

THE PROGNOSTIC AND THERAPEUTIC SIGNIFICANCE OF SKELETAL METASTASES IN CARCINOMA OF THE BREAST*

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THE operative procedures for carcinoma of the breast as elaborated by Willy Meyer and Halsted in the United States, Rotter in Germany, and Handley in England, increased considerably the chances for a radical cure of the disease. Indeed, in its early stages, according to the statistics of Halsted, fully 85 per cent. of the cases remain well for the period of three years after the operation. Nevertheless, even to-day the ultimate results obtained with the most radical methods of surgical treatment of carcinoma of the breast are far from being satisfactory. The reason for this lies in the difficulty in having the patients submit to the operation in the early stages of the disease.

It is impossible to form a perfectly correct estimate of the true therapeutic value of the radical amputation of the breast for carcinoma, since in the majority of the publications the authors do not state the percentage of cases which were considered entirely inoperable and therefore were not submitted to any surgical treatment. It is self-evident on the other hand, that the differences in the conceptions of the operability of the cases influence to a great extent the postoperative results. Nevertheless a fairly accurate idea of the results may be formed from an analysis of the recent publications. In the years 1907-1908 there appeared a number of publications with reports of a decade of work with Halsted's and similar methods of radical operations for carcinoma of the breast. Chart I, taken from Halsted's¹ publication, may serve as an example of the results obtained.

CHART I

	Cases	Cured	Per cent.	Cured 3 years	Per cent.
Axilla and neck negative	60	45	75	51	85
Axilla positive, neck negative....	110	27	24.5	34	31
Axilla and neck positive.....	40	3	7.5	4	10
Total	210				

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Halsted reports in all on 293 cases. Eighteen cases could not be traced and 65 cases had only palliative operations. The remaining 210 cases are divided into 3 groups. The first group consists of early cases in which there is no involvement of the lymphatic glands. In the second group, there are placed the advanced cases with the involvement of the axillary glands, and in the third group the far advanced cases with the involvement of both the axillary and neck glands.

Of the 60 cases of the first group, 51 cases, or 85 per cent., remained well three years after the operation. It is remarkable to note in this connection that even the cases of the Johns Hopkins Hospital, notwithstanding the active educational propaganda carried out by Bloodgood, only 20 per cent. of all the cases reported were in the first group, or in the early stages of the disease. It is probable that were the cases in which even a palliative operation was refused added to the report, then the percentage of the early cases would have been even smaller.

CHART II

Group	Series	Number of cases operated	Number of cases cured	Per cent.
I	I	14	11	78.5
	II	7	6	84.7
II	I	68	20	29.4
	II	25	8	32
III	I	7	0	0
		5	0	0

Chart II presents a very interesting analysis of 200 cases operated upon by Steinthal.² He divided 126 cases which were followed up in 3 groups, similar to those described by Halsted. Each group is again divided into 2 series. The first series of cases were operated by the old methods, and the second series by the modern radical methods. The analysis of his material shows that while in the first group, or the early cases, the radical operation produced better results than the old operations, the difference in the results in the advanced cases is not so marked. In the third group no advantage was obtained from the radical operation, either by Steinthal or Halsted, though the latter reports that 10 per cent. were cured, while all the cases of Steinthal in this group died, notwithstanding the operation. Thus the more advanced the disease, the smaller is the probability of obtaining permanent results, even from the most radical surgical treatment. In his latest publication Steinthal expresses the opinion that the increase in the percentage of cured cases is not due to the improvement in the operative technic, but to the earlier recognition of the disease.

The limitations of the surgical treatment of carcinoma of the breast are due to the following reasons: R. R. Greenough, C. C. Simmons and J. D. Barney³ have shown that 52 per cent. of the cases in which the operation fails do not show any local recurrence in the operative field, but only metastases in distant regions. In these cases the removal of the local growth was complete, and the metastases were either formed before the operation, or else a tumor embolus was carried away from the primary tumor in the course of the operation. In either event the extent of the operation could not influence the final result. Thus it is self-evident that in the advanced cases which represent three-quarters of all cases submitted to the operation, the probability of the existence of a metastasis before the operation, and of a consequent failure of even an ideal operative method, is great.

Handley⁴ attempts to prove that embolism has no significance in the formation of metastasis of carcinoma of the breast. According to his conception, metastasis is formed by a process of "lymphatic permeation." The tumor cells grow along the lymphatic vessels until they reach the nearest lymph-glands, and from these glands the cells enter the next lymphatic vessel. This process is continuous, and the appearance of an apparently isolated tumor nodule is due to the fact that a perilymphatic fibrosis destroys the permeated lymphatic vessels which form the lines of communication. The formation of metastases in distant organs Handley ascribes to the proliferation of cancer cells which escape from the subserous lymphatic plexuses into the serous cavities, pleura, or peritoneum. The cells are then distributed through these cavities under the influence of gravity and of visceral movements and implanted on the serous surface of the viscera. As a proof of this contention he cites the fact that parts of the skeleton distal to the elbow and knee-joints usually escape cancerous invasion. Now, in the first place Case VII shows skeletal metastases distal to the elbow (Fig. 9). Moreover, it is impossible to conceive even on the basis of Handley's theory how a distant metastasis without a local recurrence after an operation occurs, unless the transport of the cancer took place before or during the operation.

CHART III

Years after operation patients are alive	Number of cases	Per cent.
4	123	43.20
8	48	16.9
10	35	12.32
15	23	8.1
20	7	2.46
	328	

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Similar conclusions must be drawn from the analysis of Chart III obtained from the report of a French surgeon, Heurtaux.⁵ He operated during the 30 years previous to the date of his report on 341 cases. The operation consisted in the removal of the breast and the axillary lymphatic glands without the disturbance of the pectoral muscles. Though his operation is not as thoroughly radical as Halsted's, 43.3 per cent. of the 284 cases which could be traced remained well 4 years after the operation. This remarkable result may be partly due to a special selection of cases for the operation, but what makes the investigation of Heurtaux of the greatest value is the fact that he watched and controlled his patients for 30 years. He was thus enabled to estimate the ultimate results at long intervals after the operation, and as Chart III shows twenty years after the operation only 2.46 per cent. of the cases remained alive and free from the disease. While there are many reports in the literature of isolated cases of late recurrence of carcinoma of the breast, Heurtaux is the only investigator who showed the remarkable frequency with which these late recurrences take place.

Thus the analysis of the cases of Steinthal and Heurtaux demonstrate clearly two facts in relation to the true value of the radical amputation of the breast for carcinoma. In the first place in advanced cases, the result of the radical operation is not better than the results of simpler surgical procedures, furthermore in the greater part of the cases which are apparently cured 3, 4 and 5 years after the operation, the disease recurs at a later date. This latter phenomenon is due in over half of the cases, not to a local recurrence of the disease, but to metastases in distant regions.

Now, carcinoma of the breast metastasizes most frequently in the lungs, bones and the liver. The involvement of the latter organ is probably due in accordance with the theory of Handley to a lymphatic permeation, *i.e.*, a local outgrowth from a neighboring region. Metastasis in the liver occurs usually late in the course of the disease and is secondary to an extensive local recurrence and metastases in the lungs or bones. The formation of metastases in the latter organs is undoubtedly due, as the writer stated in several publications,⁶ to an embolic transport of cancer tissue before or during an operation and may take place without a local recurrence. The development and the course of metastases in the lungs is usually quite rapid and is accompanied by early clinical symptoms indicative of the condition. The metastases in the bone are apparently the most frequent cause of the late recurrence in carcinoma of the breast. The condition may con-

tinue for a long time without causing any symptoms, and when at an autopsy metastases are found, both in the bones and in many other organs, it is highly probable that the latter appeared subsequently to the formation of the skeletal metastases. The fact that E. Kaufman⁷ found skeletal metastases in the bones in 52.3 per cent. of the cases that died of carcinoma of the breast is a true indication of the frequency of the condition.

PRE-OPERATIVE DIAGNOSIS OF SKELETAL METASTASES

A radical operation for carcinoma implies an attempt at complete eradication of all cancer tissue within the organism. While a radical amputation of the breast is not accompanied by a high postoperative mortality, it is nevertheless a severe operative procedure. It is usually followed by a prolonged after-treatment, and frequently by disability, pain and swelling of the arm. Moreover, the thorough clearing out of the axilla may be followed by a dissemination of cancer tissue into distant organs and subsequent formation of metastases. In view of all this, it is imperative to ascertain before the operation whether there are any metastases present in any distant region of the organism of the patient.

Metastases in the lungs and in the liver as a rule produce clinical symptoms and are easy to recognize. Skeletal metastases, on the other hand, as stated above, may continue for a long time without causing any symptoms whatever. The frequent reports of pathological fracture occurring in patients who apparently enjoyed previously perfect health, and in whom only the accident revealed the presence of carcinoma, bear out this assertion.

The mechanism of the development and growth of skeletal metastases, as will be shown later, shows the reason for the late development of the clinical symptoms, but in any event, it is certain that a case of carcinoma of the breast with the involvement even only of the axillary glands may harbor metastases in the bones which do not manifest themselves in any way. The only method by the aid of which many of such metastases may be detected is the röntgenographic examination of the skeleton.

The röntgenogram usually reveals a central focus of bone destruction which is evidently replaced by carcinoma tissue. It must be admitted that a negative finding is not conclusive, since the tumor nodule in the bone may be too small and has not destroyed as yet a sufficient amount of the bone tissue to present a shadow on the plate, but a positive result makes the diagnosis of the condition certain. In

view of the importance of the subject it is remarkable how little attention is being paid to this method of diagnosis of skeletal metastasis.

As stated above metastases, usually in the bones, may be present at the time of the operation in 52 per cent. of the advanced cases of carcinoma of the breast, even with involvement only of the axillary glands. It is therefore imperative that in every advanced case, or better still, in every case of carcinoma of the breast, a röntgenographic examination be made of the skeleton before the operation. If it is too expensive or difficult to explore the whole skeleton, then those parts should be examined in which metastases most frequently occur, namely the spine and the femurs.

REPORT OF CASES

At the service of the writer in the Montefiore Hospital, the röntgenographic examination of the skeleton of all cases of carcinoma of the breast is a routine procedure. During the past three years the writer observed 10 cases of carcinoma of the breast complicated by skeletal metastases. The clinical, röntgenographic and pathological study of these cases presented several points of interest in connection with the questions of prognosis and therapy of carcinoma of the breast. The following is a brief résumé of the clinical histories of the cases:

CASE I.—Mrs. B., aged thirty-nine, an advanced carcinoma of the right breast with involvement of the axillary and the supra-clavicular glands. A radical amputation of the breast was done on November 17, 1913. Pain in the hip-joints developed two months after the operation; six months after the operation the patient became bedridden, developed perfect clinical evidence of metastases in both femurs, and died nine months after the operation. No autopsy could be obtained.

CASE II.—Mrs. G., aged forty-three, was admitted to the Montefiore Hospital on December 3, 1913. Two years previous to the admission to the hospital the patient underwent a radical amputation of the right breast for carcinoma. The patient died on December 31, 1913. Autopsy showed metastases of carcinoma in the viscera and in the sternum. The latter served for pathological study.

CASE III.—Mrs. B. H., aged forty-one, admitted to the Montefiore Hospital on January 21, 1914, with an inoperable carcinoma of the right breast, painful spine and inability to walk. Clinical and Röntgen examination showed metastases in the eighth, ninth and tenth ribs, and in both femurs; the patient died on May 20, 1914. Autopsy showed carcinoma of the breast and metastases in the axillary lymph-glands, pleura, both trochanters and the

eighth, ninth and tenth ribs. A microscopic study was done of the ribs and trochanters.

CASE IV.—Mrs. T. S., aged thirty-nine, admitted to the hospital May 14, 1914, with a recurrence of a carcinoma of the right breast which was amputated about six months previously. Clinical and röntgenographic examinations revealed metastases in the right femur. Patient died June 17, 1915. Autopsy showed medullary carcinoma of the breast, metastases in the axillary, cervical, mediastinal, bronchial and retroperitoneal lymph-glands and in the head of the right femur. The metastasis in the femur served for pathological study.

CASE V.—Miss R. S., aged forty-two. A radical amputation of the right breast was done in August, 1915, for carcinoma with involvement of axillary and supraclavicular lymph-glands. Four months later there developed a kyphosis, a swelling at the regions of both trochanters and inability to walk; two months later the patient began to complain of severe headaches, became delirious, then developed a right hemiplegia which was followed by death two days later. No autopsy could be obtained, but there was undoubted clinical evidence of metastasis in the spine.

CASE VI.—Mrs. R. E., aged fifty-six. A radical amputation of the left breast for carcinoma was done in the Brooklyn Jewish Hospital in August, 1913. Three weeks after the operation there set a pain in the right thigh, later the left thigh became involved. The patient was admitted to the Montefiore Home and Hospital on November 10, 1914. One month after admission she sustained a fracture of the right femur. The patient died on January 1, 1916. Autopsy showed metastases in the liver, ribs and both femurs. This case showed a very slow progress of the skeletal metastases; pain in the thighs developed three weeks after the operation, consequently the metastases were already present during the operation, since the cancer nodule in the bone must obtain a certain size before the pains appear and still the patient lived two and a half years after the operation.

The analysis of the röntgenograms gives very interesting indications of the pathological development of the process, the plates taken immediately after the fracture occurred show the fracture in the right femur (Fig. 1) and destruction of bone, *i.e.*, tumor masses further down the shaft (Fig. 2), and reveal nothing abnormal in the left femur (Fig. 3); röntgenograms taken ten months later show in the right femur (Fig. 4) bridges of newly-formed bone in the area of the old fracture. Indeed the latter appears to be firmly healed, a fact which was noted clinically. Below the old fracture there has taken place a new fracture. The left femur (Fig. 5) shows now distinct areas of metastases. It is



FIG. 1.—Case VI. Röntgenogram of the neck of the right femur. The arrows show the line of fracture.

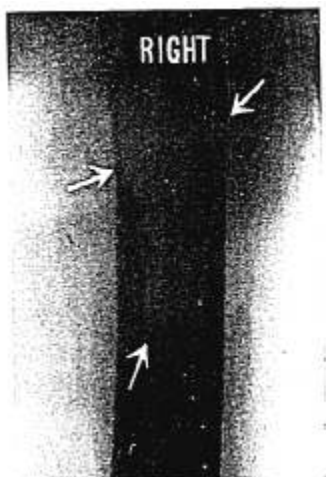


FIG. 2.—Case VI. Röntgenogram of the shaft of the right femur. The arrows show the metastatic tumors.



FIG. 3.—Case VI. Röntgenogram of the neck of the left femur. It shows no abnormality.



FIG. 4.—Case VI. Röntgenogram of the neck of the right femur, taken ten months later. Shows double fracture.



FIG. 5.—Case VI. Röntgenogram of the neck of the left femur, taken ten months later. The arrows show the light spots of bone absorption—metastases.



FIG. 6.—Case VI. Sawed open surface of the left femur. Shows metastases and hemorrhages.



FIG. 7.—Case VII. Röntgenogram of femur and pelvic bones. Shows irregular bone destruction.

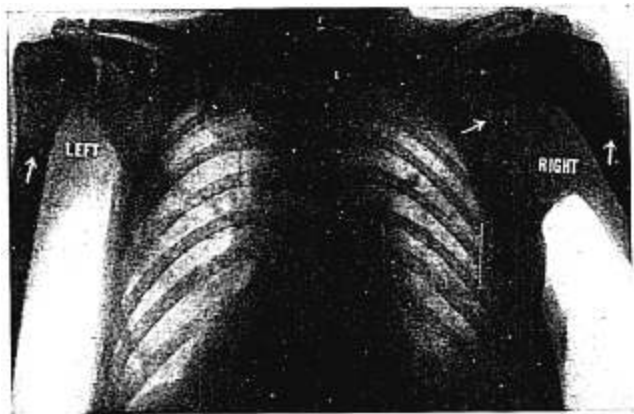


FIG. 8.—Case VII. Röntgenogram of chest. Shows absorption of bone.



FIG. 9.—Case VII. Röntgenogram of humerus, radius and ulna. Shows extensive irregular bone destruction.

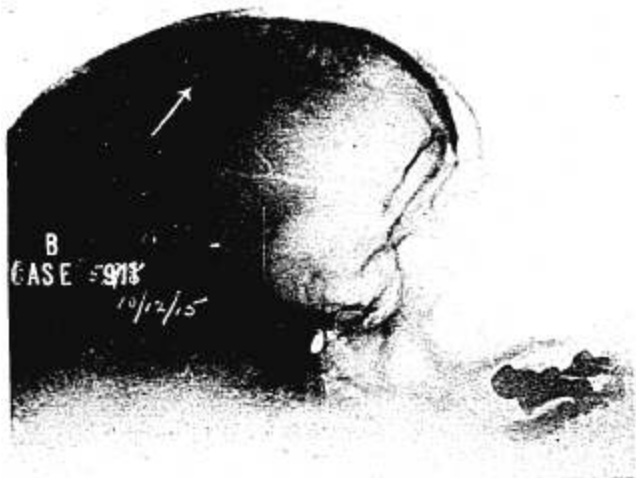


FIG. 10.—Case VII. Röntgenogram of skull. The arrow shows bone absorption.



FIG. 11.—Case VIII. Röntgenogram of spine. Shows absorption of bone of the eleventh and twelfth dorsal vertebrae.



FIG. 12.—Case VIII. Röntgenogram of the neck of femur. The arrow shows bone absorption in the upper portion of the neck.



FIG. 13.—Case IX. Röntgenogram of the left half of the chest. Shows destruction of bone in the left clavicle.



FIG. 14.—Case X. Röntgenogram of the spine. Shows bone destruction in the centre and new bone formation in the periphery (two bridges) in the contiguous portions of the second and third lumbar vertebrae.



FIG. 15.—Case X. Röntgenogram of the spine taken one year later. Shows some increase in the new bone formation.

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very striking that the sawed open surface of the left femur (Fig. 6) shows the metastases practically in the same positions as on the röntgenogram.

CASE VII.—Mrs. A. B., aged forty-five, previous illness began a year ago with pain in the left hand, radiating down from the shoulder. She consulted a physician who called her attention to little lumps in the left breast: she went to Mt. Sinai Hospital where her left breast was amputated; after leaving the hospital the patient experienced great pains in various regions of the body, chest, legs, back, etc. The pain grew gradually worse, until six months later she went to Gouverneur Hospital, where she stayed fourteen days. The patient became gradually weaker, paler, and complained of headaches, pains in various regions of body, loss of weight and impairment of vision. On October 1, 1915, she was admitted to the Montefiore Home and Hospital. On admission röntgenograms of nearly the whole skeleton of the patient were taken with the following results:

Hips: Marked irregular bone destruction of the upper part of both femurs and the pelvic bones (Fig. 7).

Shoulders: Advanced irregular bone absorption of all the bones entering into the formation of the shoulder-joints.

Ribs: The posterior parts of almost all the ribs, especially on the left side, show a great number of spots of bone destruction. Fig. 8 shows the condition of both shoulders and the ribs and Fig. 9 the same in radius and ulna.

Skull: All the bones of the skull show a great amount of irregular bone destruction of both tabulæ (Fig. 10).

All the abnormalities in the skeleton stated above were due to multiple metastases of carcinoma in the bones.

December 30, 1915: The palpation of the skull shows a protuberance over the left temporal region, consisting of a soft diffuse mass, about 2 inches in diameter (a massive bone metastasis).

Palpation of the left side of the chest wall is painful. Second, third and fourth ribs feel rough and nodular. The left knee-joint is swollen and painful; an enlargement is apparent at the head of the tibia.

January 13, 1916: A swelling has developed in the middle of the right clavicle, which is soft on palpation, and indicates a complete destruction of the bone in this section of the metastatic area.

January 19, 1916: Patient's speech is not clear, slow and confused; complains more of pain than heretofore, and in addition to the already found swellings, she developed a swelling over the right Poupert's ligament which is soft, doughy and easily compressible, but not tender.

January 22, 1916: Patient was unconscious for the last two days; the patient died on January 22, 1916. An autopsy could not be obtained, but the clinical history, which was given here at greater detail than in the other cases, as well as the röntgenograms prove conclusively the presence of an extensive skeletal carcinoma. The case presents the most extensive involvement of the skeleton of any described in the literature and shows that skeletal metastases may develop below the elbow. This last fact is important since, as stated above, Handley bases his pathological conception and operative technic to a great extent on the fact that skeletal metastasis in carcinoma of the breast does not develop below the elbow or knee-joint.

CASE VIII.—Mrs. R. R., aged forty-three, admitted to the Montefiore Home and Hospital January 16, 1916. Present illness began May, 1915, when the patient noticed a very small lump, the size of an orange seed, underneath the skin of the left breast. In August the breast was amputated at Beth Israel Hospital. In October the patient began to complain of pain in lower extremities and back.

A röntgenogram taken on January 20, 1916, showed great absorption of bone of the eleventh and twelfth dorsal vertebræ (Fig. 11). The entire lumbar spine had a worm-eaten appearance: the upper portion of the neck of the right femur (Fig. 12) shows multiple areas of bone absorption. Patient died on February 13, 1916. The autopsy performed by Dr. B. S. Kline showed carcinoma of breast with recurrence in wound following removal. Metastases to the regional lymph-glands, liver, pancreas, lung, right femur and in the eleventh and twelfth dorsal vertebræ. The metastases in the bones were studied microscopically.

CASE IX.—Mrs. B., aged fifty-four. The patient underwent a radical amputation of the left breast for carcinoma in 1911. In the summer of 1914 there developed a swelling measuring 2 inches long, $\frac{3}{4}$ inch wide, and 1 inch high, adherent to the left clavicle. The röntgenogram (Fig. 13) shows partial destruction of the bone and consequently a metastasis in the left clavicle. The case was referred to the writer (by Dr. Bodenheimer) in August, 1914. Under a combined radium and Röntgen treatment the swelling disappeared. The case was reported in September, 1915.⁸ Now nearly two and a half years after beginning of the treatment, the patient is clinically well and does not show any recurrence of carcinoma anywhere.

CASE X.—Mrs. D. L., aged forty. The patient had a radical operation of the right breast for carcinoma done in May, 1915. On leaving the hospital the patient felt perfectly well for two

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weeks, when she began to experience pain for the first time. This pain was situated in the region of the lower lumbar vertebræ, the patient claiming that the pain was similar to that felt during child-birth. The above has persisted ever since. With the onset of pain there developed loss of weight and general weakness. The pain was very severe and the patient has been confined to bed. The patient was admitted to the Montefiore Home and Hospital on November 10, 1915. A röntgenogram of the spine taken on admission (Fig. 14) showed a slight destruction of the contiguous portions of the second and third lumbar vertebræ with some bone condensation and very marked new bone formation in form of bridge formation on both sides.

The patient received Röntgen treatment both over the chest and the region of the second and third lumbar vertebræ. At present, one year after admission, the patient left the hospital greatly improved, able to walk around and work. A later röntgenogram (Fig. 15) shows apparently some increase in the bone formation in the region of the second and third vertebræ.

CLINICAL AND PATHOLOGICAL CONSIDERATIONS

The clinical and röntgenologic study of the cases shows that the skeletal metastases undoubtedly were present in all of them at the time of the operation. Pain in the different parts of the skeleton either appeared before or very soon after the operation. The röntgenograms taken upon the admission to the hospital showed usually an extensive involvement of the bone, and the identical condition was found at the autopsy. All this shows that the metastases were of long standing. Statistical investigations as stated above indicate that skeletal metastases of carcinoma may be very slow in their development. It may take years before clinical manifestations of any kind present themselves. The pathological studies of the writer bear out and elucidate the reasons for this phenomenon.

The metastasis of carcinoma in the bone begins its development within the marrow, and when the group of cancer cells are small, the surrounding bone-marrow appears quite normal. Figs. 16 and 17 present microphotographs of two such small cancer nodules within a bone-marrow space. Von Recklinghausen claims that the development of the metastasis is preceded by a hyperæmia and hæmostasis due to the obstruction of the capillaries by endovascular tumor emboli. In the specimens studied by the writer hemorrhages and hyperæmia were noted frequently around large tumor masses, in the femur, for instance (Fig. 6), but not around minute metastatic nodules. In

the latter instances as stated above no morphological abnormality could be found in the bone-marrow.

As the tumor nodule increases in size it approaches and invades the compact osseous tissue or the compact osseous partitions of the cancellated bone, and then there begin to appear the characteristic changes in the bone tissue. It is generally accepted that there are two classes of skeletal metastases of carcinoma: *osteoplastic*, in which there takes place a great deal of new bone formation around the metastatic tumor, and *osteomalacic*, in which the change of the normal tissue surrounding the metastasis consists in extensive destruction of the compact bone. These two distinct conditions can be easily differentiated on the gross inspection of skeletal metastases. However, the microscopic study of the cases of the present investigation by the writer has shown that both conditions are usually present side by side, and only in one case *osteosclerosis*, or new bone formation, predominates, while in another *osteoporosis*, or the destruction of the old bone, is mainly evident. Figs. 18 and 19 show an extensive new bone formation, while Fig. 19 presents only destruction of the old bone, and both specimens were obtained from different regions of the same metastatic tumor.

The mechanism of the bone destruction in metastases of carcinoma differs from the one observed in inflammatory osteoporosis. Von Recklinghausen⁹ first made the observation that the large polynuclear osteoclasts which destroy the bone in osteoporosis are very seldom found in the lacunæ of the bone surrounding a growing metastasis of carcinoma. This fact was confirmed by most of the subsequent investigators. In view of the absence of the large osteoclasts, Von Recklinghausen presumed that there takes place in the bone a softening by the removal of the inorganic salts, and a subsequent absorption without the aid of any cells; a condition similar to the one found in osteomalacia. Apolant,¹⁰ Erbslöh,¹¹ Askanazy,¹² are also of the opinion that osteoporosis in skeletal carcinoma may take place without the aid of special cells. On the other hand, Wolff¹³ and Goetsch¹⁴ believe the cancer cells act as osteoclasts and destroy the compact bone, and Axhausen¹⁵ maintains that the small elongated mononuclear connective-tissue cells, frequently found close to the walls of the lacunæ, are special osteoclasts derived from the cancer stroma. In the specimens studied by the writer both carcinoma cells, as well as the small connective-tissue stroma cells, are found in close immediate apposition to the walls of the lacunæ. The carcinoma cells were so frequently the only cellular elements within the lacunæ of the bone that there

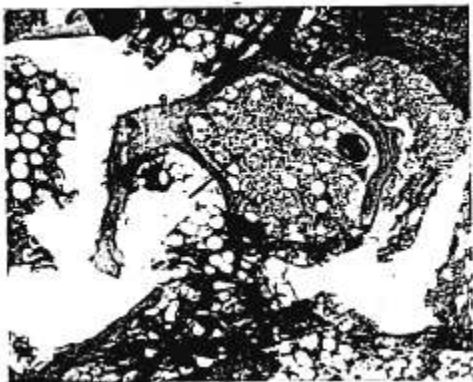


FIG. 16.—Microphotograph of a bone-marrow space. The arrow shows a small island of cancer cells. (Low magnification.)

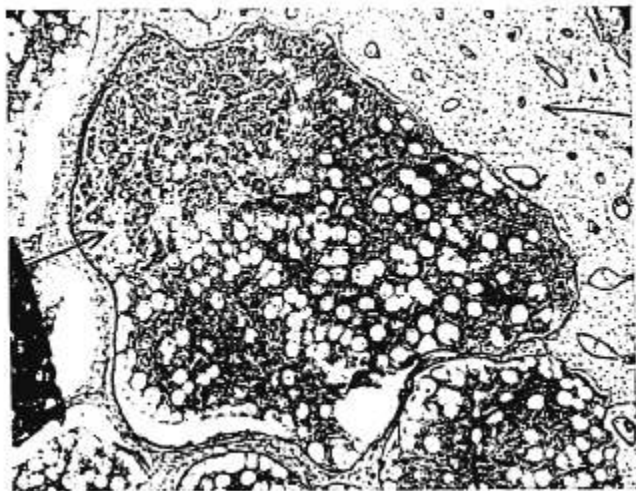


FIG. 17.—Microphotograph of a bone-marrow space with a small nodule of carcinoma (larger than in Fig. 16). The arrow *a* shows the carcinoma. The arrow *b* shows compact bone. (Low magnification.)

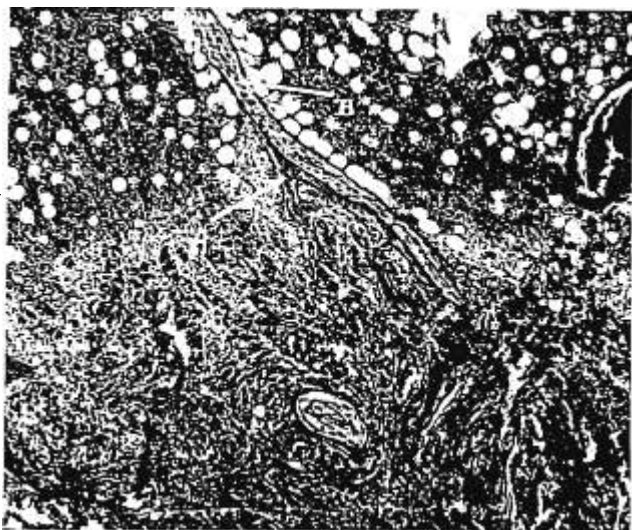


FIG. 18.—Microphotograph shows a great deal of new bone formation in the vicinity of an old bridge of compact bone tissue. *B* shows old bone; *A*, new bone.



FIG. 19.—From a microscopic section of a skeletal metastasis stained with Van Gieson. Shows collagen fibrils emerging from the old bone and uniting with other fibrils.



FIG. 20.—Microphotograph, two bone lacunæ filled with carcinoma cells. A, shows bone; B, carcinoma. (Low magnification.)



FIG. 21.—Röntgenogram of case of sarcoma of mandible taken before treatment. Shows tumor with two radium tubes *in situ*.



FIG. 22.—Röntgenogram of case of sarcoma of mandible taken after treatment. The arrows show the new bone formation.

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cannot be any doubt that carcinoma cells act as direct osteoclasts. Fig. 20 shows lacunæ filled with carcinoma cells. The impression gained by the writer is that the small stroma cells only subsequently enter between the bone and the carcinoma cells. But even if the possibility be admitted that occasionally the stroma cells may act as osteoclasts, it seems quite apparent that the tumor itself, by the aid of its formed elements, first destroys the bone and then grows by occupying the produced space.

While the mechanism of osteoporosis in skeletal metastasis as stated above is at least similar to the mechanism of the destruction of any normal tissue surrounding a growing malignant tumor, the osteosclerosis, or the extensive formation of new bone tissue, is characteristic of skeletal metastases.

Von Recklinghausen claims that this extensive new bone formation is due to the hyperæmia described by him and mentioned above. Courvoisier¹⁶ and Kaufman⁷ maintain that a metastasis in the bone is always surrounded by a zone of inflammation, and this latter caused the osteosclerosis. Askanazy¹² thinks that the metastasis at first produces an osteoporosis, which is followed by a bone necrosis, and the necrotic bone acting as a foreign body caused a new bone formation. Wolf,¹³ Courvoisier,¹⁶ and Kaufman,⁷ are of the opinion that carcinoma cells may act as osteoclasts and form new bone tissue. Fig. 19 presents a picture very frequently observed by the writer. It shows collagen fibrils developing in abundance from the old bone. These fibrils gradually unite in thick bundles and subsequently form new bone tissue. The latter is clearly formed from the constituent parts of the old bone tissue. On the other hand, as stated above, the writer did not observe any hyperæmia, inflammation or any other abnormality of the bone-marrow at the beginning of the development of the metastases. Neither did the writer find any necrosis of the bone in any of the specimens examined. It must be concluded in agreement with Axhausen's¹⁵ conception that some unknown chemical irritant emanating from the carcinoma cells acts on the old bone tissue and stimulates its proliferation.

Thus there constantly and side by side take place in skeletal metastasis two processes. On one hand the tumor cells destroy the normal bone tissue and occupy its place, and on the other hand the remaining bone tissue proliferates and creates new bone. The latter is quite probably an attempt at self-defense on the part of the organism. The newly-formed bone tissue may compress and destroy the cancer cells, or at least inhibit their proliferation. Case VI shows such a condition. There took place a pathological fracture in the right femur, which

subsequently became firm and seemed clinically healed (Fig. 4), while later a second fracture took place below the first. Here apparently nature succeeded in healing one metastatic focus in the bone, while in another place the tumor grew unchecked. Such temporary healing of a pathological fracture within a skeletal metastasis was described in several instances.

Thus the microscopic study of skeletal metastasis gives a clear evidence of the interaction which always takes place between the normal organ tissue and the cancer cells in the beginning of the development of a metastatic tumor from a transported cancer embolus. Upon the result of such an interaction depends the success or failure of the formation of metastasis. In the bone the conditions are evidently more favorable for at least temporary suppression of the proliferation of the cancer cells by the newly-forming bone tissue, and therefore skeletal metastases develop only slowly and appear late.

THE PROGNOSTIC SIGNIFICANCE OF SKELETAL METASTASES

The radical operation for a malignant tumor means a complete eradication of all tumor tissue from the organism. It is patent that a radical operation in this sense of the word is impossible as long as a skeletal metastasis was diagnosed before the operation. Furthermore, Heurtaux has shown that ten years after a breast amputation only 12.32 per cent. remain free of the disease and twenty years after the operation only 2.46 per cent. remain free. It would then seem that in the overwhelming majority of all the cases of carcinoma of the breast the best surgical methods of treatment do not completely eradicate the disease, but only prolong life. But on the basis of the latter interpretation of the therapeutic results in carcinoma of the breast skeletal metastases give a better prognosis than metastasis in other organs, since they are much slower in their development and may therefore be more readily controlled.

RADIUM AND RÖNTGENOTHERAPY OF SKELETAL METASTASES

As stated above, the radical amputation of the breast in the presence of skeletal metastases cannot cure completely the disease. On the other hand, the operation if correctly performed may prolong the life of the patient, since the removal of the primary tumor diminishes the possibility of subsequent formation of metastases in other organs than the bone. But the operation, while aiming at a complete as possible removal of the main mass of the tumor, does not need to be entirely radical. It is more important not to handle and massage the tumor too energetically during the operation and thereby transport cancer cells

into the circulation, than to remove every vestige of it. The writer⁸ has shown in a previous publication that small islands of tumor cells can be destroyed by radium and Röntgen rays, even at a great distance from the skin, and it should therefore be easy to eradicate by the aid of the radiations small remnants of the tumor located in the axilla, or over the chest wall. The diathermic coagulation of tissue which the writer¹⁷ discussed in previous publications, and which destroys the carcinoma cells *in situ* without opening the blood and lymph channels, may become the operative methods of choice for such incomplete operations when the correct technic is developed.

Thus the correct treatment of carcinoma of the breast, complicated with skeletal metastases, consists in the operative removal of the gross tumor mass, combined with radium and Röntgen therapy. The radiations in a postoperative case of carcinoma of the breast should not be given only over the operative field and over the chest wall, which is the procedure generally adopted to-day, but should include, if not the whole skeleton, at least the spine and the heads of both femurs. Moreover, this combination of surgery and radiotherapy should be the method of choice in all advanced cases of carcinoma of the breast, even when there is as yet no evidence of skeletal metastases.

The writer has shown¹⁸ that one of the important effects of radium and röntgenotherapy consists in the formation of an extensive connective-tissue stroma, surrounding and compressing the tumor cells. In skeletal metastases this stroma, as the pathological study reported above shows, is transformed into bone. It is thus self-evident *a priori* that the radiotherapy must enhance the results of the attempts at cure produced by nature.

In a case reported by the writer in 1915, though not a metastatic carcinoma, but a primary sarcoma of the bone (right mandible), new bone formed under the influence of radium and Röntgen therapy. Eight weeks after the beginning of the treatment, the tumor had completely disappeared, and instead there was present a large cavity lined by a shell of bone. Fig. 20 shows a röntgenogram taken immediately at the beginning of the treatment, with the radium tubes *in situ*. There is seen a nearly complete loss of bone around the tumor. Fig. 21, a röntgenogram taken after treatment, shows that the swelling is surrounded by a great deal of new-bone formation. The Cases IX and X of the present report clearly show that radium and röntgenotherapy may cure clinically skeletal metastases of carcinoma. Case IX is clinically well and shows no recurrence in other regions of the body for two and a half years.

Case X is now clinically well one year after admission to the hospital, while a year ago it presented the picture of a most hopeless condition, ever met even among cases of inoperable carcinoma. Though it cannot be stated as yet for how long the patient's life will be prolonged, the achievement in this case is certainly sufficient to encourage further attempts at the same method of treatment.

It would lead too far to go here into details of the technic of radiotherapy, but one point must be considered, the treatment must be continued at stated intervals for a long time, and if it is interrupted too soon, the metastatic tumor may become active again, destroy a large area of bone and then the subsequent radiations will be of no avail.

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