RESPONSE OF BONE TO TUMOR INVASION

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CANCER metastases in bone are frequently thought of as being divisible into two presumably distinct roentgenographic types: an "osteolytic" type, characterized by relative radiolucency, and an "osteoblastic" type, characterized by relative radiodensity. A fairly extensive radiological literature describing in detail the radiographic features of the various types of neoplasm most frequently disseminated to the skeleton has arisen, supplementing this belief.[1, 12, 24, 52, 54] Curiously, however, histological data relative to cancer metastases in bone are quite scarce. Most morphological studies have been concerned primarily with the demonstration of neoplastic tissue in bone; there are very few records of the structural characteristics of the host bone.

Data have been presented from this and other laboratories,[23, 30, 33, 35, 37, 38, 43-47, 53, 58, 64, 67] however, that would make such knowledge of significant import to the clinician and particularly to the clinical investigator. The present study was undertaken, therefore, in an attempt to delineate the various morphological features of metastatic cancers in bone and to provide thereby a histological background for the interpretation of physiological studies and serial roentgenograms in patients with cancer metastases in the skeleton.

MATERIAL

Seven hundred and eighty-three microscopic sections from 241 different patients were studied. Each represented a routinely taken bone specimen obtained at postmortem; approximately two thirds were sections of lumbar vertebrae. The specimens had been decalcified in 10 per cent nitric acid and stained with hematoxylin and eosin. A careful review of pertinent clinical data to establish with certainty that the bone specimen represented a true metastasis constituted the only attempt at selection of cases for study.

There were twenty-eight different groups of neoplasms in the series (Table 1). Seventy-one cancers were of the endocrine system or of hormone-dependent organs, including fifty-two carcinomas of the breast (two in men), twelve of the prostate, and five of the thyroid and two chorioepitheliomas. Sixty-eight of the cases were of the lymphoma group. There were twenty-four cancers of the digestive tract and twenty-three of the respiratory system. Eight tumors (exclusive of the cases of chorioepitheliomas and prostatic cancer considered here as "hormone dependent" tumors) arose from the genitourinary tract. The remainder constituted a miscellaneous group of fourteen neuroblastomas, twelve plasma-cell myelomas, seven malignant melanomas, seven rhabdomyosarcomas, three of Ewing's tumor, one retinoblastoma, and three malignant tumors of unknown site of origin (Table 2). The cases of leukemia, myeloma, lymphosarcoma, and Ewing's tumor were considered clinically to be true metastases that had originated from lesions in the soft tissues or bones other than the bone section that was studied.

METHOD

Sections were reviewed with particular reference to the architecture of the host bone and to the general configuration of the invading tumor. Little attention was directed specifically to the morphological characteristics of the cancer cells per se, but special care attended the search for osteoblasts, osteoclasts, and areas of osteoid deposition, cartilaginous metaplasia, and connective-tissue proliferation.

Except in instances in which different areas of the same section or different sections from the same bone differed markedly one from the other, the most usual findings were accepted as generally covering the case. Cases showing marked alterations in different microscopic

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TABLE 1

BONE RESPONSE TO CANCER INVASION

Origin or type	No. cases	Grade of response 0	1	2	3	4
Breast	52	6	10	11	16	9*
Leukemia	38	33	5	0	0	0
Lung	20	7	6	2	4	1
Neuroblastoma	14	2	7	4	0	1
Hodgkin's disease	13	7	5	0	1	0
Myeloma	12	6	3	0	0	3*
Prostate	12	0	1	0	2	9*
Reticulum-cell sarcoma	10	7	3	0	0	0
Lymphosarcoma	7	6	1	0	0	0
Melanoma	7	2	4	1	0	0
Rhabdomyosarcoma	7	6	1	0	0	0
Stomach	7	3	3	1	0	0
Urinary bladder	6	3	2	0	1	0
Rectum	5	4	0	1	0	0
Thyroid	5	0	2	1	1	1
Ewing's tumor	3	2	0	1	0	0
Unknown	3	1	0	1	0	1
Cholangiocarcinoma	3	2	1	0	0	0
Colon	2	1	0	0	0	1
Chorioepithelioma	2	2	0	0	0	0
Esophagus	2	1	0	0	0	1*
Kidney	2	1	1	0	0	0
Nasopharynx	2	1	1	0	0	0
Pancreas	2	1	1	0	0	0
Tongue	2	0	1	1	0	0
Antrum	1	1	0	0	0	0
Hepatoma	1	1	0	0	0	0
Retinoblastoma	1	1	0	0	0	0

*One case showed all patterns.

fields were considered separately. For purposes of description only, subperiosteal osteoid deposition was considered as distinct from trabecular new-bone formation and was separately noted.

Grade of Response. After reviewing all sections in each case, the case was summarized in terms of the total extent and relative proportions of bone-destroying and bone-producing elements. A semiquantitative "grade of response" was then assigned it.

GRADE-0 lesions were those that were predominantly destructive in nature. They showed little or no evidence of either osteoblastic-cell proliferation or of new bone-matrix formation but presented considerable evidence of bone destruction and necrosis.

GRADE-1 lesions were those that appeared to be characterized predominantly by bone-destroying elements but in which definite evidence of a limited amount of bone production was also evident.

GRADE-2 lesions were those in which both bone production and bone destruction were clearly demonstrable and of approximately similar magnitude morphologically.

GRADE-3 lesions were those that presented evidence of coexistent bone destruction and bone production but in which the productive processes appeared to be of considerably greater magnitude.

GRADE-4 lesions were those that showed both bone production and bone destruction but in which bone destruction appeared quantitatively of minor importance. No distinction could be drawn between subperiosteal new bone formation and trabecular new bone formation in these cases.

In lesions graded zero to three inclusive, cortical (or subperiosteal) osteoplasia could be differentiated from trabecular new bone and was independently graded on the basis of its over-all extent in all of the microscopic sections of each case. The absence of any appreciable cortical response was considered CORTICAL GRADE 0. Maximal new cortical bone formation where the new cortical bone was distinct from subjacent or adjacent new trabecular bone was designated CORTICAL GRADE 3. Grades 1 and 2 represented cortical responses of intermediate relative extent and magnitude.

RESULTS

Predominantly Destructive Lesions. One hundred and seven of the 241 cases were considered to show a grade-0 response and fifty-eight were designated as grade 1. Considered collectively, grade-0 and grade-1 lesions comprised approximately two thirds of the total number of study cases and represented virtually all of the tumor types that, as a group, are classically considered to present roentgenographically "lytic" cancer metastases in bone. The group included twenty-one of the seventy-one tumors of the endocrine system, sixty-seven of the sixty-eight lymphomas, nineteen of the twenty-four neoplasms of gastrointestinal origin, seven of the eight cancers of the genitourinary tract, sixteen of the twenty-three respiratory-system neoplasms, and thirty-five of the forty-seven cases included in the miscellaneous group of malignant tumors. Two cases of the twenty-one endocrine-system or hormone-dependent tumors that showed little or no bone production were chorioepitheliomas; two, thyroid cancers; one, a prostate

TABLE 2

BONE RESPONSE TO CANCER INVASION

Group	No. cases	Grade of response 0	1	2	3	4
Endocrine	71	8	13	12	19	19
Lymphoma	68	53	14	1	0	0
Gastrointestinal	24	13	6	3	0	2
Respiratory	23	9	7	2	4	1
Genitourinary	8	4	3	0	1	0
Miscellaneous	47	20	15	6	1	5
TOTAL	241	107	58	24	25	27

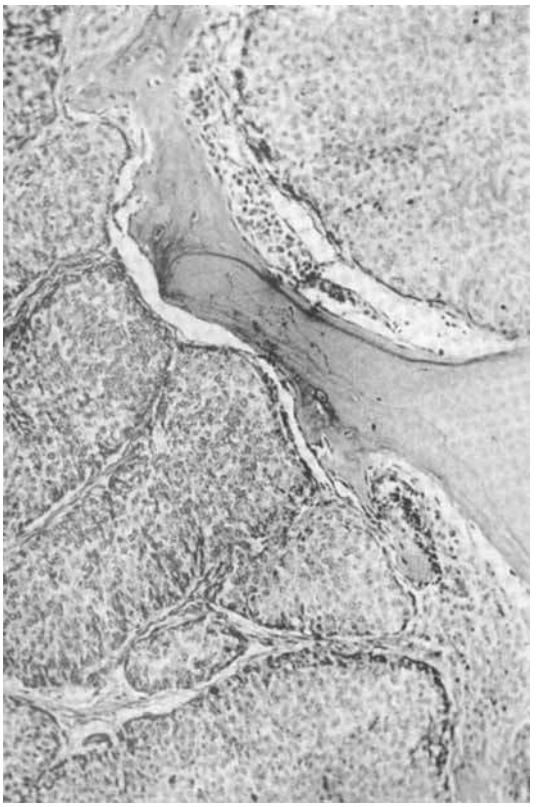

FIG. 1. High power of grade-1 bone response in a patient with carcinoma of the urinary bladder.

carcinoma; and sixteen, cancer of the breast.

In composite, grade-0 and grade-1 lesions displayed an essentially uniform histological appearance characterized by: (1) a decrease in number and size of the remaining bony trabeculae; (2) the direct erosion, destruction, and necrosis of the bony spicules by dense sheets and masses of tumor; (3) the frequent, but inconstant occurrence of polynuclear tumor giant cells in areas of bone destruction; (4) the almost complete absence of cytologically typical "osteoclasts"; (5) occasional destruction and direct invasion of bony trabeculae by non-neoplastic cells derived from the tumor stroma; (6) patchy necrosis within the tumor; and (7) normoplastic or hyperplastic appearance of the surviving marrow elements.

Exclusive of differences in the characteristic morphological appearance of the specific cell types and quantitative differences in the amount of new bone formation (grade-1 as opposed to grade-0 lesions), no qualitative differences could be found in the nature of the bone response in any of these cases. In all, differences of bone response were differences of degree rather than of kind.

In three cases, two carcinomas of the breast and one rectal cancer, that had been considered to show a grade-0 response, only isolated microscopic foci of tumor could be discerned. The tumor nidus in each of the cases bore no direct anatomical relationship to the bony trabeculae and had no demonstrable histological effect either on adjacent or more distal osseous structures. In cases in which larger amounts of tumor were present, however, the trabeculae were constantly directly impinged upon by the invading neoplasm, which appeared in and by itself to promote erosion of the bony spicules. Areas of trabecular serration owing to the intrusion either of tumor masses or of individual cancer cells not infrequently presented a small space between the tumor and the bone spicule. A similar phenomenon was evident in areas of tumor giant-cell formation and in those remarkably few regions in which typical "osteoclasts" could be identified.

New bone formation at microscopic but distinct distances from such areas did occasionally occur. This was a more frequent concomitant of cortical grade-1 than of cortical grade-0 lesions. Eighty-two of the cases having an over-all bone response characterized as grade 0 were interpreted as also possessing a cortical grade 0. Twenty-two of these were assigned cortical grade 1, two were given cortical grade 2, and only one was designated cortical grade 3. On the other hand, of the fifty-eight lesions given an over-all grade-1 response, thirty-four were interpreted as being cortical grade 0, seven as cortical grade 1, ten as cortical grade 2, and seven as cortical grade 3.

Predominantly Productive Lesions. Seventy-six of the 241 cases were considered to show an over-all grade of response characterized either as grade 2, grade 3, or grade 4. Each demonstrated, by definition, impressively greater amounts of the new trabecular and subperiosteal (cortical) new bone production than did lesions graded 0 and 1.

Grade-2 lesions, in which the morphological stigmata of bone production and bone destruction appeared to be of approximately equal order of magnitude, encompassed twelve endocrine-system tumors (eleven breast, one thyroid), two lung cancers, three gastrointestinal-tract neoplasms (one each of the tongue, stomach, and rectum), and seven miscellaneous malignant tumors, including four neuroblastomas, one malignant melanoma, one Ewing's tumor, and one cancer of unknown

site of origin. Grade-3 lesions included sixteen breast cancers, two prostatic carcinomas, one thyroid cancer, four malignant tumors of the lung, one cancer of the urinary bladder, and one case of Hodgkin's disease. Grade-4 lesions comprised a group of 19 endocrine-system tumors (nine cases each of breast and prostate cancers and one carcinoma of the thyroid gland), three plasma-cell myelomas, one case each of cancer of the lung, esophagus, and colon, one neuroblastoma, and one malignant tumor of unknown origin.

The histological sections in five of the grade-4 cases posed particularly interesting problems. In two, one breast cancer and one cancer of the colon, the final autopsy diagnosis had been established by others as metastatic cancer and coexistent Paget's disease of bone. Each disclosed a distinctly mosaic pattern of irregularly interwoven cement lines, but, nevertheless, lacked the increased intertrabecular fibrosis and the striking number of osteoblasts and the cytologically characteristic "osteoclasts" that are the morphological features of Paget's disease. Such pagetoid alterations, however, were never as prominent as those present in the cases considered to show true Paget's disease. The histological appearance was compatible with the so-called "resting" phase of Paget's disease. Pagetoid changes were occasionally observed in other lesions in which bone destruction and bone repair were concurrently present.

The remaining three cases considered grade 4 showed, in diverse locations, changes consistent with all other grades of response. They have been considered here to show a grade-4 bone response but, depending upon the precise region examined, could equally well have been either grade 0, grade 1, grade 2 or grade 3.

When viewed collectively, bone lesions of grades 2, 3, and 4 presented a bone pattern that was as strikingly uniform as that observed in grade-0 and grade-1 lesions. The histological appearance was, however, quantitatively quite different and was characterized by: (1) an irregularly interlacing network of an increased number of moderately to markedly thickened bony trabeculae; (2) the depositon of osteoid both within and around tumor masses, ingress of osteoblastic cells probably derived from the surviving portions of the bone spicules, and undifferentiated mesenchymal cells in the in-

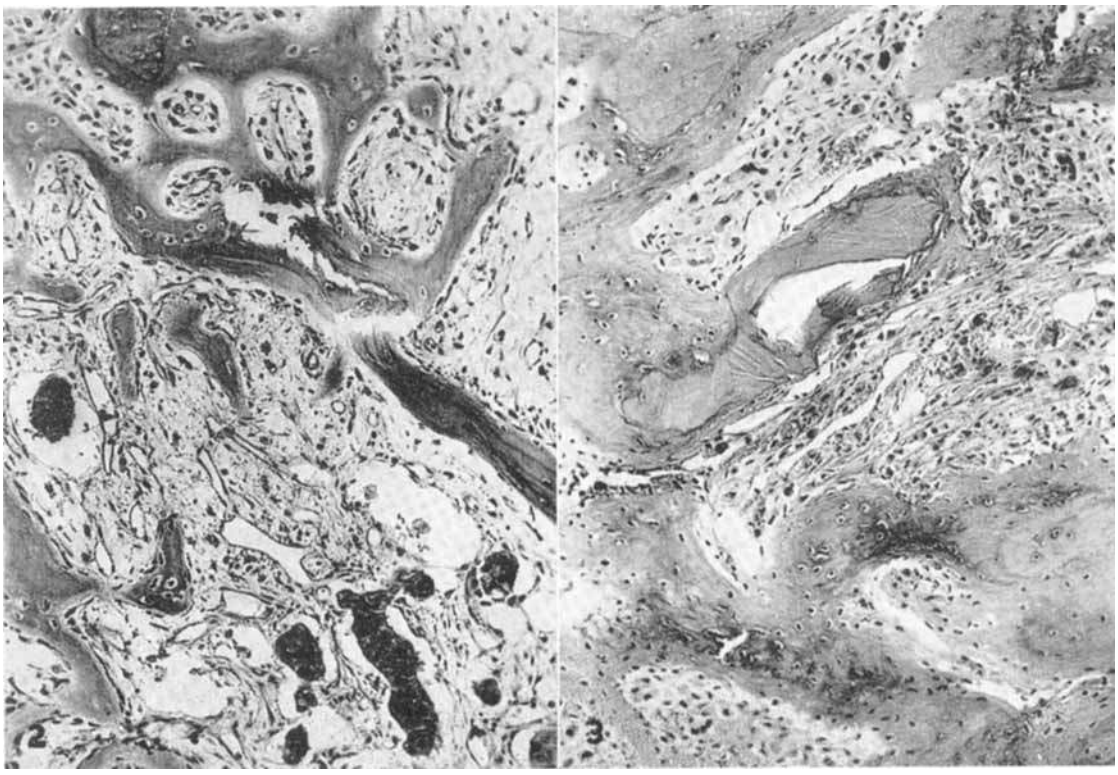

FIG. 2. Grade-3 cortical bone response in a patient with carcinoma of the breast.
FIG. 3. Grade-4 bone response in a patient with carcinoma of the breast.

tertrabecular spaces or, perhaps, directly from pre-existent connective-tissue cells; (3) the prominent subperiosteal new bone formation; (4) clumps, isolated islands, and small masses of tumor cells; and (5) a tendency to hypoplasia, by direct stenosis of the spaces of the surviving marrow.

In grade-2 and grade-3 cases, trabecular and cortical new bone formation could be readily distinguished. Of forty-nine cases so graded, seven were interpreted as possessing a grade-3 cortical response, fourteen a grade-2 cortical response, eighteen a grade-1 cortical response and only ten, of which seven occurred in lesions assigned a grade-2 over-all response, as a grade-0 cortical bone response. Although quantitative differentiation into the various grades of bone response could be made, qualitative differentiation could not be made of the cases in the group of lesions with grade-2, -3, and -4 over-all bone responses. In fact, in all essential respects, the bone response in any given grade differed only quantitatively from the general response of a lesion assigned any other grade of response. Differences in all of the grades were clearly differences in degree only.

Other changes, such as difference in the general configuration of the invading tumor and the structural features of the surviving marrow, could be adequately accounted for in terms of the relative extent of response on the part of the host bone. On purely mechanical grounds, dense sheets of tumor tissue and a proliferating marrow could not be expected to occur in lesions characterized by progressive replacement stenosis by new bone formation, as especially seen in grade-3 and -4 lesions.

In none of the cases were any major alterations in the tumor stroma observed. A tumor characterized by a dense stroma in its site of origin was similarly apt to possess a dense stroma when it had metastasized to the skeleton.

A peripheral rim of nonspecific connective tissue was occasionally observed in sharply circumscribed metastatic foci but appeared of little importance in respect to the response of host bone. Two cases showed foci of fatty metamorphosis and twenty-two cases, including eighteen grade-3 and grade-4 lesions, three grade-2 metastases, and a single lesion considered grade 1, disclosed areas of cartilaginous metaplasia in juxtaposition to the surviving and proliferating bony trabeculae.

Clinical Findings. There were 124 male and 117 female patients in the present series. They ranged in age from 10 months to 86 years and were predominantly of Caucasian racial origin. One, a 61-year-old man with carcinoma of the lung, was an Oriental.

Roentgenographic information was available in 187 of the 241 cases. The presence of metastatic foci in the skeleton had been demonstrated in 108 of these 187 cases. (Despite the fact that nearly three quarters of the study sections had been removed from the lumbar vertebrae, it was possible precisely to identify the tissue studied with the roentgenographically established location of the lesion in only twenty-three of the 108 cases.) Three of these twenty-three cases had roentgenographically "blastic" metastases from cancer of the prostate. The bone specimens in two were considered histologically Grade III, and in one, Grade IV. Sixteen cases, two carcinomas of the thyroid, five plasma-cell myelomas, one carcinoma of the pancreas, and eight carcinomas of the breast, which were roentgenographically considered to be "osteolytic," had grade-0 or grade-I bone response histologically. Three cases, two breast cancers and one neuroblastoma, considered "osteolytic" by virtue of their roentgenographic appearance, were interpreted histologically as Grade II; a single case of breast cancer considered roentgenographically "mixed" but predominantly "lytic" in type, was considered histologically Grade IV.

Calcium and phosphatase data were, with a few exceptions, available only in patients with endocrine-system tumors, plasma-cell myelomas, and in some with carcinoma of the lung. Although few in number, the data, in general, did conform with the established concept that bone-destroying cancer metastases are frequently associated with hypercalcuria, occasionally hypercalcemia, and, in the presence of the increased osteoblastic activity of bone repair, with elevated levels of serum alkaline phosphatase.

The endocrine status in all but the breast and prostate cancers bore no evident relationship to the histological grade of the bone metastases. The age of the patients, in the other tumor types, bore only an indefinite relationship to the grade of the bone response at the time of necropsy examination. In these, as in tumor types in general, the grade of the lesion histologically tended to reflect the type and extent of histological undifferentiation of the tumor and consequently the postulated rate of growth of that tumor.

TABLE 3
RELATION OF AGE AT NECROPSY TO GRADE OF BONE RESPONSE

Age in yr.	Grade of bone response				
	0	1	2	3	4
21–30	0	0	1	0	0
31–40	0	2	2	2	1
41–50	2	3	2	9	2
51–60	2	2	3	3	5
61–70	2	2	3	2	1
71–80	0	1	0	0	0

Three of the patients with thyroid cancers had normal gonads at autopsy. One was a 36-year-old woman with a grade-3 bone response, one a 59-year-old woman with a grade-4 bone response, and the other a 45-year-old man with a grade-1 response. The gonads of two patients were reported to be atrophic; one was a 43-year-old man with a grade-2 response; the other, a 55-year-old woman with a grade-1 response.

Both patients with chorioepitheliomas were men. One died at 28 years of age and the other at 33 years. Both had previously submitted to orchiectomy and both had bone responses that were interpreted as grade 0.

All twelve patients with carcinoma of the prostate gland had either atrophic testes or else were therapeutic castrates. Four patients were 70 years or older, four were between 60 and 70, three were between 50 and 60 at the time of necropsy, and one patient was 47 years old. Nine patients, two of whom had a grade-3 and one of whom had a grade-4 bone response, had atrophic testes and had not undergone surgery. One patient, aged 71 years, had had elevated acid phosphatases with a normal alkaline phosphatase and, at autopsy, had multiple small microscopic metastases in his testes. All bone sections in this case were classified grade 1. Another patient, age 70, had slightly elevated alkaline and serum phosphatase levels, atrophic testes, and bone responses that were graded 0 to 4 in varying areas.

Two male patients with carcinoma of the breast had undergone radical mastectomy and orchiectomy. One was 41 years old and had a grade-4 bone response; the other was 62 and had a grade-2 bone response.

There were fifty women, ranging in age from twenty-four to seventy-two years, with carcinoma of the breast. Eighteen had normal ovaries at the time of autopsy, nine had had bilateral salpingo-oophorectomies, and twenty-three had abnormal ovaries. Nine of these latter (seven atrophic; two replaced by tumor) had grade-1 bone response; three cases (two replaced by tumor; one atrophic) had grade-2 lesions; eight cases (four tumor; three atrophic; one cystic) had grade-3, and three cases (two atrophic, one tumor) had grade-4 responses in the particular skeletal lesions that were studied. Four patients of the nine with previous surgical removal of the ovaries had grade-2 bone responses, three each had grade-3 and grade-4 skeletal foci, and one patient had a grade-0 bone response. Five patients with normal ovaries had grade-0 bone responses; one had a grade-1 response; four, a grade-2 response; five a grade-3 type of lesion, and three patients had grade-4 bone responses in their skeletal metastases. No particular attention was accorded to the question of cortical stromal hyperplasia in any of the forty-one patients with intact ovaries. Patient age and the status of the ovaries at the time of postmortem examination with respect to the particular bone lesions studied here is noted in Tables 3 and 4. Owing to the nature of the material under study, reference is made only to the particular lesions examined and not to the entire case. Since it is not uncommon to observe a roentgenographically "blastic" cancer metastasis in one skeletal site, while at an adjacent or more distant location a "lytic" lesion may be noted, conclusions can be arrived at only with respect to the particular area studied histologically.

COMMENT

Route of Origin of Skeletal Metastases. No microscopic evidence was found in this study to substantiate the opinion of some[13, 29, 36, 51, 62] that lymphatics play any significant role in the dissemination of tumor cells to the bones. All the evidence noted here suggests that they are blood-borne. Although a few cases showed involvement of periosteal vessels in the presence of a centrally located intraosseous metas-

TABLE 4
RELATION OF STATE OF OVARIES AT NECROPSY TO GRADE OF BONE RESPONSE

Ovaries	Grade of bone response				
	0	1	2	3	4
Normal	5	1	4	5	2
Absent	1	0	4	3	3
"Abnormal"	0	9	3	8	3

tasis and still fewer cases showed concomitant involvement of blood vessels and vessels that could be interpreted as lymphatics, the overwhelming majority of the cases failed to present such microscopic evidence. In routine histological preparations there is little structural difference between periosteal blood vessels and periosteal lymphatics and the conclusion that such vessels were certainly lymphatic in nature and necessarily accounted for the spread of cancer to bone would have to be documented beyond reasonable doubt. Such evidence appears to be lacking.

Although periosteal lymphatic vessels have been demonstrated by several investigators, none has been demonstrated in the marrow,[16, 22] where practically all true metastases are located. To our knowledge, only Kolodny has claimed to have demonstrated lymphatic drainage from bone marrow to the regional lymphatics and, as Willis[65, 66] has indicated, these conclusions are open to different explanation. The same is true with respect to data cited in support of the view that perineural lymphatics may play a role in the spread of cancer to bone, especially cancer of the prostate gland.[59, 62]

It is possible that the deep fascial "lymphatics" described by Handley and by Roberts[51] were not lymphatics at all but rather tributaries and communications of the vertebral system of veins, so well described by Hunter,[32] Cloquet, Bell, and Cruveilhier, and to which Batson[6, 7, 8] and others[18, 19, 31] have more recently directed attention.

With but few modifications as regards details, an accumulating body of evidence[42, 48, 60, 61, 63] tends to support the original concept of von Recklinghausen[49] that all cancer metastases in bone are blood-borne. In fact, more recent information strongly suggests that "the distribution of metastases in the bones is almost exclusively dependent upon the anatomical arrangement of the blood vessels into which tumor emboli are released and by means of which they gain access to capillary beds."[20, 31, 68] The findings of the present study are entirely consistent with this hypothesis.

Intraosseous Spread. Despite differences in opinion regarding the spread of cancer metastases to bone, practically all published accounts agree that, once established in bone, subsequent spread of the tumor occurs via the medullary cavity and through the Volkmann and haversian canals.

This was repeatedly observed in practically all of the sections here studied. Such evidence was strikingly apparent in those cases in which only small, circumscribed deposits of metastatic cancer were present and was somewhat less notable in instances where bone destruction owing to the tumor was more extensive.

Intraosseous spread along preformed anatomical channels in all probability accounts for the remarkably long interval not infrequently observed in some patients between the time of onset of bone pain and the roentgenographic demonstration of a bone metastasis.[26, 31, 57] Similarly, this may account for the accepted fact, again demonstrated in this study, that extensive metastatic involvement may be present within a bone without the presence of the tumor being disclosed roentgenographically.[11, 15, 50, 55, 56]

Bone Destruction. A number of hypotheses have been offered to account for bone destruction after invasion by cancer cells. These include destruction as a result of (1) the action of cells derived from the tumor stroma; (2) the action of specific bone-destroying cells, so-called "osteoclasts"; (3) the elaboration by the cancer cell of more or less specific bone resorptive substances, or the initiation by it of physiochemical processes that alter the physiological environment of the bone; and (4) the mechanical effect of compression of bone by tumor cells.

In a very few microscopic fields, minimal invasion of bone by connective-tissue cells was observed. This could not, however, account for the amount of destruction noted even in the very microscopic field in which it was present. Moreover, the extreme rarity of its occurrence would tend to minimize its importance as a significant mechanism of bone destruction.

There was very little evidence in this study that "osteoclasts" had any direct role at all in promoting bone destruction. Cytologically, typical polynuclear "osteoclasts" were almost completely absent from areas of active bone destruction. Multinucleated giant cells, however, were not uncommon. When present, these were almost certainly tumor giant cells and not so-called "osteoclasts," since, save for the number of nuclei, they possessed all of the histological features of the other tumor cells. Strikingly enough, they tended to appear in areas where bone production was more conspicuous than bone destruction.

Details of the argument against the role of or, indeed, the presence of the cell known as

the "osteoclast" are not germane here. It should be noted, however, that there is an accumulating body of evidence against any factual role of this cell. Data have been presented to suggest that these cells are not distinct cellular entities at all.[3, 10, 27, 28]

To the best of our knowledge, no direct evidence has been presented to support the hypothesis that specific resorptive substances are elaborated by cancer cells. No evidence either for or against this theory can be expected on the basis of the present histological study.

Although histological evidence of bone destruction in practically every instance here studied could be attributed to the direct action of intruding neoplastic cells, a small space between the tumor and a bony spicule was frequently observed. Some of these were undoubtedly artifacts resulting from the fixation and staining processes. Others, however, may have been the morphological representation of distinct physicochemical processes, such as those suggested by Ham.

On the other hand, the dense massing of tumor cells in the more destructive phases of cancer metastases strongly suggests the possibility that the bone destruction can be accounted for on purely mechanical grounds. The disappearance of bone under the influence of externally applied pressure is well established, and there is no necessity to assume that the same mechanism may not be operative as a consequence of mechanical forces exerted from within the bone. There was, however, no histological evidence to permit of any conclusive statement of whether or not mechanical forces were the sole or the major element in promoting bone destruction.

Bone Production. Bone production in the metastatic cancers seemed in no way similar to the processes of metastatic or dystrophic "calcification," such as may be seen in benign tumors or other conditions. With some noteworthy differences, it seemed to be much like that observed in the course of fracture healing.

In an uncomplicated dissolution of continuity after trauma, the injury is unitary in sense of time and is normally succeeded by characteristically progressive repair phenomena. As a result of fracture, the vascular supply is interrupted, with resultant bone necrosis for variable distances on both sides of the fracture line. Healing involves the preliminary removal of a considerable amount of dead tissue on either side of the line of injury. Bone cells, unlike connective-tissue cells elsewhere in the body, cannot readily participate, since they are entombed in lacunae and repair is necessarily effected, therefore, by osteogenic cells derived from the frequently relatively distant periosteal and "endosteal" linings of the bone. To a lesser extent, new bone may appear in consequence of metaplastic transformation of undifferentiated marrow cells. The over-all appearance is that of two more or less complete rings of new bone formation, one SURROUNDING and one LINING the bone at the site of injury.

Metastatic cancers in bone, on the other hand, present chronologically continuing injuries. Since they are usually centrally located in the bone marrow, the extent of interruption in blood supply is proportionately less than that after fractures, and repair more closely resembles that seen in soft tissues. Attempts at repair are participated in by osteoblasts of neighboring trabeculae, as well as by adjacent cells derived from the periosteum and "endosteum." Most importantly, surviving portions of the involved bony trabeculae may themselves participate in attempts at repair. Thus, the over-all appearance in this type of bone injury is that of gradual filling in of defects primarily from the CENTER of the bone, concomitant with continuing processes of bone destruction.

The initiating and modifying stimuli responsible for the sequence of events remain unclarified. Although the literature is replete with references suggesting (1) the role of venous stasis and hyperemia[49, 50] and the role of diminished blood supply,[14] (2) the capacity of cancer cells to function directly as osteogenic cells,[34] (3) the direct conversion of stromal fibrous connective-tissue cells into functional osteoblasts,[24, 40] (4) the role of necrotic bone acting as a foreign body,[4] and (5) the role of acid phosphatase or other "diffusible chemical substances"[2, 5, 25] from tumor cells as the factors responsible for bone production in metastatic cancers in the skeleton, very little evidence, even of a histological nature, has been presented to substantiate these views. Such histological data as have been presented are indirect and circumstantial; essentially nothing has been recorded from a physiological point of view.

In this series, histological evidence of hyperemia and venous stasis appeared to be of little import with respect to the over-all appearance in cases showing a predominance of bone pro-

duction over bone destruction. No evidence at all was found to substantiate the hypothesis that cancer cells can act as osteogenic cells. There was some evidence to suggest the direct conversion of connective-tissue cells into functional bone-forming cells, but, qualitatively, such conversion occurred mainly about the periphery of the lesions and, quantitatively, could hardly have accounted for the total extent of new bone formation. Bone necrosis per se did not appear to play any significant role as a stimulant to bone production. On the contrary, bone necrosis was more pronounced in the bone destroying than in the bone producing lesions. This could not have been expected were the bone necrosis itself the responsible stimulant to new bone formation.

Much has been said about the role of acid phosphatase in forming the typically "osteoblastic" metastases noted in metastatic carcinomas of the prostate gland. There is no evidence that abnormally elevated levels of serum acid phosphatase and the productive bone lesions considered characteristic of metastatic carcinoma of the prostate are necessarily quantitatively and directly related. Since, as a matter of clinical experience, the relationship between growth of prostatic tumor and serum acid phosphatase appears to be of a direct nature, the relationship between bone repair and serum–acid-phosphatase levels would appear, a priori, to be of an indirect nature. It is generally accepted that a decrease in the acid phosphatase in the serum, and therefore in the extracellular fluid compartment, is indicative of regression of tumor. It can hardly be expected, therefore, that bone that is in equilibrium with the extracellular-fluid compartment would behave differently from other tissues in the body that also are in equilibrium with the extracellular-fluid compartment. Thus, if acid phosphatase plays any role, which is as yet not established, in bone metastases from prostatic cancers, it would appear to be that of restraining rather than of stimulating bone growth.

In this connection, it is important to note that four patients with bone metastases from carcinoma of the prostate have been observed in whom the roentgenographic appearance of the involved bone was initially that of a typical "osteolytic" lesion. All had elevated levels of serum acid phosphatase and a concomitant increase of radio-opacity in the skeletal lesions. The fact that in these patients there appeared to be a decrease in tumor growth, as indicated by serum–acid-phosphatase levels, during precisely the same periods when there was increased bone repair, as indicated by the roentgenographic appearance of the involved bones and the levels of serum alkaline phosphatase, suggests that acid phosphatase probably is not the responsible stimulus of bone production in metastatic cancer of the prostate.

In metastatic cancers from tissues other than the prostate gland, in which acid phosphatase does not enter into question, it is evident that factors other than the presence of this enzyme must be considered to explain bone production.

Reaction Rates and Bone Density. Contrary to the common belief that increased radio-opacity indicates activity in carcinoma of the prostate, it is significant to note that, in other tumors that metastasize to bones, the consensus is that progressive radio-opacity of the metastatic bone lesions represents healing of bone and, consequently, diminished growth of the tumor.

Histologically, however, the appearance of bone response in all metastatic cancers is qualitatively identical in every respect. Clinical measures directed to decrease the rate of growth of both breast and prostate cancers are associated with objective decrements in the clinical criteria of growth rate in both. Pearson and others (vide supra) have presented considerable evidence to indicate that calcium-balance studies provide a prompt and sensitive indirect index of the rate of tumor growth in patients with "osteolytic" cancer metastases. In patients with progressive and rapid bone destruction resulting from cancer invasion, there is almost always a markedly negative calcium balance, hypercalcuria, and, in some instances, hypercalcemia. If the rate of tumor growth is rapid, all of these parameters are proportionately increased. When tumor growth is relatively slow or when therapeutic measures have effected a regression in growth, the patients characteristically show a decline toward normal values in all of these indexes. All of these studies and the clinical data obtained in the present study tend to confirm the belief that the effect of therapy, at least in the endocrine-system tumors and presumably in all others as well, is to alter their rate of growth. Since in all other respects the bone response is identical, it seems valid to suggest that the roentgenographic appearance represents the result of bone destruction and bone production. In this sense, roentgenographic

opacity, characteristic of the "osteoblastic" lesion, represents a preponderance of bone production over and above bone destruction, while the radiolucent areas of "osetolytic" lesion are indicative of precisely the opposite.

As a general principle, increase in bone density and, consequently, in roentgenographic opacity can arise from varying proportions in the degree of bone repair and bone destruction. Of all the possible combinations only two are critical: when (1) the rate of bone production is greater than that of bone destruction and the density of new bone is either equal to or somewhat less than the old, or (2) the rate of destruction is less than or even equal to that of bone production and the density of new bone is greater than that of old bone. In a theoretical, purely physical sense, it follows that a roentgenographically "osteoblastic" lesion (i.e., one with a bone density greater than that of established bone) could be interpreted as "progression of disease," only in the event that newly formed bone is of greater density than that of established bone. All experimental evidence is strongly against this view, since in various multidisciplined studies new bone appears to be considerably less dense than established bone.[41]

The conclusion seems inescapable, therefore, that progressive radio-opacity of cancer metastases in bone represents increased new bone formation (i.e., bone repair) and that its interpretation as progression of disease (i.e., increased bone destruction) is erroneous.

SUMMARY AND CONCLUSIONS

Seven hundred and eighty-three microscopic sections of bone metastases obtained at autopsy from 241 different patients have been examined in an attempt to delineate the various histological features of cancer metastases in bone. Based upon these findings, the following concept of metastatic cancer in bone is offered:

1. Bone metastases are blood-borne in origin.

2. When once established in a bone, further spread of the metastasis occurs at first along the preformed anatomical channels within the bone (the medullary cavity, and the Volkmann and haversian canals) and after, and frequently concomitant with, this intraosseous permeation by tumor takes place.

3. The process of bone destruction results either from (1) the direct mechanical pressure exerted by the tumor cells and/or (2) from a physicochemical process at the bone surface promoted by the tumor cell in destroying the normally continuous layer of cells covering and lining the surfaces of the bone crystals.

4. Bone production is an attempt on the part of the host bone to repair the injury represented by cancer invasion; there is no evidence to suggest that any abnormal substance is responsible for this aspect of repair phenomena.

5. There is no essential histological difference, insofar as the host bone is concerned, between so-called "osteolytic" and so-called "osteoblastic" cancer metastases; the histological appearance in both is distinct only in a quantitative sense. Qualitatively, the histological appearances of predominantly destructive and predominantly productive cancer metastases are identical. Differences in bone response to the invasion of the various types of neoplasms are merely differences in degree and not differences in kind.

6. The histological details in any given cancer metastasis in bone can be accounted for mechanically on the basis of the amount of new bone formed as a "stromal response" to the invasion of the cancer into the bone.

7. The histological grade of the bone response (grade 0-grade 4, defined in text) is a morphological representation of the resultant of two biological-rate phenomena: the rate of bone destruction and the rate of bone repair.

8. The result of an increased rate of tumor growth and, consequently, an increased rate of bone destruction is roentgenographically represented as an "osteolytic" lesion.

9. An increased rate of bone repair such that the rate of repair is greater than the rate of destruction results in the production of a lesion that appears roentgenographically "blastic."

10. Progressive roentgenographic opacity of a cancer metastasis in bone is indicative of bone repair, irrespective of the site of origin of the original neoplasm; "osteoblastic" metastases from carcinoma of the prostate gland and roentgenographically osteoblastic metastases from any other site of origin represent instances of bone repair and not of "progression of disease."

11. The age and endocrine status of the patient are relevant only insofar as the rate of growth of the tumor is concerned. In patients with neoplasms known to be affected by endocrine therapy, the histological grade of bone response in general can be directly correlated with the antemortem clinical findings.

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