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OSTEOSCLEROTIC ANEMIA SECONDARY TO EPIDERMOID CARCINOMA *

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Anemia is so frequently associated with carcinoma that we accept it as a concomitant feature, rather than showing surprise at its appearance. This anemia, however, as emphasized by Harrington and Kennedy,¹ and others, is almost invariably of the secondary type. von Grawitz² in 1879 described three cases of "malignant osteomyelitis" in which the blood pictures simulated that of pernicious anemia. Since that time a number of cases, more or less similar, have been reported and MacCallum,³ in classifying the anemias, speaks of this unusual type due to destruction of the bone marrow by tumor growth as "osteosclerotic anemia." The following case is one of this type that recently came under our observation.

CASE REPORT

Clinical History. G. S., a farmer 52 years old, complaining of pain over both thighs, arms, shoulders, chest and neck, and a fracture of the right femur, was referred to the medical service of the University of California hospital on Oct. 28, 1922, by Dr. Seawell of Healdsburg.† The family history is negative, but his past history is of interest, in that at the age of 14, when firing a rifle the ejected shell struck him over the left malar bone causing some injury to the skin. At the age of 32 he again injured in some manner the skin in the same area. This was followed by a chronic ulceration which lasted until four years ago when he went to a local "Cancer Institute" for treatment. The condition was diagnosed rodent ulcer and treated with arsenic paste: it cleared up with no subsequent local recurrence.

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† For the clinical notes we are indebted to Dr. N. C. Moffitt, Dr. W. J. Kerr and their associates.

His present complaint apparently started about one year before entry, with a dull, aching, non-radiating pain in the right thigh which was worse at night. About one month later similar pains made their appearance across his chest, arms and shoulders, and became so severe that they prevented sleep. Six months later while walking down the road, and without any apparent cause, a spontaneous fracture of the right femur occurred. He was placed in a local hospital and a cast applied to the limb. However, during his five months' stay there, before entry to the University hospital, no union occurred in the fracture, the pains became progressively more intense and the patient noted that his right chest, especially the lower ribs, was gradually sinking in, causing considerable dyspnea.

Physical Examination: An emaciated man appearing older than the age stated, with a generalized brownish pigmentation of the skin. There were several non-tender nodules varying in size from a pea to a hazelnut scattered over the frontal bone, and a scar about the size of a half-dollar over the left malar region. Eyes, nose, and ears were negative except for slight impairment of hearing on the right side. The teeth showed some dental caries and pyorrhea, and there were a few pin-point hemorrhagic areas on the hard palate. There were no palpable glands in the neck. The chest presented a marked deformity on the right side with a funnel-shaped depression in the center (Fig. 1); dullness over the apex of the right lung, with increased vocal and tactile fremitus over the entire lung, and bronchovesicular breath sounds with moist râles at the base; dullness over the apex of the left lung, increased breath sounds and vocal and tactile fremitus over the whole lung and a friction rub over the base in the axillary line. The heart was negative, pulse rate 116, arteries normal, the blood pressure systolic 115 and diastolic 70. The abdomen showed a firm, smooth, slightly tender tumor mass with rather indistinct edges, occupying the left upper quadrant, extending down to the umbilicus and to the midline and moving with respiration. The liver dullness extended 4 cm. below the tip of the ensiform cartilage but the liver could not be felt below the lateral costal margin. Examination of the genitalia, rectum and prostate was negative. The extremities were emaciated, and the right thigh and leg which were splinted showed some slight edema. The reflexes were normal.

The laboratory findings, with the exception of the blood examination which is detailed in the chart below, were essentially negative. The blood Wassermann was negative and at no time was Bence-Jones albumose found in the urine.

Röntgenologic Examination: Numerous fractures of the ribs and transverse processes with many irregular areas of rarefaction in them and in the vertebral bodies. About two inches below the lesser trochanter of the right femur a T-shaped fracture was seen, with rounded ends and some callus formation. On the inner side of the right tibia, about the middle of the shaft, was another small irregular area of rarefaction (Figs. 2, 3 and 4).

On November 4, about 5 cm. of the right seventh rib was removed for diagnostic purposes. This was examined by Dr. E. I. Bartlett who reported that the weight of evidence was in favor of carcinoma, but felt that the microscopic picture was not conclusive.

During the following week the tissues in the region of the left mandible became inflamed, the second and third molars on that side loosened and were extracted. A small incision was made above the angle of the mandible and about 15 cc. of very foul pus evacuated, from which an anaerobic streptococcus was cultured.

TABLE I
Blood Values

Date	Red blood cells <i>per c. mm.</i>	Hemoglobin <i>per cent</i>	Color index	White blood cells <i>per c. mm.</i>	Differential <i>per cent</i>	Abnormalities
10-28-22	3,968,000	75 Sahli	.94	6,700	Polymorphonuclears 72	Slight poikilocytosis. Some central pallor. No nucleated reds. Reticulated reds 8 per cent.
11-7-22	2,816,000	50 Talquist	.88	4,200	Polymorphonuclears 70 Small Mononuclears 8 Large Mononuclears 22	Marked central pallor. Moderate anisocytosis and poikilocytosis. No nucleated reds.
11-16-22	2,592,000	50 Sahli	.96	6,400	Polymorphonuclears 70 Small Mononuclears 12 Large Mononuclears 6 Myelocytes 12	Marked central pallor. Moderate anisocytosis and poikilocytosis. One normoblast seen.
11-24-22	2,080,000	40 Talquist	.96	7,200	Polymorphonuclears 80 Small Mononuclears 8 Large Mononuclears 4 Myelocytes 8 Myelocytes 12	Moderate anisocytosis and poikilocytosis. Three normoblasts seen.
11-26-22	Blood smear only					Moderate poikilocytosis and anisocytosis. Embryonic cells of all types; giantoblasts, megaloblasts, normoblasts. Several nucleated reds with dividing nuclei, some pyknotic. Many megalocytes.

On November 17, thrombosis developed in the right femoral vein which resulted in a marked edema spreading up into the perineum and right buttock.

On November 23, a splenic puncture was made. The smear from this was chiefly blood cells resembling the picture of pernicious anemia, with marked poikilocytosis and anisocytosis of the red corpuscles, megalocytosis and many normoblasts and myelocytes. In addition there were many abnormal cells about the size of small lymphocytes, each with a heavily stained nucleus and a basophilic cytoplasm containing from seven to nine chromotoid bodies.

On November 26, the right superficial epigastric vein became greatly distended with the blood flow directed cephalad. The abdomen, especially the lower portion, felt doughy, and the findings suggested a block of the inferior vena cava.

During his month's stay in the hospital, the patient's condition became progressively worse; the brownish pigmentation of the skin deepened and, during the last three weeks of life, the tumor in the left upper quadrant gradually decreased in size to three-fourths of its size on entrance, resembled the consistence of tense muscle and presented a smooth sharp edge that could be definitely followed around from midline to flank. Later, this tumor mass was definitely diagnosed as spleen, but until this time hypernephroma, adrenal neurocytoma and plasma cell myeloma of the bones with splenic involvement and especially a primary tumor of the spleen had been considered.

The patient died at midnight November 29.

The necropsy, the positive findings of which are recorded below, was performed eleven hours later.

NECROPSY REPORT

A ventral incision shows pale, flabby musculature and a decrease of the fatty tissues which appears hyperchromatic.

Peritoneal Cavity: The liver edge extends 3 cm. below the ensiform cartilage, and the spleen which is covered over by omentum extends 6 cm. below the costal margin in the left midclavicular line. Distally from the third lumbar vertebra, the vena cava and bilaterally the common iliac veins with all their branches, including the hemorrhoidal and prostatic plexuses and the median sacral vein, are widely distended by a firm, dark red thrombus which has originated somewhere below the origin of the external iliac veins.

Thoracic Cavity: There are a few old fibrous pleural adhesions to the apex of the left lung, about 50 cc. of clear straw-colored fluid in the pericardial sac, and multiple fractures of the second to tenth ribs inclusive on the left side, and third to tenth on the right.

Heart: Weight 250 gm., shows moderate dilatation of the right auricle, an anatomically patent foramen ovale, fenestrations of all cusps of the aortic valve and of the median cusp of the pulmonary;

considerable atheromatous sclerosis about the base of the aorta, and cloudy swelling of the myocardium.

Right Lung: Crepitant throughout and has a smooth and glistening but slightly opaque pleura. Scattered over the surface of the lung but more numerous on the interlobar septa are a few small, firm, white, puckered areas which when sectioned are firm and almost cartilaginous and appear to be quite superficial. Some of these areas have pale yellowish centers. At the apex of the lung there is some puckering with increase in fibrous tissue and slight calcium deposition, but no evidence of recent tuberculosis. Elsewhere the lung shows nothing more than hypostatic congestion of the dependent portions.

Left Lung: A similar picture is seen except that there is also thrombosis of the median branch of the left pulmonary artery with a resultant small, firm, red infarct with brownish borders in the middle lobe.

Liver: A little paler and firmer than normal, and over the lower anterior surface of the right lobe are two small, white circular non-elevated areas about 3 mm. in diameter, and sharply demarcated from the liver parenchyma and surrounded by a slight zone of congestion. These are quite superficial but, on sectioning the liver, similar yellowish areas are scattered throughout, apparently bearing no relation to the liver lobules. The gall bladder is negative.

Spleen: Weight 750 gm., and symmetrically enlarged. It is uniformly firm, about normal in color and the rather opaque capsule is smooth everywhere except over an area on the anterior surface, where it is adherent to the omentum by recent adhesions into which there has been some hemorrhage. The rather firm pulp shows a fine diffuse grayish mottling and does not readily scrape away with the knife; the Malpighian corpuscles are less distinct than normal, and there is slight fibrous thickening of the trabeculae.

Kidneys: Weight 250 gm. Negative except for cloudy swelling in both, and a superficial cortical cyst in the lower pole of the right.

Prostate: Negative except for a small round white phlebolith in the periprostatic vein over the right lobe.

Gastro-Intestinal Tract, Pancreas and Adrenals are essentially negative.

Lymph Nodes: The bronchial group are moderately anthracotic but appear normal in size and consistence. The mesenteric nodes

are small, discrete, freely movable and but slightly firmer than normal. The fresh surface has a diffuse chrome yellow color but shows no evidence of hemorrhage or necrosis.

Skeletal System: The cranium, all vertebrae and ribs, the left ilium and both femora show similar changes, and a description of the cranium will suffice for all. On reflecting the scalp, the pericranium was detached from the calvarium with the greatest ease because it was almost entirely separated from the latter by diffuse collections of clear, pale yellow, viscid fluid in which great numbers of discrete, irregular, firm, white, flattened sand-like particles varying up to 2 mm. in diameter are suspended. The surface of the skull is extensively eroded by broad, shallow, sharply chiseled out furrows which cover the entire surface in an interlacing, geographical pattern. The calvarium likewise separates from the dura with remarkable facility and the same condition is found between the calvarium and dura as between the calvarium and pericranium.

The ribs and femurs seem to be lying in distended tubes of thickened periosteum, and separated from the latter by the same type of viscid fluid and granular particles, which are described above. These fluid accumulations are most marked along the ribs and in the left iliac fossa. Under the periosteum of the left ilium there is a fluctuating tumor mass bulging out into the false pelvis, which contains about 150 cc. of viscid brown-stained fluid and many thick gelatinous clots. The periosteal surfaces of all the bones are diffusely roughened by small irregular depressions giving a granular appearance. These depressions are all filled with the characteristic fluid and, in the areas of greatest fluid accumulation, erosion of the bone surface is most marked. All the bones, but especially the ribs, are more pliable than normal, fracture very easily and may be cut with the knife or sawed with greater facility than normally; and the sawdust resembles that of wood, being soft, dry and flaky. The marrow from the femur is yellowish white, fibrous with scattered edematous or gelatinous areas, and with a diffuse distribution of fine spicules of bone. The marrow spaces of the ribs are likewise filled with firm yellowish white material and a few gelatinous areas. Neither red nor fatty marrow is found in any of the examined bones. The fracture of the right femur shows fibrous union with very slight callus formation, limited motion between the fragments and some rarefaction of their ends.

The Cranial Contents: There is an increased amount of cerebrospinal fluid and an old pachymeningitis with a very fine network of new capillary blood vessels over the tentorium. With the exception of edema of the meninges, most marked over the frontal lobes, the brain is negative.

The microscopic examination of the lungs, bones and spleen is of particular interest.

MICROSCOPIC REPORT

Lungs: The small, firm, white areas which are scattered over the pleural surfaces, consist of irregular clumps of epithelial cells surrounded by a desmoplastic reaction and, though rather superficial, lie not within the pleura but in the underlying lung tissue. These cell clumps vary greatly in type. In some areas they consist of scattered cells with lightly staining, irregularly ovoid or spindle-shaped nuclei, surrounded by scant, pale cytoplasm which extends in spider-like threads in all directions to unite with similar protoplasmic threads from adjacent cells. Between these cells there is a non-staining or faintly eosinophilic matrix, while about and extending throughout such a clump will be strands of fibrous tissue. In other areas, which are apparently younger and where desmoplasia is less marked, the cells are more uniform in type with round or oval, lightly staining nuclei surrounded by a moderate amount of pale cytoplasm. In such areas the cells are arranged in compact groups which show a tendency toward cornification and pearl formation in their centers. Though intercellular bridges are present in such groups they are not as prominent as in the previously described type. In a few other areas, probably older, a different picture is seen. This consists of dense, more or less hyalinized fibrous tissue within which a few scattered irregular strands of tumor cells are found (Figs. 5 and 6).

Bones: Sections for microscopic study were taken from the sternum, ribs, stenocondral junctures, femurs and pelvic bones. All these sections show a more or less similar picture, characterized by a complete infiltration of the marrow spaces, and considerable infiltration of the periosteum by tumor tissue which is accompanied by an extreme desmoplastic reaction. Associated with this, is a condition analogous to osteoid fibrosis, a decalcification of bone leaving a hyaline-like matrix and, in some areas, actual bone erosion.

In none of the sections is either red or fatty marrow to be found. Extending through the marrow spaces between the bony trabeculae, strands of fibrous tissue are seen; young in some areas and rich in large cells, and in others, largely hyalinized containing but a few small, thin, deeply staining nuclei and representing a much older fibrosis. Interspersed throughout this fibrous background are found groups of tumor cells varying greatly in character. Some groups in the younger fibrous strands are round clusters of plump cells showing cornification and pearl formation, while others show an irregular separation of the cells making conspicuous many intercellular bridges. The arrangement of such cells suggests the appearance of the diffuse epithelial masses seen in adamantinomas. Within the older more or less hyalinized fibrous tissue there is an occasional clump of a few, small, densely packed, deeply staining tumor cells (Fig. 7).

The changes in the cortical bone are most marked in the ribs, where the cortex is largely replaced by irregular layers of osteoid tissue covered on either side by new fibrous tissue, containing various groups of tumor cells. The periosteum is greatly thickened and infiltrated with the tumor tissue which in some areas is seen as broad sheets that have either split longitudinally or undergone central necrosis and become more or less cystic. Invading the original periosteum are strands of tumor cells which are clustered about blood vessels. Many small hemorrhagic areas are found in the regions of more recent growth, especially subperiosteally, while areas of cystic, gelatinous and hyaline degeneration are more common in the older growth.

Spleen: The changes here are well shown in Fig. 8. Scattered throughout the pulp and largely replacing its normal constituents are many myelocytes both singly and in groups of three to six, which are predominately eosinophilic though many are neutrophilic and occasionally there are seen myelocytes with less abundant cytoplasm which contain but a few, relatively large basophilic granulations. In addition to the definite myelocytes there are cells which have scant, poorly outlined cytoplasm in which no granules are evident, and large round nuclei that show deeply staining chromatin about the periphery and a few thin strands of chromatin crossing the pale central portion. These cells are probably myeloblasts and frequently one or two of them are surrounded by a group of myelo-

cytes. Though a few normoblasts are encountered in the pulp tissue it is more likely that they have been swept in with the circulation than that they are the result of erythropoiesis, because they do not occur in groups but only as isolated cells, and no cells resembling megaloblasts can be found. The lymphoid follicles are not prominent and are relatively far apart, due to the increase of pulp.

With the exception of the infarcted region of the left lung, slight general passive congestion and parenchymatous degeneration, there is nothing further of interest in the microscopic examination of the tissues. The nodular areas seen during the gross examination of the liver are areas of senile sclerosis of the liver parenchyma. There is no tumor tissue in any of the sections of lymph nodes.

Briefly summarizing the case, we have, in a 50 year old man, an epidermoid carcinoma, arising probably in the skin over the left malar region, giving rise to metastases to the lungs and to the bones, where the marrow has been practically obliterated by the carcinoma, resulting in multiple spontaneous fractures of the bones and a peculiar type of anemia associated with a myeloid reaction in the spleen.

Cases similar to the above with metastatic involvement of bone marrow by tumor growth resulting in a specific anemia, are of rather rare occurrence in the literature. Piney⁴ in 1922 collected ten published cases and added four of his own. Since then a case has been reported by Miller,⁵ and by reviewing the literature we have been able to collect a total of twenty-three cases of bone marrow metastases that showed the blood changes characterizing osteosclerotic anemia. The location of the primary tumor in each of the accepted cases and the names of the authors who report them are listed below.

In addition to this list, several cases have been reported that may belong in it; but because of insufficient blood pictures, lack of definite bone marrow involvement, or some other important factor they cannot be definitely grouped with the above. Of these, von Grawitz has reported three cases; Schleip,⁶ one, a jaw tumor; Kurpjuweit,¹¹ one, related to lymphosarcoma; Waldstein,¹⁸ one, probably chloroma; and Israel and Leyden¹⁹ have reported a possible case due to osteosarcoma.

All of the twenty-four cases, in addition to being cases of metastatic involvement of the skeletal system, are alike in that they

TABLE 2

Location of Primary Tumor	Total No. of Cases	Reported by
Stomach.....	9	Schleip, ⁶ Parmentier and Chabrol, ⁷ Harrington and Teacher, ⁸ Harrington and Kennedy, ¹ Ellermann, ⁹ Fresé, ¹⁰ Kurpjuweit. ¹¹
Breast.....	5	Epstein, ¹² Houston, ¹³ Ward, ¹⁴ Piney, ⁴ Hirschfeld. ¹⁵
Prostate.....	2	Miller, ⁵ Braun. ¹⁶
Esophagus.....	1	Reichmann. ¹⁷
Appendix.....	1	Schleip. ⁶
Rectum.....	1	Piney. ⁴
Gall bladder.....	1	Kurpjuweit. ¹¹
Uterus.....	1	Hirschfeld. ¹⁵
Lung (alveolar).....	1	Piney. ⁴
Lung (bronchial).....	1	Piney. ⁴
Cheek (epidermoid carcinoma) ?	1	Rusk and Miles (present case).

show a peculiar blood picture, the outstanding features of which are as follows:

1. A marked reduction in the erythrocyte count with a similar reduction in hemoglobin, resulting in a color index that is usually slightly under 1.
2. Anisocytosis and poikilocytosis of the erythrocytes.
3. The appearance of immature red cells, both normoblasts and megaloblasts, in the circulation.
4. The appearance of myelocytes and less frequently myeloblasts in the circulation.
5. Usually a slight leucocytosis due principally to an increase in the myeloid series of white cells though frequently there is a leukopenia.
6. Frequently a terminal reduction in the blood platelet count.

DISCUSSION

One of the first questions brought to mind by our case is, why were metastases so extensive to the bone marrow and so limited elsewhere? There was no evidence of lymph node involvement anywhere in the body or of visceral metastases, with the exception of several relatively small foci in the peripheral portions of the lung parenchyma. The old conception, advanced by von Grawitz, that bone marrow tumors were the result of a "cancerous diathesis" that

could occur in several parts of the body simultaneously, is now untenable. At present, metastases are regarded as carcinomatous emboli occurring in either the vascular or lymphatic channels⁴ or due to lymphatic permeation.²⁰ With this in mind we present three possibilities that might account for this condition:

1. There may be a predisposition of certain tissues to metastasize to the bone marrow.
2. Mechanical or chemical factors may be present in the bone marrow which favor the development of metastases there.
3. The bone marrow, unlike the other tissues, may not possess sufficient resistance to prevent the development of the metastases of a carcinoma of a certain virulence.

The first becomes a very convincing argument when we recall the frequency with which carcinomas of the thyroid, prostate and breast metastasize to bones. Paget²¹ was one of the first to note this, and records the fact that of twenty cases of carcinoma of the thyroid which came to necropsy, ten showed metastases to bones. Risley²² states that Fischer-Defag, studying a series of prostatic carcinomas, found that twenty-five per cent showed skeletal metastases. More recently Moore²³ reports that of 1600 cases of carcinoma of the stomach, studied at the Mayo clinic during a period of ten years, not one gave evidence of metastases to bone; while of sixty-five cases of metastatic malignancy of the bones which he studied roentgenologically, thirty-six were from the breast, eleven from the prostate, seven from the kidney, (hypernephromas?) and two from the thyroid.

Not only are some carcinomas more apt than others to metastasize to bones but, as Paget, von Recklinghausen²⁴ and many others have observed, these metastases occur most frequently in certain bones and in certain parts of these bones. The spine is most frequently involved and after this the bones of the pelvis, the femurs, the humerus, the ribs and the flat bones in general. In relation to the femur and humerus, Pfahler²⁵ has emphasized that the metastases occur in the heads of these bones. von Recklinghausen conclusively demonstrated that the earliest bone metastases are in the centers of the bones within the marrow cavities. If we recall the anatomy of bone marrow, we note that normally red marrow persists throughout adult life in the head of the femur and of the humerus, and generally throughout the marrow spaces of the other

bones mentioned. In other words, the bony metastases tend to locate within red marrow.

If we accept von Recklinghausen's conception that bone metastases occur by way of the blood stream, the above statements may bear some relation to the possibility that such metastases are the result of favorable mechanical or chemical factors in the red marrow. von Recklinghausen showed, and Drinker²⁸ has more recently reviewed the subject, that within the red marrow the blood vessels break up into many wide and tortuous thin-walled channels which results in a marked slowing of the blood stream. If cancer cells were free in the blood stream, it would seem that the partial stasis there would give them an excellent opportunity to gain a foothold within the many crevice-like outpocketings of these vascular sinuses. Ewing²⁷ while considering other possibilities, believes that the particular susceptibility of some tissues to develop secondary tumors is explicable on the basis of mechanical peculiarities of the circulation in those tissues. In addition to stasis, von Recklinghausen believed that physical strain and thermal changes were also important factors in the location of the bone metastases but his arguments are not so convincing.

The third possible factor namely, that metastases are dependent upon cancer cell virulence versus tissue resistance, may seem rather difficult to accept. However, it is well known that the bones and bone marrow show relatively poor resistance to infections, thus, regarding the carcinoma cells as invading organisms, it is conceivable that a carcinoma of relatively low virulence, which would be readily overcome by most of the tissues, could, providing it gained entrance to the bone marrow, obtain a foothold there and develop in this area of lower resistance.

The route by which cancer cells arrive in the bone marrow has for many years been a subject of dispute. Piney champions von Recklinghausen's conception that the metastases are blood borne; while Sampson Handley²⁰ is the outstanding exponent of the theory of lymphatic permeation. That the usual lymph node and visceral metastases come by way of the lymph stream can be readily shown in nearly all necropsied cases of carcinoma, and as such is generally accepted by all. However, we have been unable to find a record of any work proving the existence of lymphatics in bone marrow. Piney, using very careful technic, attempted the injection of peri-

osteal lymphatics and found that the material would readily enter the periosteal lymphatics and pass from them through the bone and into endosteal channels, but he could not force the mass from these channels into the bone marrow. The main reasons for Handley's contention that the metastases are carried by way of the lymphatics, may be briefly summarized as follows:

1. The distal bones of the limbs are rarely invaded by metastases. He states that this is incompatible with the embolic idea, because these bones would be just as liable as others to invasion and accounts for this phenomenon by saying that the patient usually dies before the process of lymphatic permeation has extended to them.
2. The liability of a bone to invasion increases directly with its proximity to the primary focus.
3. The point of attack in the limb bones is usually in that portion of the bone lying nearest to the cutaneous surface, which would be expected if the bones were invaded from the lymphatic plexus of the deep fascia.
4. Bone metastases occur almost entirely in the areas of the body that are apt to be involved by metastases to the skin.

Piney meets Handley's statements by replying that suitable soil for metastases occurs only in the red marrow, and in the adult this is not to be found in the distal bones of the limbs. As to the relation between bone metastases and skin nodule formation, he calls attention to the fact that they rarely occur together, though either singly is quite common. In addition to the above, Piney describes and gives photographs demonstrating groups of carcinoma cells lying within endothelial-lined channels in the bone marrow. He admits that he was unable to find both carcinoma cells and erythrocytes in the same channel, but states that such a picture has been observed by Assmann and by Erbslöh.

In this connection, it is worth while to mention a case of scirrhus carcinoma of the right breast which has recently been reported by Beatson.²⁸ He made an unusually thorough examination of the skeletal system, and in addition to involvement of the vertebral column, ribs and skull, all of which may possibly be explicable on the basis of lymphatic permeation or lymph stream embolism, he found metastases in both radii, ulnae, tibiae, fibulae and in the metatarsal and phalangeal bones of the left foot. Handley admits metastases beyond the elbow and knee joints are difficult to account

for by the theory of lymphatic dissemination, so it would seem that this case furnished a very definite example of spreading by way of the blood stream.

With our case it has been impossible to determine the route of invasion. The tissues have undergone such extreme carcinomatous changes that we are unable to say whether the metastases came in with the blood stream, located in the marrow, and by extension involved the bone and then the periosteum; or whether they entered the periosteum by way of the lymphatics, and then extended through to the marrow; or possibly by some combination of the two processes. However, the complete absence of demonstrable lymph node or fascial plane involvement, the fact that in general the periosteal growths appeared younger than the marrow cavity metastases, and that frequently within the original periosteum strands of tumor cells could be seen extending like cords about capillaries, lead us to believe that in this case the carcinoma was carried to the bone marrow by the blood stream and that the bone and periosteum became involved by extension from these metastases.

Anemia is the result of either increased blood destruction, blood loss, or defective erythropoiesis or a combination of the two processes. In this case there is no appreciable evidence of blood loss or destruction, and it is apparent that here the trouble is primarily due to defective erythropoiesis. As to the mechanism by which such an effect is produced upon the red marrow, little can be ventured. It may be, that as Jack and Teacher²⁹ have suggested, this effect is the result of some specific influence inherent in the invading tumor cells, but from a survey of these cases, it would seem far more probable that it is due merely to a widespread destruction of the erythroblastic tissues by the invading growth and the accompanying desmoplasia. McMaster and Haessler³⁰ have shown that the spread of the red marrow in anemia is dependent upon the available hemoglobin. Since in this case there was no blood loss and therefore no reduction in the available hemoglobin, we find that the red marrow has spread extensively to new fields but that following close upon it, extensive metastases have developed which tend to destroy the red marrow thus throwing the burden of erythropoiesis upon relatively small amounts of tissue which, in their so-called "hurried ineffectiveness," liberate many immature and abnormal cells into the circulation.

Opposed to this view are a number of cases reported by Middle-

ton,²¹ Jack and Teacher, Thompson and Keiller,²² Beatson, and Nothnagel²³ in which extensive bone metastases were noted but which did not show an erythroblastic reaction. These can be explained by the above reasoning, only by assuming that in these cases metastases had not caused sufficient destruction of the red marrow to produce this picture before death ensued.

A feature of equal interest in this case is the marked myeloid reaction of the spleen. Though other men have mentioned the presence of a myeloid reaction of the spleen, Parmentier and Chabrol, Fresé and Kurpjuweit have made particular note of it. The cause of this reaction is to be attributed either to implants within the spleen of myeloid elements which have been carried by the blood stream from the bone marrow, or to a reversion of the spleen to its embryonic function in response to the destructive effect upon the myeloid elements in the marrow. Tendeloo²⁴ mentions both these possibilities but refrains from offering an opinion and merely states that it is an open question.

Considering our case, in regard to the literature which has been cited, we feel that the following conclusions are permissible:

CONCLUSIONS

1. This case is one of epidermoid carcinoma probably arising in the skin over the left malar region and giving metastases to the lungs and to the skeletal system.
2. These metastases came by way of the blood stream and, in the case of the bones lodged first in the red marrow and then by extension involved the cortical bone and periosteum.
3. The picture here, which is primarily one of skeletal metastases, is most reasonably explained by assuming that carcinomatous emboli reached all the tissues but that only the bone marrow (excluding the lungs) furnished suitable soil and possessed the proper mechanical features to permit the development of metastatic tumor tissue.
4. The peculiar type of anemia produced is the result of widespread destruction of the marrow.
5. This anemia is characterized by the appearance of abnormal and immature erythrocytes, and myeloid leucocytes in the circulation.
6. With this anemia there is usually produced an extreme myeloid reaction on the part of the spleen, resulting in a splenic tumor.

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DESCRIPTION OF PLATES

PLATE 83

- FIG. 1. Metastasis in lung.
 FIG. 2. Metastasis in femur.

PLATE 84

- FIG. 3. Detail with pearl formation in femur.
 FIG. 4. Myelocytic infiltration in spleen.

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