skeletal Involvement Demonstrated Roentgenologically</th>
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Spine (collapse, paraplegia), skull, pelvis, femur, shoulder girdle
Skull, pelvis, femora, humeri, scapulae, tibia, spine, clavicle
Pelvis, spine, skull, (incomplete work-up)
Spine, skull, pelvis, femora, (incomplete work-up)
Skull, pelvis, spine, femora, ribs
Skull, pelvis, spine, shoulder girdle, tibia, femora, fibula, calcaneus, radius, astragalus, meta-carpals, metatarsal, phalanx
Skull, pelvis, spine, femora, tibia, clavicle, scapulae, humeri, ribs, radius
Skull, spine, pelvis, tibiae
Pelvis, spine, femora, clavicle, humerus, tibiae, skull, ribs, scapula
Skull, pelvis, femora, spine
Pelvis, spine, skull, femora
Pelvis, spine, tibia, skull, femur
Pelvis, skull, spine, femur
Pelvis, spine, skull
Femur
Femur, pelvis, skull
Pelvis, femora, spine, scapula
Pelvis, skull
Tibia, calcaneus
Humerus, scapula
Pelvis
Pelvis
Pelvis, spine
Pelvis
Pelvis, spine, skull, femora, tibiae
Pelvis
Pelvis, spine, skull (osteoporosis circumscripta)
Pelvis, femora, skull (osteoporosis circumscripta), clavicle
Tibia
Tibia
Pelvis
Pelvis
Spine, pelvis
phatase, which is excreted normally in the seminal fluid (10), escapes into the lymph or blood as the result of invasion of these channels by metastasizing prostatic carcinoma (16). The observation is of interest as an example of the possibility of determining the primary source of a metastasizing tumor by chemical identification of a secretory product in the circulating fluids.

In Paget's disease, on the other hand, the phosphatase activity of the serum at pH 4.9 usually shows no significant rise above normal levels. But in several instances, elevated values, within the lower range of variation in metastatic prostate carcinoma, have been reported (15, 16, 17), and further study seems necessary to evaluate, even provisionally, the usefulness of the determination in differential diagnosis.

Methods; Normal Values

The method of King and Armstrong (20), adapted to estimations at pH 4.9 by the use of Sørensen's citrate buffer, was employed for the determination of serum "acid" phosphatase activity (16); the method of Bodansky was used in estimating serum "alkaline" phosphatase activity (21). The results are expressed in units per 100 c.c. serum, a unit of "acid" phosphatase activity being defined as equivalent to 1.0 mg. of phenol liberated at pH 4.9 and 37°C from the specified buffer-monophenylphosphate substrate (16) in one hour. In the serum of normal subjects, male or female, 0.5 to 2.5 units of "acid" phosphatase activity per 100 c.c. are found (15). This is due to the presence in normal blood serum of an "acid" phosphatase with properties differing from those of prostate or erythrocyte "acid" phosphatase (15, 16), but resembling enzymes found in liver, spleen, and kidney tissue extracts.

The "alkaline" phosphatase activity of the serum of normal adults ranges from 1 to 4 Bodansky units per 100 c.c.

Results and Discussion

Our observations on 32 cases of Paget's disease are summarized in Table I. This series, it should be stated, is not truly representative of our experience with this disease (22) since a disproportionate number of far-advanced cases are included. Of the less advanced cases, we have cited only those in which roentgen and clinical study appeared to justify an unequivocal diagnosis. Many of these patients have been under observation for several years.

All our early and moderately advanced cases of Paget's disease—the type which roentgenologically may simulate or be simulated by osteoplastic skeletal metastases—were found to have serum "acid" phosphatase values within the normal range of 0.5 to 2.5 units per 100 c.c. Thirteen of 15 patients with Paget's disease investigated by Müller (17) 1 likewise showed no increase in

1 Müller's excellent study being difficult of access, his results in 15 cases of Paget's disease are reproduced here. The first figure quoted refers to serum "acid" phosphatase activity (determined by the same method and expressed in the same units as in our own work); the second figure, in parentheses, refers to serum "alkaline" phosphatase activity, in Bodansky units per 100 c.c. serum.
"acid" phosphatase activity of the serum. The results of Barringer and Woodard (14), who determined the phosphatase activity in 5 cases of Paget's disease at pH 6.4 by their own method, are more difficult to interpret. The phosphatase activity of the serum at pH 6.4 was found to vary with the "alkaline" phosphatase, due to incomplete inactivation of the latter enzyme, but the ratio of activity at pH 6.4 to activity at pH 8.6 was apparently within normal limits.

Our series includes 3 males and 3 females with extensive Paget's disease of the skeleton (Table I, Cases 1-4, 6, 7) showing serum "acid" phosphatase levels above 3.0 units per 100 c.c. These patients, without exception, exhibited marked elevations in "alkaline" phosphatase activity, the lowest value of the group being 79.1 Bodansky units per 100 c.c. Müller's one case of Paget's disease with significantly elevated serum "acid" phosphatase activity, 5.66 units per 100 c.c. (17), likewise had an extremely high serum "alkaline" phosphatase activity (168.26 Bodansky units per 100 c.c.). It should be pointed out in this connection that for direct comparison with "acid" phosphatase levels obtained by hydrolysis of phenylphosphate in one hour, the "alkaline" phosphatase values as expressed in Bodansky units should be multiplied approximately five times. The apparent "acid" phosphatase activity of the serum in these patients is not proportional, however, to that at pH 8.6. For this reason, and because hydrolysis of such Paget sera at pH 4.9 could be inhibited almost completely by N/100 NaF, it would seem that only part, if any, of the hydrolysis at pH 4.9 is ascribable to incomplete inactivation of the "alkaline" enzyme.

The fact that some cases of advanced Paget's disease with very high serum "alkaline" phosphatase activity show significantly elevated phosphatase activity of the serum at pH 4.9 restricts the usefulness of the method in differentiating osteitis deformans from metastatic carcinoma of the prostate. This limitation, however, is largely academic, since in such advanced stages of Paget's disease roentgen and clinical criteria suffice for a diagnosis.

Apart from Paget's disease, very high serum "alkaline" phosphatase values have been observed in severe active rickets, in protracted obstructive jaundice, and in widespread osteoplastic metastases, usually secondary to prostatic carcinoma but occasionally of other origin. The cases of this kind which we have investigated with respect to both "alkaline" and "acid" phosphatase showed "alkaline" phosphatase levels as high as 68.6 Bodansky units per 100 c.c. without any significant rise in serum phosphatase activity at pH 4.9.

Our control series, composed of more than 200 cases other than carcinoma of the prostate or Paget's disease, disclosed only 5 patients with "acid" phosphatase levels higher than 3.0 units per 100 c.c. serum: 2 females with osteolytic metastases to the bones (among 20 cases of skeletal metastases); 2 patients with hyperparathyroidism; and a female with osteopetrosis (marble bones). An "acid" phosphatase value of 8.7 units per 100 c.c. serum, the highest in our non-prostate group, was obtained on one occasion in the last-mentioned patient. Further details of these cases are given elsewhere (19). Müller's control series of 75 patients without disease of the prostate (17) yielded only one instance of significantly increased serum "acid" phosphatase values, the patient with osteitis deformans referred to above.
To illustrate how the determination of serum "acid" phosphatase activity may be helpful in differentiating Paget's disease from metastatic carcinoma of the prostate, the following case summaries from our own experience are cited.

**CASE 1: H. R.,** a sixty-six-year-old man, was admitted to the Squier Urological Service in 1938 because of urinary retention of thirty-six hours' duration. For five years he had had similar episodes of acute retention, relieved by catheterisation.

Rectal examination disclosed a markedly enlarged prostate gland, which did not, however, feel malignant. Cystoscopy showed a diffusely trabeculated bladder with cellule formation. A collar intrusion of all lobes of the prostate gland was noted, the diagnosis being benign prostatic hypertrophy. X-rays revealed osteosclerotic lesions in the pelvis and spine that could be interpreted either as Paget's disease or as metastatic carcinoma. The skull was not involved. The values for serum "acid" phosphatase and serum "alkaline" phosphatase were 1.7 units and 11.5 Bodansky units, respectively, per 100 c.c., favoring the diagnosis of benign prostatic hypertrophy, Paget's disease.

The condition of the patient was too poor for surgery but after ten days of catheter drainage he was able to void and could be discharged to his local doctor. His satisfactory course after one and a half years is believed to justify the diagnosis made on clinical and chemical grounds.

**CASE 2: J. D.,** a seventy-year-old man, was first seen in the Vanderbilt Clinic in 1936 because of cardiac failure, due to arteriosclerotic heart disease, and recent loss of 20 pounds in weight. An incidental finding was enlargement of the skull, suggesting Paget's disease. This diagnosis was confirmed by x-ray, which showed involvement of the skull, femora, and pelvis. Examination for the cause of weight loss disclosed the fact that the left lobe of the prostate gland was stony-hard and fixed to the lateral wall, suggesting malignancy. In view of this finding, it seemed possible that certain questionable areas in the bony pelvis might be osteoplastic metastases rather than Paget's disease.

The patient has been followed regularly since 1936. His clinical course has been favorable and there has been no further extension of the osteoplastic areas seen in the roentgenograms, which seem now to be quite typical of Paget's disease. The case is regarded as one of Paget's disease; the prostate gland is thought to be malignant but without definite evidence of metastases. The results of blood studies are in accord with this clinical and roentgenological opinion: the serum "acid" phosphatase activity has been within normal limits consistently, while the serum "alkaline" phosphatase activity has varied between 20 and 25 Bodansky units per 100 c.c.

**SUMMARY**

Most cases of prostatic carcinoma with bone involvement (37 of 44 recorded cases) show serum "acid" phosphatase values greater than 3.0 units per 100 c.c. On the other hand, all but 5 of more than 200 control patients with diseases other than metastatic prostate carcinoma or Paget's disease were found to have serum "acid" phosphatase values less than 3.0 units per 100 c.c. Included in the control group are 40 cases of non-prostatic carcinoma with predominantly osteolytic or osteoplastic skeletal metastases, in 2 of which (females) "acid" phosphatase values above 3.0 units per 100 c.c. serum were obtained.

The "acid" and "alkaline" phosphatase activity of the serum in 32 cases of Paget's disease is recorded in the present study. Six of the most advanced cases, with serum "alkaline" phosphatase levels over 70 Bodansky units per 100 c.c. serum, were found to have serum "acid" phosphatase levels over 3.0 units per 100 c.c.; in the remaining 26 cases, normal values were obtained. Since it is usually the latter group (early and moderately advanced Paget's disease) that may simulate or be simulated by osteoplastic skeletal...
metastases roentgenographically, the determination of serum "acid" phosphatase activity appears to be applicable to the differentiation of Paget's disease from bone metastases secondary to carcinoma of the prostate.

**BIBLIOGRAPHY**

   (Review of literature to 1936.)