SIGNIFICANCE OF INCREASED PHOSPHATASE ACTIVITY OF 
BONE AT THE SITE OF OSTEOPLASTIC METASTASES 
SECONDARY TO CARCINOMA OF THE 
PROSTATE GLAND

ETHEL BENEDICT GUTMAN, EDITH E. SPROUL AND ALEXANDER B. GUTMAN

(From the Department of Medicine and Pathology, College of Physicians and Surgeons, 
Columbia University, and the Presbyterian Hospital, New York City)

Recent determinations of serum phosphatase activity in patients with 
cancer (1, 2, 3) suggest that values obtained in cases with widespread osteo­ 
plastic metastases are, in general, significantly higher than those found in 
association with osteolytic metastases. In the series reported by Gutman, 
Tyson and Gutman (1), for example, the serum phosphatase activity ex­ 
ceeded 10 Bodansky units per 100 c.c. in 6 of 10 cases with osteoplastic 
metastases but in only 3 of 19 patients with osteolytic metastases. In 2 pa­ 
tients with very extensive osteoplastic skeletal lesions, values exceeding 100 
Bodansky units per 100 c.c. of serum were obtained, as contrasted with the 
normal maximum of 4.0 Bodansky units.

It has been assumed (1, 3) that the rise in phosphatase activity of the 
serum in such cases is the result of increased elaboration of phosphatase, 
which is subsequently released into the circulating fluids. Direct evidence 
in support of this assumption is afforded by the present investigation, which 
disclosed strikingly increased phosphatase activity of bone at the site of 
osteoplastic skeletal metastases in a patient with carcinoma of the prostate 
gland.

This observation is of interest also because it is in accord with the view, 
derived from pathological studies, that the mechanism of bone formation in 
metastatic osteoplastic neoplasms is fundamentally the same as that of normal 
bone formation. Of particular interest is the further implication that the 
capacity to stimulate production of phosphatase may play an important rôle 
in determining the osteoplastic character of the metastatic bone lesions ob­ 
served in association with certain neoplasms. In this respect, too, chemical 
studies tend to support the views of pathologists who have long postulated the 
elaboration by certain tumor cells of a chemical factor initiating bone for­ 
mination in osteoplastic metastases.

METHODS

The samples of bone studied were obtained from the following regions: (1) skull, cross-section 
of the occipital bone to include both tables and diploe; (2) lumbar vertebrae, body of vertebra in 
toto; (3) pelvis, cross-section through the ilium; (4) rib, adjacent to but not including the costo­ 
chondral junction; (5) femur, cortical bone from the middle third of the shaft. Aqueous ex­ 
tracts of 2 to 10 gram samples of bone were prepared in the usual manner. After removal of all 
adventitious tissue, the bone was broken up into small particles and ground thoroughly with a 
minimal amount of washed sand and distilled water. The mixture was then transferred quantita­ 
tively to a volumetric flask of a capacity approximately ten times the weight of the sample, and
Bone phosphatase activity was determined in duplicate on 0.5 c.c. samples of the unfiltered aqueous extract by an adaptation of the method of King and Armstrong (4) for the estimation of phosphatase activity in serum and bile. The results are expressed in King and Armstrong units per gram of fresh bone. One King and Armstrong unit of phosphatase is that amount which liberates 1 mg. phenol from a disodium-monophenylphosphate substrate in thirty minutes at 37°C. The pH of the sodium veronal buffer plus substrate at room temperature (9.6) is approximately 9.5 after addition of aqueous bone extract, as estimated colorimetrically, and approximately 9.1 during digestion at 37°C. In addition to "alkaline" phosphatase, the "acid" phosphatase activity of aqueous bone extracts was estimated at pH 5.0. The determinations were carried out in the manner just described, except for the use of Sörensen's citrate buffer.

Serum phosphatase activity was determined by Bodansky's method (5). Details of the methods used in analyses of serum are given elsewhere (1). The phosphatase activity of aqueous suspensions of ground prostate tissue was estimated by the method of King and Armstrong (4). In the determinations carried out at pH 5.0, Sörensen's citrate buffer was used and the prostate tissue extracts were diluted 200 times, as recommended by Kutscher and Wolbergs (6).

Bone phosphatase activity was determined on samples of aqueous bone extract which had not been filtered or centrifuged, since filtration or centrifugation results in variable and occasionally considerable loss of phosphatase activity (7, 8). Unfiltered bone extracts, however, or extracts filtered through gauze, contain heterogeneous bone particles which, upon the addition of trichloracetic acid, yield variable, often large amounts of dissolved phosphates. This introduces obvious difficulties in the estimation of bone phosphatase activity by methods depending upon the determination of inorganic phosphate before and after digestion, particularly in samples of bone exhibiting little phosphatase activity. Such errors can be minimized if trichloracetic acid is added simultaneously to both digested substrate and control tube and both are then filtered after one minute; or if the determination is carried out on aqueous bone extracts which have been filtered through E. & D. No. 617 paper, since this can be done with comparatively little danger of serious loss. By observing these precautions, it was found that the Bodansky method (5) could be applied to the estimation of bone phosphatase activity.

The most satisfactory solution of these difficulties, however, proved to be the application of the King and Armstrong method, using a disodium-monophenylphosphate substrate. Since this method depends upon the estimation of phenol liberated, the determination of phosphatase activity is independent of unavoidable variations in phosphate concentration in acidified aqueous bone extracts. In the more active bone samples, the results in King and Armstrong units, like those for serum phosphatase activity (and in general accord with theoretical yields), are 1.5 to 2.0 times the values in Bodansky units (8).

All values recorded represent phosphatase activity under the conditions of the methods employed. No attempt has been made, by addition of optimal quantities of magnesium and glycine, to satisfy requirements for direct proportionality between reaction velocity and bone phosphatase concentration (9).

**RESULTS**

**Phosphatase Activity of Normal Bone:** There is a wide range of variation in the phosphatase activity of normal bone, depending on species (10, 11), age (11), the bone studied (7), and even the area of bone examined (7). To make comparisons between the phosphatase activity of normal and pathological bone possible, therefore, we include a summary of orientating values on various normal bones from adult human subjects (Table I). It was found that the lumbar vertebrae, pelvis, and ribs possess appreciable phosphatase activity. The bones composing the cranial vault usually display only a negligible degree of phosphatase activity, as Franseen and McLean have shown (7), though slight phosphatase activity can be detected in some instances. The phosphatase activity of femur cortex was usually too small to determine.

**Phosphatase Activity of Pathological Bone:** In a case of carcinoma of the prostate gland (Case 1, Table II), the phosphatase activity of bone from lumbar vertebra and rib, the sites of the osteoplastic metastases, was found
to be 39.4 and 53.0 King and Armstrong units per gram, respectively. These values greatly exceed anything we have obtained in normal bone, as will be apparent upon comparison with the values recorded in Table I. It is interesting to note that these results are also far higher than those obtained for bone which was the site of osteolytic metastases secondary to carcinoma of the breast (Case 2, Table II).1

TABLE I: Phosphatase Activity of Normal Bone from Adult Human Subjects
(All values are expressed in King and Armstrong units per gram wet tissue)

<table>
<thead>
<tr>
<th>No.</th>
<th>Age and Sex</th>
<th>Skull</th>
<th>Lumbar Vertebrae</th>
<th>Pelvis</th>
<th>Rib</th>
<th>Femur</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>pH 9.1 pH 5.0</td>
<td>pH 9.1 pH 5.0</td>
<td>pH 9.1 pH 5.0</td>
<td>pH 9.1 pH 5.0</td>
<td>pH 9.1</td>
</tr>
<tr>
<td>1</td>
<td>39 ♀</td>
<td>0.1</td>
<td>3.3 0.9</td>
<td>3.6</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>2</td>
<td>54 ♂</td>
<td>0</td>
<td>4.4 0.7</td>
<td>0</td>
<td>4.5</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>31 ♂</td>
<td>0</td>
<td>5.3 4.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>65 ♂</td>
<td>0</td>
<td>4.1 0.5</td>
<td>2.6 0.3</td>
<td>1.2</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>74 ♀</td>
<td>0.6 0.1</td>
<td>6.8 1.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>48 ♂</td>
<td>0.9 0.1</td>
<td>1.6 0.5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>35 ♀</td>
<td></td>
<td></td>
<td>4.3 0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>60 ♀</td>
<td></td>
<td></td>
<td>4.7 0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>64 ♂</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>54 ♀</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

By way of further comparison, we have included in Table II values for the phosphatase activity of bone obtained from patients with other diseases affecting the skeleton. In a case of Paget's disease, increased phosphatase activity of Paget bone obtained from the skull was noted, in confirmation of the findings of Franseen and McLean (7). The phosphatase activity of a sample of bone from the vertebra, however, was within normal limits. Two circumstances may contribute to the fact that the increase in bone phosphatase activity in this case of Paget's disease was not more striking: (1) relative inactivity of the Paget lesions, suggested also by the clinical course and by only moderate elevation in serum phosphatase activity (19.7 Bodansky units per 100 c.c.) despite widespread bone involvement (1, 12); (2) centrifugation of the aqueous bone extract in this one instance, as we were unaware at that time of the loss in phosphatase activity incurred by this procedure.

The increased phosphatase activity of rachitic bone (Case 4) is well 1Our results on metastatic bone tumors are in accord with the observations of Franseen and McLean (7) on primary bone tumors. These investigators, using the Kay method, found the tissue phosphatase activity of the osteoblastic type of osteogenic sarcoma significantly higher than that of osteogenic sarcoma of the osteolytic type. It is apparent, however, that increased phosphatase activity of bone is not peculiar to primary bone sarcomas of the osteoblastic type but may be encountered also in osteoblastic bone metastases secondary to prostatic carcinoma; and presumably also in association with other neoplasms, at the site of bone metastases exhibiting pronounced reactive bone proliferation. Franseen and McLean, in fact, record a value of 26.4 Kay units per gram tissue obtained on bone (ilium) which was the site of an osteoblastic metastatic neuroblastoma of uncertain primary source, in a child of twelve. In a case of metastatic prostatic adenocarcinoma, they obtained a value of 4.5 Kay units per gram of rib tissue. Upon examination of bone from the humerus in a case of metastatic hypernephroma, the phosphatase activity was found to be too low to evaluate. No data are given regarding the degree of bone proliferation at the site of the bone metastases in the latter two cases, and we are therefore unable to make any valid comparisons with our own results.
Table II: Phosphatase Activity of Bone and Serum of Patients with (1) Osteoplastic Bone Metastases, (2) Osteolytic Bone Metastases, (3) Paget's Disease, (4) Rickets, (5) Multiple Myeloma, (6) Jaundice due to Liver Metastases

(All values for bone phosphatase activity are expressed in King and Armstrong units per gram wet tissue)

<table>
<thead>
<tr>
<th>Case</th>
<th>Age and Sex</th>
<th>Diagnosis</th>
<th>Serum Phosphatase activity (Bodansky units, 100 c.c.)</th>
<th>Ca mg.</th>
<th>Inorg. P mg.</th>
<th>Skull pH 9.1</th>
<th>Lumbar Vertebra pH 9.1</th>
<th>Rib pH 9.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67 ♂</td>
<td>Carcinoma of prostate with osteoplastic bone metastases</td>
<td>44.4</td>
<td>8.5</td>
<td>2.6</td>
<td>39.4</td>
<td>19.0</td>
<td>53.0</td>
</tr>
<tr>
<td>2</td>
<td>66 ♀</td>
<td>Carcinoma of breast with osteolytic bone metastases</td>
<td>8.9</td>
<td>10.4</td>
<td>4.0</td>
<td>30.6*</td>
<td>1.1*</td>
<td>50.2*</td>
</tr>
<tr>
<td>3</td>
<td>68 ♂</td>
<td>Paget's disease</td>
<td>19.7</td>
<td>10.0</td>
<td>3.4</td>
<td>2.0</td>
<td>0.1</td>
<td>22.5</td>
</tr>
<tr>
<td>4</td>
<td>4 mo. ♀</td>
<td>Rickets</td>
<td>73.0</td>
<td>9.8</td>
<td>3.2</td>
<td>1.4</td>
<td>0.1</td>
<td>1.5</td>
</tr>
<tr>
<td>5</td>
<td>35 ♀</td>
<td>Multiple myeloma</td>
<td>2.1</td>
<td>10.7</td>
<td>4.2</td>
<td>2.2</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>6</td>
<td>52 ♂</td>
<td>Carcinoma of tail of pancreas with jaundice due to liver metastases</td>
<td>35.2</td>
<td>10.6</td>
<td>3.8</td>
<td>0.1</td>
<td>3.9</td>
<td>2.8</td>
</tr>
</tbody>
</table>

* Values obtained after digestion with NaF added.
known (13). The phosphatase activity of involved bone in a case of multiple myeloma (Case 5) was within normal limits. This is in general agreement with Franseen and McLean (7), who were unable to detect any phosphatase activity of bone in two instances. In Case 6, the phosphatase activity of the serum was markedly elevated as a result of hepatic metastases secondary to carcinoma of the tail of the pancreas, with jaundice (14: Case 89). The phosphatase activity of the bone in this case was within normal limits.

The results reviewed thus far have to do with "alkaline" phosphatase activity, determined at pH 9.1, and refer to that phosphatase ordinarily associated with bone. An attempt was made also to estimate the "acid" phosphatase activity (pH 5.0) of tissue from the site of osteoplastic bone metastases secondary to carcinoma of the prostate gland. Kutscher and Wolberg (6) have shown that normal prostate tissue contains an extraordinary amount of an "acid" phosphatase with optimum pH at approximately 5.0 (see confirmatory data, Table III). The high values for "acid" phosphatase activity obtained in our patient with prostatic carcinoma (Case 1, Table II) suggest that metastatic tumor cells arising from carcinoma of the prostate gland retain their capacity to elaborate an "acid" phosphatase in large quantity.²

<p>| Table III: &quot;Alkaline&quot; and &quot;Acid&quot; Phosphatase Activity of Normal Prostate Gland Tissue |
|-----------------------------------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>No.</th>
<th>pH 9.1</th>
<th>pH 5.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>0.4</td>
<td>997.</td>
</tr>
<tr>
<td>2.</td>
<td>0.8</td>
<td>264.</td>
</tr>
<tr>
<td>3.</td>
<td>0.5</td>
<td>605.</td>
</tr>
</tbody>
</table>

Clinical and Pathological Data on Cases 1 to 3

Case 1: F. B., a white male aged sixty-seven, was admitted to the Presbyterian Hospital in April 1936 because of pains in the extremities, shoulders, and back, for the preceding six weeks. Nocturia, frequency, and hesitancy had been noted for several years. Examination on entry revealed extreme tenderness over almost the entire skeleton and inability to move because of intense pain. The prostate was enlarged, nodular, and firm. X-rays revealed only an area of irregular increase in density in the left pubic bone, through which there was a fracture caused by a recent fall from bed.

The course was progressively down-hill, terminating in death seven weeks after admission. During this period, marked secondary anemia and thrombocytopenia developed. Many myelocytes and an occasional myeloblast appeared in the blood. The serum phosphatase activity was markedly elevated (44.4 Bodansky units per 100 c.c.). Two

² The "acid" phosphatase found in metastatic prostate carcinoma cannot be derived to any appreciable extent from erythrocytes, etc., since the values obtained in Case 1 greatly exceed those obtained in samples of normal or pathological bone (Tables I and II), some of which appeared to be fully as hemorrhagic. The "acid" phosphatase activity found in the latter is ascribed wholly or in large part to erythrocytes, and the levels found are regarded as representative of the range ascribable to that source. It should be noted also (Table II) that increased "alkaline" phosphatase activity was associated with increased "acid" phosphatase activity only in Case 1, not in our patient with rickets or in our case of Paget's disease. That the "acid" phosphatase activity observed in Case 1 is not residual "alkaline" phosphatase activity at pH 5.0 is evidenced further by almost complete inhibition upon addition of NaF, as contrasted with the only slight effect of this agent upon "alkaline" phosphatase activity.
weeks after admission, small sclerotic areas in the 4th and 5th lumbar vertebrae were observed in roentgenograms. X-rays taken four days before death revealed a collapse of the 3rd lumbar vertebra. The area of bone involvement in the pelvis had definitely increased in size. A similar bone lesion was now demonstrable in the intertrochanteric region of the right femur. The ribs appeared to be normal. A definite x-ray diagnosis of osteoplastic bone metastases in the pelvis and femur could be made for the first time on these films.

Necropsy performed nine hours after death established a widely metastasizing carcinoma of the prostate gland, usually assuming the form of compact masses of small, regular cells, with little or no supporting stroma. Portions of several ribs, the sternum, lumbar vertebrae, and the pelvis were examined microscopically, and in every instance the marrow was either completely or in good part replaced by tumor tissue. In all of the skeletal sections, with the exception of that of the 3rd lumbar vertebra, there was a striking production of new bone in the form of small trabeculae, partially calcified, to which numerous osteoclasts were closely applied (Fig. 1). No abnormal cartilage formation was found. There was little evidence of destruction of bone except in the 3rd lumbar vertebra, which presented areas of necrosis and hemorrhage. No metastases were found in the liver. The weight of the parathyroid glands was within normal limits and no abnormalities were observed on section.

In view of our findings regarding the bone phosphatase activity in this case, it is interesting to note that the period of metastatic bone involvement was relatively short; that the course was rapid; and that the widespread osteoplastic skeletal metastases were still in so early a stage of development as to escape detection, for the most part, by roentgenographic examination.

CASE 2: G. B., a white female aged sixty-three, was admitted to the Presbyterian Hospital in 1933 for excision of a nodule near the right axilla. This proved to be a poorly differentiated carcinoma, the site of origin, apparently, a supernumerary mammary gland. No skeletal metastases were demonstrable by x-ray at that time. Six months later, lower back pain became severe and percussion tenderness was elicited over the 5th and 6th thoracic vertebrae, and also over the 1st to the 4th lumbar. Roentgenograms revealed decalcification of the spine, most marked in the lumbar region. The serum phosphatase activity was 6.5 Bodansky units per 100 c.c.; serum calcium and inorganic phosphorus were within normal limits. The patient received extensive radiation at intervals, but with little relief of pain. In December 1935, definite osteolytic metastases to the pelvis and upper femora were demonstrable by x-rays. The decalcification of the spine was more marked. Serum phosphatase activity was now 8.9 Bodansky units per 100 c.c. Death ensued in June 1936.

Necropsy failed to disclose any remnant of tumor in the axilla, but revealed widespread secondary involvement of the viscera and skeleton. Microscopically, the vertebrae, ribs, and femur were invaded by tumor tissue to an extent reminiscent of Case 1, but in this instance only minimal new bone formation was found (Fig. 2). There was massive displacement of cancellous bone and marrow by closely packed masses of small, round tumor cells, among which fragments of necrotic bone were numerous. Osteoclasts, however, were not conspicuous. There was no invasion of the liver. The parathyroid glands were small and cytologically normal.

CASE 3: M. S., a white male aged sixty-eight, was admitted to the Presbyterian Hospital in July 1935 for symptoms referable to a pulsion diverticulum of the esophagus. Marked kyphoscoliosis of the spine, which had been present for an indeterminate period of years, led to x-ray studies, disclosing advanced Paget's disease involving the skull, spine, pelvis, clavicles, ribs, and left femur. Serum phosphatase activity was 19.7 Bodansky units per 100 c.c. Following exteriorization and excision of the diverticulum, mediastinitis and pneumonia developed. Death occurred in October 1935.

At necropsy, the bones indicated by roentgenographic studies were found to present the classical changes of osteitis deformans. The occipital bone, which exceeded 2.0 cm. in thickness in some areas, was densely sclerotic exteriorly, spongy, and very hemorrhagic on its inner surface. Sections showed the typical picture of Paget's disease. The parathyroid glands were not enlarged and appeared to be normal on microscopic examination.
FIG. 1. CASE 1: CARCINOMA OF THE PROSTATE, SECTION THROUGH METASTASIS IN LUMBAR VERTEBRA

There is striking production of new bone in the form of numerous small trabeculae, partially calcified. Osteoblasts in large numbers can be seen closely applied to the surface of the trabeculae.

FIG. 2. CASE 2: CARCINOMA OF THE BREAST, SECTION THROUGH METASTASIS IN LUMBAR VERTEBRA

The invasion of tumor cells has caused extensive bone destruction. Fragments of necrotic bone are numerous. Evidences of reactive bone proliferation are lacking.
Discussion

The data included in this study, while obviously insufficient to be conclusive, are considered to be of enough interest to encourage further investigation. Certain implications of general interest, which have been touched upon in the introduction, will be considered more fully at this point.

Relation of Increased Bone Phosphatase Activity to Increased Serum Phosphatase Activity: There can be little doubt that the increased bone phosphatase activity observed in our case of carcinoma of the prostate gland was due to increased production of phosphatase at the site of osteoplastic bone metastases, and that the elevated serum phosphatase activity was the result of the escape of increased amounts of phosphatase into the blood stream. The mechanism involved in the rise of serum phosphatase activity would appear to be analogous to that which seems to operate in rickets (13), Paget's disease (7), and the sclerotic phase of osteoporosis circumscripta of the skull (15), osteogenic sarcoma (7), hyperparathyroidism (1), and possibly in certain other bone diseases. The observation is regarded as substantiating further the view initially expressed by Robison (13) that increased phosphatase activity of the blood results from an increase in specific cellular activities leading to formation of bone.3

Relation of Local Increases in Bone Phosphatase Activity to the Mechanism of Bone Formation at the Site of Osteoplastic Skeletal Metastases: The rôle of bone phosphatase in the mechanism of normal bone formation, as elucidated by Robison and his collaborators (18), may be outlined as follows: the intercellular fluids bathing osteogenic cells contain salts of phosphoric esters, which are hydrolyzed by the phosphatase elaborated by those cells. In this manner, the concentration of phosphate ions is increased locally to a point exceeding the solubility product of calcium phosphate and of the related compounds composing bone. A second calcifying mechanism effects the deposition of bone salts from the locally supersaturated solution upon the bone matrix.

The studies of Franseen and McLean (7) have shown that the high phosphatase content of neoplastic tissues in the osteoblastic type of osteogenic sarcoma is related, like that of normal growing bone, to increased osteogenesis. It seems likely that the increased phosphatase activity of bone at the site of osteoplastic skeletal metastases has a similar significance, and makes possible or inevitable the new bone formation which takes place. This analogy between the chemical aspects of new bone formation under normal and pathological conditions is in accord with the morphological similarities revealed by Axhausen's extensive histological studies (19).

Relation of Phosphatase to the Tendency of Certain Neoplasms to Yield Osteoplastic Skeletal Metastases: It has never been made clear why certain neoplasms, notably carcinoma of the prostate gland, usually give rise to predominantly osteoplastic skeletal metastases, whereas most tumors secondarily involving the bones are chiefly osteolytic, with varying degrees of reactive

3 This generalization associates increased phosphatase activity specifically with bone formation as contrasted with bone destruction or, more vaguely, bone involvement. Increased serum phosphatase activity may be the result, however, not only of increased production of phosphatase but also of obstruction to the excretion of phosphatase in the bile (16, 14). There may be other conditions in which increased serum phosphatase is of non-osseous origin (17).
bone proliferation. A number of theories have been proposed by way of explanation, of which the best known are the following:

(1) von Recklinghausen's suggestion that thrombosis of small veins in the bone marrow by tumor cells causes local congestion, to which the bone cells react by formation of new bone (20).

(2) The view that osteogenesis is the result of inflammatory changes in the bone marrow (21).

(3) Assmann's theory that primary bone necroses initiate the osteoplastic bone reaction (22).

(4) The conclusion drawn by Thiele (23) that the less invasive and rapidly growing the metastasis, the greater the tendency for osteoplastic changes.

(5) The view that certain tumor cells liberate a chemical factor or stimulus which initiates the formation of bone either by cells in the surrounding bone (20) or by cells in the connective-tissue stroma of the tumor itself (19). This possibility was mentioned by von Recklinghausen as a mechanism secondary to that already cited.

Of these theories, 1 to 3 are of historical interest only. The invasiveness and rapidity of growth of tumor metastases undoubtedly influence the degree of proliferative bone reaction, as Geschickter and Copeland have recently emphasized (24), but osteoplastic skeletal metastases may develop quite rapidly (Case 1), whereas osteolytic metastases may exhibit comparatively little bone reaction even after a protracted course (Case 2). The view, derived from pathological studies, that some chemical factor elaborated by certain tumor cells initiates the osteoplastic reaction has received most support, notably by Goetsch (25), Schmorl (26), Axhausen (19), Levin (27), Žemgulys (28), Sutherland, Decker and Cilley (29), and Willis (30).

Whether any relationship exists between this hypothetical chemical factor and the increased bone phosphatase activity found at the site of osteoplastic metastases in our case of carcinoma of the prostate, remains to be determined. Normal prostate tissue, as shown in Table III, contains only minimal amounts of "alkaline" phosphatase, which is the enzyme usually associated with bone formation. The significance of the presence in normal prostate tissue (6; and Table III) and in prostate carcinoma metastases (Table II) of large amounts of an "acid" phosphatase is not known. Further study may show whether or not its presence in metastatic prostate carcinoma cells in such concentration has any bearing upon the production of "alkaline" phosphatase and upon the osteoplastic tendencies of skeletal metastases secondary to prostate carcinoma.

In any event, it seems likely that the production of bone at the site of osteoplastic metastases is contingent upon the local elaboration of bone phosphatase in adequate amount. The data now available favor the view that certain metastatic tumor cells stimulate the production of bone-producing phosphatase by osteogenic cells at the site of the metastases; and that the capacity to stimulate production of bone phosphatase determines, in part, the osteoplastic character of metastatic lesions. An analogous relation is known to exist with respect to the phosphatase content of ossifying and non-ossifying cartilage (31) and with respect to the heterotopic ossification of bladder transplants (32).
SUMMARY

1. The King and Armstrong method for determining the phosphatase activity of serum and bile has been applied to the estimation of bone phosphatase activity. The use of a method depending upon the estimation of phenol liberated was found to be advantageous in determining the phosphatase activity of unfiltered aqueous bone extracts.

2. Values for the phosphatase activity of normal bone from adult human subjects are recorded. Lumbar vertebrae, pelvis and ribs exhibit appreciable phosphatase activity; cranium and femur cortex often possess too little phosphatase for quantitative determination.

3. Markedly increased phosphatase activity of bone from the site of osteoplastic skeletal metastases was noted in a patient with carcinoma of the prostate gland. Bone sections revealed very active new bone formation. The phosphatase activity of bone from the site of osteolytic skeletal metastases secondary to carcinoma of the breast was within normal limits. Bone sections of involved areas in this case showed virtually no reactive bone proliferation. Examination of a case of Paget's disease revealed increased bone phosphatase activity of the cranium, which was in an advanced stage of the disease.

4. It is pointed out that the marked increase in phosphatase activity of bone at the site of osteoplastic metastases satisfactorily explains the rise in serum phosphatase activity previously noted in a number of patients with widespread osteoplastic skeletal involvement. It is suggested that increased production of bone phosphatase at the site of osteoplastic skeletal metastases makes the local formation of new bone possible or inevitable.

5. The intrinsic capacity of certain tumor cells to stimulate production of adequate amounts of bone phosphatase appears to determine, in part, the osteoplastic tendencies of the metastases to which they give rise.

6. In addition to increased "alkaline" phosphatase activity (pH 9.1), markedly increased "acid" phosphatase activity (pH 5.0) of bone was noted at the site of osteoplastic metastases secondary to prostate carcinoma. Metastatic tumor cells arising from carcinoma of the prostate gland apparently retain their capacity to elaborate the "acid" phosphatase found by Kutscher and Wolbergs in normal prostate tissue. It remains to be determined whether the presence in metastatic prostate carcinoma cells of "acid" phosphatase in such concentration is related to the production of "alkaline" phosphatase and to the osteoplastic character of most prostatic carcinoma metastases.

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INCREASED PHOSPHATASE ACTIVITY OF BONE 495