EWING'S SARCOMA OF BONE *

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When one studies Ewing's reports of 1921,[1] 1924,[2] and 1928,[3] it is clear that he was attempting to single out among the primary malignant tumors of bone an entity which he first called "diffuse endothelioma" and subsequently "endothelial myeloma" of bone. He thought that the tumor cells were derived from angio-endothelium in the broadest sense. He described the type cell as a small polyhedral cell with pale cytoplasm, small hyperchromatic nucleus, and well defined cell border, and stressed the idea that the tumor cells showed no osteogenic potentialities. He stated that, although tending to be arranged in compact broad sheets, the tumor cells, at least in some places in a given tumor, were often found lying around tiny or larger vascular spaces in "perithelial" arrangement or still circularly, but not around a vessel, in "rosette" formation.

Ewing also consistently stressed certain clinical features as likewise being important in the delimitation of the bone tumor he was discussing. In his opinion, these included: youthfulness of the patients (on the whole); a rather characteristic roentgenographic appearance of the presenting bone lesion; a gratifying initial response of this lesion to radiation therapy; and eventually (in all but a few cases) the appearance of lesions in other bones and especially in the lungs, with fatal result.

However, the concept of Ewing's sarcoma as delineated above has undergone certain criticisms and modifications. Some investigators have even doubted the validity of the basic concept itself, pointing out that it had been founded on, and largely sustained by, clinical and biopsy findings, rather than by study of cases followed through to the end and systematically autopsied. In relation to diagnosis, so much faith has long reposed in the clinical aspects, as sketched above, that, summarized as constituting "Ewing's syndrome," they often took precedence over tissue examination in arriving at a diagnosis—a point of view which has proved itself unjustified. Many, including Neely and Rogers,[4] Swenson,[5] and Barden,[6] have pointed out that evidence is lacking that the roentgenographic picture is sufficiently characteristic for the condition to be of high diagnostic value. Colville and Willis [7] and Willis [8] also emphasized the pitfalls involved in arriving at a diagnosis even through biopsy, and the diagnostic surprise frequently encountered when a case suspected of being Ewing's sarcoma is finally subjected to detailed post-mortem examination.

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With due allowance for all these reasons for diagnostic caution, the weight of evidence sustains the existence as an entity of a primary bone sarcoma to which, because of Ewing's pioneer efforts to single it out, the name of Ewing's sarcoma of bone can justifiably be applied. Yet, without prejudice to that central fact, it should be noted that Oberling [9] and Oberling and Raileanu,[10] among others, have dissented from Ewing on the histogenesis of the tumor cells, as well as on the details of the cytology of the tumor. As to histology, Oberling found that the cells of the neoplastic tissue proper tend to appear in a sort of network in which nuclei are prominent, cell cytoplasm is meager, delimiting cell membranes are lacking, and the cells are connected by short or long cytoplasmic processes. He further described the nuclei as uniform in size and generally roundish or ovoid, and as having powdery chromatin and often one or more nucleoli.

On the basis of our own material (17 cases, 4 of which were autopsied) we found that, provided the neoplastic tissue was definitely viable and well fixed and well stained, and irrespective of whether it came from the presenting bone lesion or from a metastatic focus, the appearance of the basic tumor cells corresponded rather to the description given by Oberling than to that given by Ewing. Also, we could not convince ourselves that perivascular orientation of the tumor cells was a characteristic cytologic feature of the tumor in question, although we found that tumor areas which had been heavily invaded by blood vessels, especially in the wake of hemorrhage, often showed tumor cells about capillary spaces or around larger vascular spaces in so-called "perithelial" arrangement. Furthermore, our material failed to provide evidence of the presence of the true rosette (or pseudorosette) formations which have been stressed as part of the cytologic picture of Ewing's sarcoma.

As to histogenesis, Oberling maintained that the tumor develops from the immature reticular cells (the supporting mesenchymal cells) of the bone marrow. For this reason, he conceives and designates Ewing's sarcoma as a reticulosarcoma of bone marrow, and also believes in the kinship (falling short of identity) between reticulosarcoma of bone marrow and the generally recognized reticulosarcoma of lymph nodes. Also, basing his idea on the view that the reticular cells of the bone marrow are totipotent, he maintains that, in some areas of a reticulosarcoma of bone marrow (Ewing's sarcoma), these cells may differentiate in the direction of endothelial cells (cells capable of forming vascular and lymphatic channels) or even in the direction of hemocytoblasts (cells capable of forming myeloid or lymphoid cells). Ewing, taking cognizance of Oberling's views, rejected this conception of the histogenesis of the tumor. Instead, he reiterated, both in 1939 [11] and

in 1940,[12] that the tumor denoted by his name must be conceived as arising from cells which are strictly of angioblastic nature and possess no wider potentialities than the formation of vascular channels.

Like Stout,[13] we saw no evidence in our material that the basic cell of the Ewing sarcoma is totipotent, as Oberling believes, and able to differentiate in the direction of cells capable of forming vascular and lymphatic channels, or even in the direction of cells capable of forming myeloid or lymphoid cells. Like Stout, too, however, we favor Oberling's interpretation of the tumor as a sarcoma of a primitive form of connective tissue and specifically of the mesenchymal supporting framework of the bone marrow. Nevertheless, we feel that designating the lesion as a reticulosarcoma is open to misunderstanding because of the confusingly varied interpretations existing as to the neoplastic potentialities of the mesenchymal reticular framework of the lymphoid and myeloid tissue. Also, it should be pointed out that Parker and Jackson [14] described, under the name of "primary cell sarcoma of bone," a tumor which they hold akin to reticulum cell sarcoma of lymph nodes but distinct from Ewing's sarcoma. For these reasons, and because one might also be thought to believe with Connor [15] that it should be classed as a tumor of the reticulo-endothelial system, we have preferred to use the neutral name of "Ewing's sarcoma" instead of "reticulosarcoma" for the tumor in question.

Clinical Features

Age and Sex Incidence and Localization

At the time of admission to the hospital, the 17 patients in our series ranged between 4 and 39 years. However, all but 4 of them were 12 to 19 years of age (these 4 being 4, 8, 24, and 39 years). Correspondingly, the median and average age of the group as a whole were about 16 and 17 years, respectively. It may be that the strikingly narrow age range in our series is favored by the small number of cases, but at any rate our data are in line with the general observation that a very large proportion of the cases in any series (see, for instance, Hamilton [16]) fall within the second decade of life.

Eleven patients (65 per cent) were males, which is in agreement with the experience of most observers that the disorder is slightly more common in males than in females. At any rate, the sex difference in incidence of the disorder is not striking.

Usually, only one skeletal lesion was causing complaint and was demonstrable roentgenographically at the time of the patient's admission to the hospital. In an occasional case, even on admission roentgenographic examination of the rest of the skeleton revealed one or more

additional but clinically silent foci of bone involvement or even pulmonary metastases. However, in connection with localization, we shall refer only to the presenting lesion—the one giving rise to the complaints which brought the patient to the hospital.

In 12 of our 17 cases, the presenting lesion was in one of the bones of the trunk. Specifically, this bone was an ilium in 4 cases, an ischium in 2, a pubis in 1, a rib in 2, a scapula in 1, a clavicle in 1, and a vertebra in 1. In the remaining 5 cases, the presenting lesion was in a long bone, and, specifically, it was in a humerus in 2 cases, a femur in 2, and a fibula in 1. Why, in our cases, the presenting lesions were preponderantly in bones of the trunk we do not know, but this has been true, also, in the experience of others.

History of Trauma

In only 5 of our cases was there a history of definite, fairly recent trauma to the site in which the presenting tumor developed, the trauma having antedated the discovery of the tumor by 1 to 6 months. As to the other cases, 1 patient stated that he had twisted his ankle 4 years before admission for a tumor in the fibula, but the actual complaints which had brought him to the hospital were of only 1 year's standing. Two patients implicated functional trauma of very recent occurrence: handball playing by one and broad-jumping by the other. In 2 additional cases, the site of the trauma mentioned by the patient was near, but not the same as, the site of the presenting tumor. In the remaining 7 cases, the patients gave no history of antecedent trauma to the region of the presenting lesion.

From these data, it is difficult to draw any conclusion as to a possible causal relation of trauma to Ewing's sarcoma. The 5 cases in which a definite history of possibly relevant antecedent trauma was recorded are counterbalanced by the 7 in which there was no history of such trauma. In the remaining 5 cases, the weight of the evidence is against the significance of the trauma, since the trauma was merely a mild functional one, or was not at the site of the subsequent tumor, or preceded the appearance of the tumor by an implausibly short period. Certainly, the data constitute no overwhelming evidence in favor of a causal relation between trauma and Ewing's sarcoma.

Clinical Complaints and Findings

Survey of the clinical histories of the patients in our series shows that local (and/or referred) pain was the one consistent complaint. With few exceptions, the pain was of at least some months' standing, and in several cases it had been present for at least 1 year before admission. Usually, also, it had become increasingly severe and persistent

during some weeks or months immediately before admission. With the local pain, there were often complaints related to spread of the tumor beyond the limits of the bone and varying with the location of the presenting lesion. Thus, for instance, from patients in whom some part of an innominate bone was involved, there were usually complaints of disability relating to the hip joint and sometimes also of radiating pain down the lower limb. In connection with presenting lesions near the end of a long bone, there were sometimes complaints of lameness or stiffness of the corresponding joint, and, in one case in which the lesion was near the lower end of the femur, there were repeated serous effusions into the knee joint. In the cases in which the presenting lesion was in a lumbar vertebra, there were, in addition to the local pain, complaints ascribable to implication of nerve trunks in the area, such as pain radiating down the limbs, and tingling sensations and weakness in the latter. Location of the presenting lesion in a rib was found associated with pleural effusion in one case. Other locations of the presenting lesion (for instance, in the skull) are associated with their own special clinical disabilities.

Just as local pain was the dominant clinical complaint, so the presence of a local tumor mass was the dominant clinical finding at the time of admission. On admission, a more or less prominent tumor mass was palpable at the site of the presenting bone lesion in all but 3 of our 17 cases. This fact indicates the strong tendency of Ewing's sarcoma to break out through the cortex of the bone and spread in the surrounding tissues. Notably large tumor masses were palpable in some cases in which the tumor appeared in an innominate bone. Spreading internally toward the pelvic cavity, the tumor beyond the limits of the bone could then sometimes be palpated as an elastic, irregular, globular mass, through the rectum if the tumor was low down, or in the lower quadrant of the abdomen if it was higher up. Spreading externally, a tumor springing from an innominate bone sometimes produced a large tumor mass palpable in the groin or in the gluteal region. In one of our cases in which the presenting lesion was in the shaft of a humerus there was likewise a very large extra-osseous tumor mass connected with the bone. When the presenting tumor was in a superficially located bone such as a clavicle or a rib, the mass produced by extra-osseous spread could be seen as well as palpated.

Tenderness to pressure at the site of the lesion was recorded in practically all cases. Frequently, the subcutaneous veins overlying the presenting lesion were found to be prominent. However, it was only exceptionally that increased local heat was mentioned in connection with the physical examination.

A survey of the temperature charts and the laboratory findings in

our cases revealed what appeared to be significant information of clinical value. Many of the patients were in the hospital for almost a week before specimens were secured for biopsy. During this time they had a slight fever, with daily rises in temperature to about 101° F.* These patients generally presented a secondary anemia (with a red blood cell count of about 3,500,000), and sometimes also a leukocytosis. In addition, they usually showed a high sedimentation rate of the blood. Taken together, these findings proved to be more significant in respect to the immediate prognosis than the size of the presenting lesion. Specifically, the cases in which some fever and secondary anemia, together or even alone, were noted ran a fulminating course, ending in death within a few months after admission to the hospital. On the other hand, those patients who had no fever on admission, and no anemia or increased sedimentation rate, tended to survive for a year or more after admission.

Roentgenographic Features

Roentgenographic Appearance of the Presenting Bone Lesion

By the presenting bone lesion we mean, as already indicated, the one causing the complaints which led the patient to enter our hospital. This was often the only lesion discernible even when the entire skeleton was roentgenographed on admission, and in any event it was the one which guided roentgenographic diagnosis. One need only review the presenting lesion in a series of cases to appreciate the difficulty of making a diagnosis of Ewing's sarcoma by x-ray examination alone. If the amount of bone involvement in the presenting lesion roentgenographically is still small and no lesions are found elsewhere, the picture may be misconstrued as an inflammatory lesion. However, in most cases the picture of the presenting lesion suggests a malignant tumor, although often misinterpreted as some malignant tumor other than Ewing's sarcoma.

* One case presented a diagnostic problem not only because of a definitely febrile course but because of atypicalness of the local clinical complaints and findings. The patient was admitted to the hospital complaining of difficulty with the right knee joint, dating back 8 months. The knee was painful, warm, tender, and swollen from the presence of fluid in it. Some rarefaction of the cortex and spongiosa of the medial condyle of the femur was noted roentgenographically, but there was no clear-cut indication of the presence of a tumor in the bone or overlying soft parts. The clinical impression was that the condition of the knee joint proper and of the condyle had its basis in some infection, as indicated by the fact that the patient had repeated bouts of fever, sometimes reaching 103° F., and that serous fluid could be aspirated again and again from the joint. Repeated bacteriologic studies of the joint fluid, and various agglutination tests on the blood failed to give evidence of infection. However, in the ensuing 5 weeks there was progressive destruction of the medial condyle, and the assumption of an infectious lesion became less tenable. Biopsy revealed Ewing's sarcoma of the lower end of the femur, and the limb was disarticulated. The patient died 5 months after admission, and at autopsy widespread metastases were found.

The only fairly consistent roentgenographic finding is evidence of lysis of bone, by itself a rather nondescript feature. Thus in some cases the presenting lesion may appear merely as a small zone of mottled rarefaction reflecting destruction of the spongiosa and, to a lesser degree, of the overlying cortex, associated with what is as yet only a trace of periosteal new bone apposition in reaction to the neoplastic tissue which has penetrated beyond the cortex. This picture (which may also include some areas of condensation) is very likely to suggest an inflammatory lesion (pyogenic or tuberculous osteomyelitis) rather than a tumor, but within a month or so the roentgenogram presents evidence of rapid extension of the pathologic area within and beyond the bone, now strongly supporting a diagnosis of malignant neoplasm. Although the roentgenogram still shows only a relatively small area of bone destruction, this cannot be taken as indicating the actual extent of involvement of the bone, the marrow spaces of which may already be riddled by neoplastic tissue (Figs. 1, 2, and 9).

When the initial roentgenograph of the presenting lesion shows rather clearly that one is dealing with a malignant tumor, one usually notes a large area of bone destruction, often with a large overlying soft-tissue mass. The affected area in the bone may show distention of its outline, but, if present, this is not pronounced. However, the affected area appears irregularly rarefied and mottled from the presence of smaller or larger foci of relative radiolucency and shows disruption of the cortical outline over a variable region. From a series of cases it can be stated that reactive deposition of new bone by the periosteum, where the neoplastic tissue is penetrating the cortex, is certainly not conspicuous. When, as is commonly the case, Ewing's sarcoma involves bones other than long bones, evidence of periosteal new bone apposition, although not uncommon, is not a striking finding (Figs. 3 and 4). It may not even be such in connection with involvement of long bones.

When the shaft of a long bone is the site of Ewing's sarcoma, one does not commonly observe the concentric onion-skin-like layers of periosteal new bone of a laminated pattern held to be so characteristic of the roentgenologic appearance of this tumor. Rather, a substantial portion of the shaft may show irregular mottled rarefaction, perhaps with complete absence of significant periosteal bone apposition (Fig. 5). In one of our cases of Ewing's sarcoma of the shaft of a humerus, there was considerable onion-skin-like periosteal new bone apposition, but this was not circumferential, being limited to the lateral surface, while on the medial side the bone was overlaid by a thick mass of neoplastic tissue which had broken out from the interior of the bone. In this case (Fig. 6), on the basis of the roentgenologic appearance, the

lesion was regarded clinically as an osteogenic sarcoma without evidence of exuberant new bone formation (that is, as a so-called "osteolytic" osteogenic sarcoma). In another case of Ewing's sarcoma of a humerus, the roentgenogram of the affected portion of the shaft showed an irregular moth-eaten appearance of the cortex without thickening, associated with more or less transverse streaks of radiopacity in the soft portion of the tumor mass overlying the outer surface of the bone. Again the lesion was interpreted clinically as an osteogenic sarcoma (Fig. 7).

Altogether, the only conclusions that can be drawn in regard to the roentgenographic appearance of the presenting lesion are that bone destruction (osteolysis) is the dominant feature of Ewing's sarcoma and that there is no typical appearance for this lesion. In general, Ewing's sarcoma is a tumor difficult to diagnose on a roentgenographic basis, often being mistaken in its early stage for an inflammatory lesion and in later stages for malignant tumors of other nature, including metastatic neoplasms. In many cases it may be quite difficult to make a differential diagnosis, on a roentgenographic basis, between Ewing's tumor and chondrosarcoma, "osteolytic" osteogenic sarcoma, malignant lymphoma, or metastatic neoplasms (including metastatic neuroblastoma). Sometimes, too, a solitary lesion of eosinophilic granuloma may be mistaken for Ewing's sarcoma. To make certain that a suspected tumor is Ewing's sarcoma, tissue examination is essential, but it cannot be emphasized too strongly that a pathologist confronted by a specimen taken from a suspected case for biopsy may easily be mistaken in his opinion on this basis also, especially if the tissue available is meager. However, in this connection, the error is more likely to be that of misidentifying other lesions (anaplastic carcinoma, metastatic neuroblastoma, malignant lymphoma) as Ewing's sarcoma than the reverse.

Roentgenographic Appearance of the "Metastatic" Bone Lesions

Whether the additional lesions found roentgenographically on admission or subsequently, represent metastases from the presenting lesion or are independent primary growths does not concern us precisely here. Roentgenographically, these additional lesions, like the presenting lesion, show evidence of lysis of bone. They appear first as rather faint, slightly mottled areas of rarefaction. As the resorption of the bone increases, the small, multiple, roundish foci of rarefaction become more distinct and may merge into larger, more clear-cut areas of radiolucency. In flat bones, such as those of the skull or the ilium, multiple, clear-cut, punched-out areas of rarefaction may appear in

consequence of lytic destruction of the spongiosa and overlying cortex (Fig. 8). Even a neoplastic fracture of a long bone from destructive resorption may become manifest. It is important to bear in mind, however, that the actual extent of involvement of the skeleton at any one time is never adequately reflected roentgenographically. This is true even in fatal cases in which a number of destructive lesions have been demonstrated roentgenographically in bones other than the one containing the presenting lesion. At autopsy, if many additional bones are opened, they, too, will be found to have been far more extensively invaded than was suspected from roentgenographic study of the skeleton shortly before death.

Morphologic Features

Gross Description

Our experience supports the idea that Ewing's sarcoma arises in the marrow spaces of the interior of the affected bone, rather than in the haversian spaces of the cortex or beneath the periosteum. Also, as has been indicated, anatomic examination of an affected bone will reveal much more extensive involvement than the roentgenographic or clinical findings would suggest. This can be effectively demonstrated in cases in which the presenting lesion is in a long bone, which is made available by amputation. Roentgenographically, in a femur from such a case, the disease seemed to affect only the medial condyle and the adjacent part of the shaft. The cortex in this region was fuzzy and had a superposed soft-tissue swelling, about 2 cm. in thickness. When this femur was stripped of its surrounding muscles and cut in the frontal plane, it showed neoplastic tissue not only in the medial condyle but also in the lateral condyle and contiguous portions of the shaft, in the major marrow cavity, and even in the marrow spaces of the spongiosa of the upper end. The neoplastic tissue in the region of the medial condyle and that which had penetrated beyond the cortex in this region was, for the most part, discolored by hemorrhage and interspersed with yellowish areas due to necrosis of both neoplasm and spongiosa. Elsewhere, for the most part, the neoplastic tissue was not modified by hemorrhage or necrosis, was whitish, and, notably in the major marrow cavity, took the form of massed, soft, glistening tumor nodules. Thus the diseased area clearly visible in the pre-amputation roentgenogram of this femur was merely the area in which the changes were most advanced and destructive (Figs. 1, 9, and 10). Neither the inguinal nor the popliteal lymph nodes were enlarged or involved by tumor. Furthermore, in spite of the extensive implication of the femur,

no tumorous involvement was discernible in the tibia, fibula, or bones of the foot, all of which were opened and examined. These negative findings are of interest because at autopsy, 3½ months after the disarticulation of the right lower limb, widespread involvement of the skeleton and visceral metastases were found.

In contrast to a small tumor mass beyond the limits of the bone proper, as demonstrated in the femoral lesion just described, one finds, relatively often, a very large tumor mass beyond the limits of the bone, as part of the presenting lesion. This was well demonstrated in the case of a young girl whose presenting lesion was in the left ilium and whose complaints were of only a few days' standing at the time of admission to the hospital, but who then showed a firm tumor mass of the size of a neonate head, fixed to the ilium and palpable in the lower quadrant and groin. Although this patient appeared to be in good general health on admission, roentgenograms showed pulmonary metastases, and she died 4 months later. So far as the presenting lesion was concerned, autopsy revealed a huge mass overlying the inner surface of the left innominate bone, which had pushed the urinary bladder and the genital organs anteriorly and the sigmoid and rectum medially. On removing the left innominate bone, it was found that the tumor had extended posteriorly through the ilium and was bulging into the gluteal muscles and penetrating the capsule of the hip joint. The extra-osseous neoplastic tissue was soft, friable, extensively hemorrhagic, spongy and cystic on the whole, and in many places almost diffluent. The iliac bone was riddled by neoplastic tissue which was cystic in many places and there were many defects in its cortex, both on the inner and outer aspects, from which, as noted, the tumor had spread beyond the limits of the ilium proper into the surrounding soft tissues (Figs. 3 and 11).

As previously mentioned, 4 of the 17 cases upon which this report is based were autopsied. Two of the autopsies were performed by us. The other two were performed at Montefiore Hospital, New York City, and we are indebted to Dr. Samuel H. Rosen of the Laboratory of Pathology of that hospital for the opportunity of studying the protocols and slides. These autopsies were carried out with full awareness of the general lack of thorough autopsy studies in cases of Ewing's sarcoma.

At the time of death, 2 of these patients were 16 years of age; the other 2 patients were 18 and 19 years old, respectively. Three were females. The youthfulness of these patients makes it improbable that the skeletal lesions represented metastases from a carcinoma, although the possibility cannot be excluded. If we were dealing in these cases with metastases of carcinoma from an unrecognized primary growth,

whatever its site and however anaplastic the metastases might be, it is highly improbable that these lesions would consistently present the cytologic pattern peculiar to well preserved Ewing's sarcoma, to wit: cells of rather uniform size, with ill defined borders, little cytoplasm, and fairly large and rather uniform roundish or oval nuclei showing scattered chromatin.

Also, the findings, at least in the 2 cases (one male and one female) which we personally autopsied, clearly ruled out the presence of a hidden carcinoma. The breasts and testes were carefully searched for neoplastic tissue and none was found. In both cases, the lungs were given particular attention. In one no grossly visible tumor nodules were found anywhere in the pulmonary parenchyma. The bronchi, which were opened to the very small branches, as well as the hilar lymph nodes showed no gross evidence of involvement, reducing the likelihood that we had overlooked a primary bronchial carcinoma. In the other case, although all lobes of the lungs were riddled with hundreds of soft, richly cellular, largely hemorrhagic and liquefied tumor nodules of various sizes, they showed no single massive tumor, and it was plain from the gross appearances that the lesions were metastatic. In the course of the autopsies, full consideration was given to the fact that the gastrointestinal tract, and especially the stomach, can be the site of unsuspected carcinoma, but neither the gastrointestinal tract nor the lymphoid tissue regional to it showed tumorous involvement. Every precaution was taken to exclude the possibility that one was dealing not with a tumor primary in the skeleton but merely with metastases to the skeleton from a carcinoma which, in its primary site, was overlooked because it was inconspicuous or, although observed, was misinterpreted as a metastasis.

In a case thought to represent Ewing's sarcoma, the problem posed by neuroblastoma (primary in the adrenal medulla or in sympathetic nervous tissue elsewhere) is an even greater challenge than that raised by carcinoma. Sympathicoblastoma must always be ruled out in such a case, since this tumor not only has a strong tendency to metastasize widely to the skeleton but may bear a confusing cytologic resemblance to Ewing's sarcoma. This point was rightly stressed by Willis,[8] although he has often been misinterpreted as rejecting entirely the entity of Ewing's sarcoma and holding that all such cases represent merely metastases, particularly from neuroblastoma. Be that as it may, the adrenals in all 4 of our autopsied cases failed to show, on detailed gross examination, evidence of tumorous involvement or of any other abnormality. In the 2 cases which we autopsied personally, an extended search of the areas around the adrenals and of the sym-

pathetic chains along the vertebral column failed to show evidence of an extra-adrenal sympathicoblastoma.

As to the viscera, we have already pointed out that the lungs grossly may be found free of neoplastic tissue or, on the contrary, riddled with metastatic nodules. Under the latter conditions, we also have found the parietal pleura studded with tumor masses, some of which were large and fungating. In 2 cases, the liver presented numerous metastases, mainly in the form of nodules a few millimeters to somewhat more than a centimeter in diameter. In one case or another, metastases were noted in one or more of the following organs: heart, spleen, kidneys, pancreas, and thyroid. Finally, it should be noted that the lymph nodes, by and large, tended to be free of neoplastic tissue, although in one case some of the paravertebral and pelvic lymph nodes showed, microscopically, some nests of tumor cells in the peripheral sinuses as extensions of the neoplasm from the underlying vertebrae. The striking lack of involvement of the lymph nodes is additional evidence against the possibility that an occult primary carcinoma or neuroblastoma was present.

As already indicated, one can expect to find at autopsy that much of the skeleton, in addition to the bone with the presenting lesion, is affected, and much more extensively than one would have suspected from the ante-mortem roentgenographs. The question which cannot be answered definitely is whether the wide dissemination through the bones represents metastatic spread of the neoplasm or its autochthonous appearance in multiple sites.

At any rate, the calvarium is likely to show the neoplasm permeating the diploic spaces, and, in addition, areas in which neoplastic tissue has eroded or completely destroyed the tables. In the latter case, the calvarium will show actual defects, frequently several centimeters in diameter, filled with cellular, gray white or even greenish yellow neoplastic tissue which may elevate or even penetrate the regional calvarial coverings. The marrow spaces of the ribs and sternum, too, are likely to be filled with neoplasm, and thinning and erosion of the cortex may be associated with focal masses of neoplastic tissue beneath the periosteum. In both cases which we autopsied, large sections of the vertebral column were removed, and here too we found the marrow spaces of the bodies, arches, and spinous processes extensively infiltrated. In one case in particular, practically every dorsal and lumbar vertebral body showed areas in which the neoplasm in the marrow spaces and the supporting spongy bone appeared yellowish in consequence of necrosis (Fig. 12). Where there was no necrosis, the neoplastic tissue was grayish, soft, and obviously cellular. In many places the neoplastic

tissue was extending through the bodies and beneath the anterior vertebral ligament. From the third dorsal segment to the first lumbar segment, the new growth had also extended beneath the dura, narrowed the spinal space, and cuffed and compressed a large section of the spinal cord, with resultant degeneration of the latter.

Microscopic Description

Although Ewing's sarcoma does have a characteristic cytologic pattern (as Melnick [17] also maintained), secondary changes may obscure it or make it difficult to demonstrate in an individual specimen taken for biopsy, even if it has been obtained by surgical incision. Thus, a specimen may show large fields in which the appearance of the individual tumor cells has been altered by degeneration and necrosis, areas in which the neoplastic tissue as a whole has been modified by hemorrhage and reparative reaction to it, and even areas in which reactive inflammatory changes dominate the picture. It is because such secondary changes are not relegated to the background that the reputation of Ewing's sarcoma for variability and inconstancy of its cytologic pattern in biopsy specimens from case to case has developed and persists.

However, secondary changes in the neoplastic tissue do not present the only difficulty with which one is confronted in attempting to make a diagnosis of Ewing's tumor on the basis of a biopsy specimen. The diagnosis "Ewing's sarcoma" often has become a mere refuge when one is confronted by a puzzling malignant tumor in a bone, and is likely to be applied rather loosely and by default of a better opinion unless one's anatomic conception of Ewing's sarcoma is definite. This has been discovered by others, too, when they have re-evaluated their cases. It was brought home to us by restudy of all the material (27 cases) listed in our files under the heading of Ewing's sarcoma during the past 20 years. Among the cases so listed, there were some in which the material was so poor in well preserved tumor cells that we would now hesitate to make the diagnosis of Ewing's sarcoma on that basis alone. Although some of the lesions may have been Ewing's sarcomas, we must have been largely guided by the clinical, and especially the roentgenographic, findings in arriving at that diagnosis. There were also a number of cases in which restudy showed that our original diagnosis of Ewing's sarcoma had been incorrect, and, specifically, that we had erroneously included under this diagnosis some cases in which the bone lesion under consideration was actually a myeloma, a lymphocytic lymphoma, an anaplastic metastatic carcinoma, or a metastatic neuroblastoma. After excluding all cases in which the available tissue was defective in quality or inadequate in amount and those in which the

original diagnosis now seems clearly to have been erroneous, there remained the 17 cases upon which the present report is based.

The characteristic cytology of Ewing's sarcoma, irrespective of the source of the neoplastic tissue, is manifested through the presence of smaller or larger fields of tumor cells which lack clearly delimited cell boundaries, the nuclei being crowded together and of fairly uniform appearance. These nuclei are round or ovoid, are about twice as great in diameter (or, in the case of the ovoid ones, perhaps three times as great in the longer axis) as the nucleus of a lymphocyte, and have finely divided or powdery chromatin and often one or more nucleoli. As a rule, the individual nuclei appear enmeshed in, and slightly separated by, a loose, more or less vacuolated cytoplasmic fabric. In some fields, however, they may be found crowded together (perhaps to such an extent that many of them are even pressed into an oval shape), and in such fields there is but little cytoplasm between them. It should also be noted that in the fields presenting the general cytologic picture just described, vascularity is usually not a prominent feature (Figs. 13 and 14).

Cellular areas showing the characteristic cytology described above have to be searched for in the specimen taken for biopsy from the presenting bone lesion in an individual case, since the neoplastic tissue may have undergone abundant secondary changes, such as degeneration and necrosis. Degeneration is indicated in the nuclei by pyknosis and reduced size, and such nuclei are likely to be surrounded by a narrow zone of cytoplasm with a delimiting cell border. It is such cells that approximate most closely the picture given by Ewing for the type cell, to wit: a small polyhedral cell with pale cytoplasm, a small hyperchromatic nucleus, and a well defined cell border. Intermingled with the fields in which the tumor cells are undergoing degeneration there are usually areas in which the cells have undergone necrosis. Degenerating, but particularly necrotic, neoplastic tissue may, in some places, be heavily infiltrated by polymorphonuclear leukocytes (Fig. 15). Hence, if only a limited fragment of tissue is examined and sufficient care is not taken, this picture may be misinterpreted as representing an infectious process rather than a tumor. In connection with the presence of polymorphonuclear leukocytes in degenerating and necrotizing neoplastic tissue, we have found no evidence in favor of the concept once suggested that Ewing's sarcoma usually arises in marrow previously altered by fibrosing or sclerosing osteomyelitis.

Free hemorrhage into fields of neoplastic tissue, especially if it is extensive, comes to be associated with the ingrowth of many blood

vessels into those fields. If the neoplastic tissue in these areas is not necrotic, one will note that many of these vessels are collared by tumor cells. However, the vessel spaces are not lined by tumor cells, and between the latter and the lining cells there is tissue representing the wall of the vascular space. Thus, while it is true that in such fields one does see tumor cells about capillary spaces or around larger vascular spaces in a so-called "perithelial" arrangement, one does not see this orientation of tumor cells to any pronounced extent except in connection with hemorrhage. It is on this account that no distinctive cytologic significance attaches to such findings. Similar perivascular orientation of tumor cells is observed in connection with sarcomas of other kinds in which focal areas have undergone extensive hemorrhage (Fig. 16).

We turn now to the question of the presence of rosette (or pseudorosette) formations. In connection with an occasional Ewing's sarcoma, authors have reported and illustrated formations in which cells are arranged circularly (although not around a vessel) in so-called rosette formation. However, in such illustrations it can be seen that the centers of these formations represent degenerated cells with shadows which are still perceptible, rather than fibrillar or granular cores as in neuroblastoma. We think that the "pseudorosettes" illustrated by Gharpure [18] in his case of Ewing's sarcoma clearly show that the core about which the viable tumor cells are circularly disposed represents a mass of necrotic tumor cells, the outlines of which are still plainly visible. Also, the "rosettes" illustrated in the case presented by Foote and Anderson [19] seem likewise to appear in tissue fields where cells are undergoing necrosis. In our own material, we also have occasionally encountered a tumor field in which viable tumor cells were disposed about cores of degenerating cells. In one case this was a rather prominent feature, but even then the formations were not clearly suggestive of the rosettes of neuroblastoma (Figs. 17 and 18).

Finally, we come to the question of reticulum fibrils in Ewing's sarcoma. It appears that these are not a consistent nor a prominent feature of the histologic picture. Indeed, there is considerable variability in regard to these fibrils, from lesion to lesion and even from part to part of the same tumor section. Some of the lesions, in part or throughout, have at most only a few stray argyrophil fibrils in an entire low-power field. Other lesions show more numerous fibrils, but even in them the fibrils are irregularly distributed and are seen only between smaller and larger groups of tumor cells. In no tumor did we regularly see large fields of tissue showing a lattice or meshwork of reticulum fibrils outlining not merely cell groups, but the individual

tumor cells. In view of this variability, it is clear that there is no characteristic histologic pattern for Ewing's tumor in so far as these fibrils are concerned.

The Problem of Primary Reticulum Cell Sarcoma of Bone in Relation to Ewing's Sarcoma

In 1939, in an article entitled "Primary Reticulum Cell Sarcoma of Bone," Parker and Jackson [14] called attention, on the basis of 17 cases, to a malignant bone tumor which they held to be distinctive and, in particular, to be different from Ewing's sarcoma, with which it is most often confused. They believed this tumor to be derived from the reticulum cells of the marrow of the affected bone, and indicated that the cell type of this tumor was identical with that of reticulum cell sarcoma of lymph nodes and other tissues, and that diagnosis of the condition must rest upon tissue examination. As to the histology of the tumor, they stated that the cell nucleus, which is from one and one-half to two times larger than in a lymphocyte, varies in shape from round to oval; frequently, it may be indented or lobulated. The chromatin may be finely divided and scattered, or, on the other hand, it may be coarser and nucleoli may be present. There may be considerable cytoplasm about the nucleus. Evidence of ameboid activity, as indicated by the oval or elongated shape of the cell and its nucleus, is frequently present and is a characteristic feature. Binucleate forms occur, but true tumor giant cells do not. Mitotic figures are often present in large number. When the neoplastic tissue is stained in order to bring out the reticulum, the latter is found to run in delicate threads and strands around groups of tumor cells and also between individual cells.

Thus, on cytologic grounds, there seem to be some tangible, although not striking, differences between the tumor described by Parker and Jackson [14] and Ewing's sarcoma. Stout,[18] however, found himself unable to distinguish between the two even on a cytologic basis, holding that they are simply variants of the same tumor. On the other hand, it is evident from the revised (1939) classification by the Registry of Bone Sarcoma of the American College of Surgeons that Ewing [11] accepted the concept of primary localized reticulum cell sarcoma of bone as a tumor entity, and equally evident that he held it to be distinct from the Ewing tumor. The article by Edwards [20] supplied further support for the concept of primary localized reticulum cell sarcoma of bone and gave details of a case which was followed through to autopsy. The article by Gall and Mallory,[21] although devoted to the problem of malignant lymphoma in general, likewise sustained this

thesis and pointed out that sometimes a malignant lymphoma arises as a solitary lesion in the marrow of a single area of bone, and tends to remain localized there for a long time before spreading even to the adjacent lymph nodes. In particular, Gall and Mallory indicated that among the relatively infrequent instances in which a malignant lymphoma takes this clinical form, cases of clasmatocytic lymphoma (one of their two varieties of so-called reticulum cell sarcoma) are prominent. In their Table IV (page 404), they list 6 cases of clasmatocytic lymphoma which appeared to be initially localized to a bone.

Clinically, a primary reticulum cell sarcoma of bone presents itself as a painful, destructive lesion, often extensive, but localized to the area of bone in question, while the general health of the patient is good. When it is a long bone that is affected (as is most often the case), the end and much of the shaft are usually involved, and a neoplastic fracture may have resulted. The roentgenographic picture is not distinctive, showing only that one is dealing essentially with an osteolytic lesion, which may have broken through the outer bounds of the cortex and extended into the surrounding soft parts. In this respect, the roentgenographic picture is interchangeable with that of Ewing's sarcoma. As to treatment, Parker and Jackson [14] stressed the practical value of early diagnosis (by biopsy) followed by immediate amputation or ablation if the lesion is in a site permitting this, and otherwise by wide local excision if possible. They further advocated that this should be followed by local radiation therapy, but pointed out that such therapy by itself is inadequate. Of the 17 patients whose cases are discussed by them, 7 who received appropriate treatment have been apparently free from tumor for 10 years or more. In several of the other cases death supervened, but in none of these was an autopsy done. However, there were indications that late in the course of the disease the tumor may extend to the regional lymph nodes and even spread distantly by way of the blood stream.

It is a knotty problem to decide whether, and if so to what degree, one should differentiate between primary reticulum cell sarcoma of bone and Ewing's sarcoma. Certainly, in view of its reliable sponsorship, the concept of reticulum cell sarcoma of bone should not be lightly pushed aside. If further clinical experience supports the current observation that primary reticulum cell sarcoma of bone has a definitely more favorable prognosis (if correctly and promptly treated) than Ewing's sarcoma, there will be a good practical reason, also, for preserving the distinction. If, in a given case, the cellular structure favors a diagnosis of reticulum cell sarcoma of bone and there is as yet no clinical evidence of distant spread of the tumor, one would be all

the more justified (when the lesion is in a suitable site) in urging prompt amputation or ablation of the affected part.

The Problem of Neuroblastoma with Skeletal Metastases in Relation to Ewing's Sarcoma

The fact that a sympathetic neuroblastoma (sympathicoblastoma) commonly metastasizes to bones has been known for a long time. Hutchison,[22] and Tileston and Wolbach [23] have pointed out that one can anticipate finding, at least at autopsy, a malignant adrenal tumor as the primary lesion in infants and children clinically presenting tumorous involvement of cranial bones, associated with proptosis from tumorous involvement of the orbital region and tumorous enlargement of the preauricular and other regional lymph nodes. From the cases reported by these authors, and from those which they collected from the literature (cases now assignable to adrenal neuroblastoma), it was evident that metastases to bones other than those of the skull are also often found, and that metastases to the liver, kidneys, and lymph nodes in general were among the other common findings.

Further progress in the understanding of sympathetic neuroblastoma has revealed that, although the adrenal medulla is the most common site of origin for these tumors, it is by no means the only one. Cases have been reported in which they arose from some part of the sympathetic nervous tissue elsewhere in the body, notably from the sympathetic chains, but sometimes even from the sympathetic tissue of organs. While infants and young children are the most common victims, occasional instances have been reported in which sympathetic neuroblastomas developed in adults. Also, it has become clear that in so far as the skeleton is concerned, the clinically presenting, destructive bone lesion (if there is one) may be in a long bone or some bone other than the skull.

In respect to cytology, Tileston and Wolbach [23] stressed the diagnostic significance, for the condition in question, of the finding (in various numbers) of tumor cells arranged in rosettes. It was Wright [24] who pointed out that these tumors take their origin from the pluripotential cells of the sympathetic nervous system, and that the rosettes are ball-like aggregations of tumor cells enclosing a small central meshwork of filamentous neurofibrils, some of which can be seen to constitute processes of the cells making up the periphery of the rosette. In addition, he pointed out that, aside from rosettes, one may be able to find, as also peculiar to neuroblastoma, masses of tumor cells interspersed with and penetrated by fibrils running parallel in bundles. But the demonstration of neurofibrils, either in parallel bundles or as a meshwork in the center of the rosettes, may be difficult. Specifically,

in a given case, few fibrils may have been laid down, or, by degeneration or post-mortem change, such fibrils as were laid down may have become transformed into hyaline or granular material and be difficult to demonstrate on this account. This is especially true of the fibrils of the rosettes. Under such circumstances, whatever rosettes are present appear as formations in which several rows of cells surround a finely granular, eosin-staining mass without a central lumen.

In a particular case, rosettes may be fairly numerous in both the primary growth and the metastases, conspicuous in the primary growth and sparse in the metastases, or difficult to find in either. As to the type cell of the tumor, there are differences from lesion to lesion, depending on the predominating level of maturation. In the most primitive type, the dominating cell maintains the lymphocytoid character of the parent stem cell. This cell is thus a small round cell (strongly resembling a small lymphocyte) with a dense hyperchromatic nucleus practically filling the entire cell so that there is little cytoplasm. Some of the cells, although maintaining this general character, may be oval, while others, especially at the periphery of the rosettes, may be piriform. In more differentiated sympathetic neuroblastomas, the cells, although mainly round, are distinctly larger than those just described and may have vesicular nuclei and a clear ring of cytoplasm about the nucleus, and even some cytoplasmic processes. In still further matured neuroblastomas, some tumor fields may even show sympathetic ganglion cells.

Against this background, we are in a position to understand Willis' point of view on neuroblastoma in relation to Ewing's sarcoma. Prior to the publication of the first relevant article by Colville and Willis [7] in 1933, it seems not to have been adequately stressed that care must be taken to exclude the possibility that one may be dealing with a sympathetic neuroblastoma metastatic to the skeleton in cases supposedly representing Ewing's sarcoma of bone. In that article a case is detailed (as is another one in 1940 [8]) in which there was a presenting tumor in a femur which had the usually accepted clinical and roentgenographic characteristics of Ewing's sarcoma. In these cases the clinical course, and in particular the susceptibility of the tumor to radiation therapy, seemed to support this diagnosis. It should be pointed out that in neither case were rosettes found in the material taken for biopsy from the femoral lesions. However, in both cases it was revealed at autopsy that the femoral tumor was a metastasis from a neuroblastoma, primary in an adrenal in one instance and in the left lumbar sympathetic chain in the other. In both cases rosettes were found only in the primary growth.

On the basis of these experiences, Willis [8] expressed great wariness

about a diagnosis of Ewing's sarcoma made on clinical (including roentgenographic) grounds alone. He cast doubt also upon the reliability of biopsy in this connection, and analyzed, largely to reject them, the findings in the relatively few cases published prior to 1940, which had been interpreted as Ewing's sarcoma proved by autopsy. His paper of 1940 bears careful reading for its evaluation of the reported autopsied cases of Ewing's sarcoma, even if it does appear that in some instances he has been over-critical in the standards he set.

There can be no doubt that Willis [8] was correct in holding that a presenting bone lesion which is in fact a metastasis of neuroblastoma may not be recognized as such on the basis of biopsy, and the following case from our own material illustrates this. The patient was a boy, 3 years of age, who was admitted because of pain in the left hip region and limping of 3 months' duration. A roentgenogram revealed a rarefying lesion in the neck of the left femur, resorptive destruction of the cortex in this area, and some periosteal new bone deposition on the cortex of the adjacent portion of the femoral shaft (Fig. 19). On the assumption that the lesion was a low-grade osteomyelitis, it was curetted, but this assumption could scarcely have been made if the child had been studied thoroughly before surgical intervention, for, on admission the child already presented a dilated left pupil, and evidences of general lymphadenopathy, especially prominent in the left cervical region. The tissue sections from the material curetted from the neck of the femur showed a malignant tumor. The tumor cells were supported in a connective tissue stroma which was loose in some places, rather collagenous in others, and tended to demarcate smaller or larger groups of the cells. The predominating type of cell was rather large and round, lacking a clear-cut cytoplasmic outline and having a large, pale, stippled nucleus. Although some smaller cells with dark hyperchromatic nuclei were present, a number of tumor giant cells, some of which had two or more nuclei, were also seen. The cytologic picture (Fig. 20) was not that which we associate with Ewing's sarcoma, nor, on the other hand, was it even vaguely suggestive of neuroblastoma. However, that the femoral lesion was in fact a metastatic neuroblastoma could be safely deduced from histologic examination of several enlarged lymph nodes from the left cervical region, which showed unmistakably the rosettes and other cytologic features of sympathetic neuroblastoma (Fig. 21). Unfortunately, we could not determine the site of origin for the neuroblastoma in this case, since there was no autopsy. The child died at home about 1 year after the onset of the complaints.

This case of sympathicoblastoma was peculiarly difficult to diagnose,

and makes us sympathetic to Willis' [8] contention that only carefully executed autopsies can prove or exclude neuroblastoma or completely justify a diagnosis of Ewing's sarcoma. However, that a large proportion of cases of sympathetic neuroblastoma have certain distinctive clinical and roentgenographic features which are useful in differentiating them from Ewing's sarcoma can be gathered from the mass of material on which Wyatt and Farber [25] have reported. As to our own 13 cases in which the diagnosis of Ewing's sarcoma was based on biopsy findings, it can be said that, in view of the uniformity of the cell type in these cases and its consistent resemblance to the cell type observed in the 4 autopsied cases, we feel reasonable confidence in assuming that we could not have been dealing in all 13 cases with metastases from neuroblastomas. This assumption seems all the more justified if one bears in mind that: None of the many tissue sections cut in these 13 cases showed the rosettes classic for neuroblastoma; if these 13 lesions represented metastases from neuroblastomas, the primary tumor in all these cases would have had to be silent and the cells in all the lesions would have had to be matured to, and only to, the sympathoblast level; all but one of these 13 patients was over 8 years of age, whereas the great majority of cases of neuroblastoma are seen in children under this age.

The Problem of Carcinoma and Other Malignant Tumors with Skeletal Metastases in Relation to Ewing's Sarcoma

The problem of the differential diagnosis of Ewing's sarcoma does not end with sympathicoblastoma, but may be raised also by metastatic carcinoma. That a solitary destructive bone lesion which is proved by biopsy to represent a metastasis may be the first clinical indication that the patient is suffering from carcinoma hardly needs to be stated. It is also common to find that, while the primary lesion is silent, the histologic picture of the neoplastic tissue in the biopsy specimen gives the clue to the site of the primary growth. Often, on the other hand, there is not sufficient cytologic differentiation to suggest the site of the primary lesion. Diagnostic difficulties arise in those cases in which the primary growth is silent and in which the neoplastic tissue in the metastatic focus is so undifferentiated as to present a more or less uniform pattern of round cells. Although this problem does sometimes arise in connection with biopsy diagnosis or even in connection with the evaluation of the autopsy findings in a suspected case of Ewing's sarcoma, it does not constitute a frequent or serious difficulty in the hands of an experienced pathologist. Still, Hirsch and Ryerson [26] pointed out that bronchial carcinomas (particularly small ones with

undifferentiated cells) may metastasize widely to the bones before being recognizable in the lung and thus raise problems of differential diagnosis from Ewing's sarcoma, a point of view also stressed by Sternberg.[27] Sternberg also cited a case in which a skeletal metastasis was regarded as Ewing's sarcoma, although he himself held that involvement of bone was secondary to an undifferentiated small-celled carcinoma of the breast.

Finally, it may not be amiss to point out that occasionally, in the course of evaluation of a biopsy specimen, one may have to make a differential diagnosis between Ewing's sarcoma on the one hand and Hodgkin's disease and lymphocytic lymphoma on the other. However, the latter conditions are so rarely primary in bones that one is not often confronted by this problem as a practical difficulty, and when they are not primary there the general clinical picture, in which involvement of lymph nodes occupies the foreground, helps to clarify the problem.

Prognosis and Treatment

With the exception of one patient, who was admitted to the hospital only 5 months ago and whose course is already downhill,* all of the patients in our series of 17 cases of Ewing's sarcoma have died. Some died within 6 months to a year, and all but 3 were dead within 3 years of the onset of the local clinical complaints. Of the 3 who survived longer, 2 lived for 3½ years and one for 5½ years after the onset of complaints. If calculated from the time of admission to the hospital, the period of survival is, of course, somewhat shorter in all cases. This doleful prognosis is also evident from the Memorial Hospital statistics recently cited by Coley,[28] who stated that of 71 cases there were none in which survival was beyond 5 years.

All of our patients received radiation therapy to the presenting bone lesion. However, it should be noted that these cases accumulated over the past 20 years, during which a good deal of progress has been made in radiation procedure, so that the results cannot be judged on a uniform basis. Also, in many of our patients, the presenting lesion was in a bone of the trunk, where the advantages of a large radiation dose are frequently more than counterbalanced by the danger of damage to internal organs. In addition, in those cases which ran a rapidly down-

* This patient died in August, 1946 (13 months after admission to the hospital) and autopsy amply confirmed the diagnosis of Ewing's sarcoma. Examination included a search for all possible primary sources of neuroblastoma. It further included the calvarium, practically all of the vertebral column (along with the sacrum), both innominate bones, the upper ends of both femora, part of a tibia, and many ribs. The marrow spaces of these bones were found extensively invaded by neoplastic tissue, which, where viable, showed the cellular characteristics of Ewing's sarcoma.

hill clinical course, it was almost certain that widespread metastases were already present at the time when radiation therapy was instituted and necessarily contributed to its ineffectiveness.

Inferences as to the influence of radiation therapy alone in the treatment of Ewing's sarcoma can best be drawn from those cases in which the disease is apparently still limited to a long bone. It is in these cases that cross-fire radiation of the whole affected bone from every possible angle is feasible, with a total tumor dose of as much as 4500 r. in one course of treatment, as advocated by Swenson.[5] Yet, in the 2 cases in our series which were adequately treated along these lines (one lesion in a fibula and the other in a humerus), and in which radiation therapy had a remarkable palliative local effect, the patients nevertheless succumbed to metastases 3½ and 5½ years, respectively, after the onset of the clinical complaints. Thus it would seem that radiation alone cannot be counted upon to produce a cure even in favorable cases. In such cases, radiation followed by surgery (amputation or disarticulation of the limb) may give better results, but our material includes no cases in which this combination has been tried. On the whole, we believe that even under the most favorable circumstances the ultimate prognosis in cases of Ewing's sarcoma is, as yet, very bad.

Summary and Conclusions

This study (based on 17 cases, 4 of which were autopsied) supports the existence, among the primary malignant tumors appearing in bones, of a tumor entity to which, because of Ewing's pioneer effort to single it out, the name of Ewing's sarcoma should be applied. Beyond the fact that it is a specific malignant tumor primary in bones, and that its cells show no osteogenic potentialities, there is still much to be learned in respect to its histogenesis. Study of the cytologic patterns in our material yields no support for Ewing's contention that the neoplastic cells are derived from capillary or vascular (or perivascular) endothelium. It is true that tumor areas which have become heavily invaded by blood vessels, especially in the wake of hemorrhage, often show tumor cells about capillary spaces or around larger vascular spaces in a so-called "perithelial arrangement," but perivascular orientation of the tumor cells is not a characteristic cytologic feature of this neoplasm. Also, when, in an occasional lesion, one finds formations in which cells show a ring-like arrangement (though not around a vessel), these formations can be seen to have resulted from degeneration of centrally located cells, the shadows of which are still perceptible. Such formations really have nothing in common with the rosette or pseudo-rosette formations of neuroblastoma.

We incline toward Oberling's idea that the tumor cells of Ewing's sarcoma are derived from the supporting framework (the reticular tissue) of the bone marrow, a framework which can be regarded as a mesenchymal or primitive form of connective tissue. Ewing described the type cell of the lesion as a small polyhedral cell with pale cytoplasm, a small, hyperchromatic nucleus, and a well defined cell border. However, as revealed in viable, well fixed and well stained neoplastic tissue, the type cell is actually found to have an ill defined cell border, little cytoplasm, and a fairly large, round or oval nucleus showing scattered chromatin. Nevertheless, to make a diagnosis of Ewing's sarcoma from a biopsy specimen, even if the latter is obtained by surgical incision, is sometimes difficult, because of secondary changes which the neoplastic tissue has undergone. Cell areas showing the characteristic structure are sometimes to be found only after many sections have been made and examined.

A diagnosis of Ewing's sarcoma on the basis of biopsy should not be made without giving consideration to the possibility that one may be dealing with a sympathetic neuroblastoma or anaplastic carcinoma metastatic to the affected bone. Such alternative possibilities as primary reticulum cell sarcoma of bone, Hodgkin's disease, malignant lymphoma, and even myeloma must be eliminated. If, in a patient suspected of having Ewing's sarcoma, enlarged lymph nodes are palpable (regionally to the affected bone, or elsewhere), these too should be examined anatomically, in consideration of alternative possibilities, since lymph nodes are not commonly involved in Ewing's sarcoma, at least in an early stage.

On the clinical side, in our cases of Ewing's sarcoma we found that the great majority of the patients were in the second decade of life. The clinical histories did not show trauma to be an instigating factor. In the majority of our cases, the presenting lesion was in a bone of the trunk. We found no evidence favoring the idea that the presenting bone lesion shows a characteristic, if not typical, roentgenographic picture of high diagnostic value.

Ewing's sarcoma has a most doleful prognosis, only one of the 17 patients in our series still being alive, and this one has been under our observation for only 5 months.* Fever, secondary anemia, and an increased sedimentation rate of the blood in a patient with Ewing's sarcoma are evidences that the course will be a fulminating one, ending in death within a few months. Radiation therapy alone, while often having a remarkable palliative local effect for some time, offers as yet but little hope so far as the ultimate issue is concerned. The combi-

* See footnote on page 64.

nation of radiation therapy with surgery in favorable cases would seem to be more promising, but has not yet received sufficient trial to warrant a statement about its effects.

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DESCRIPTION OF PLATES

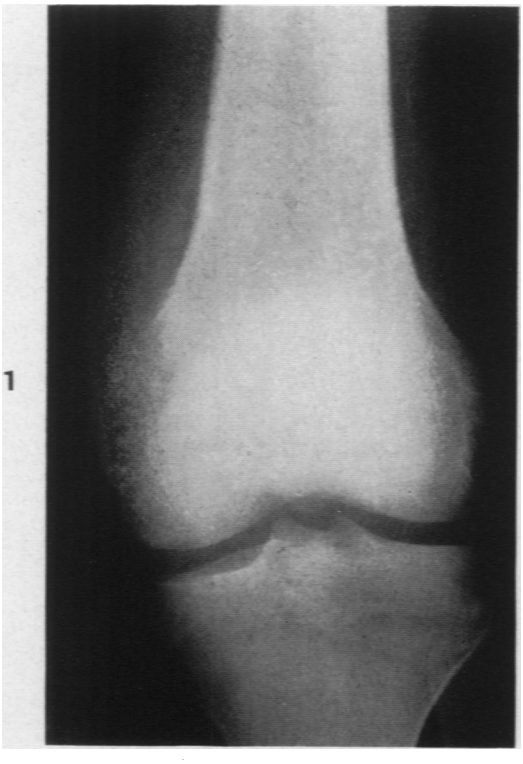
PLATE 8

FIG. 1. Roentgenograph showing rarefaction of a medial femoral condyle and of the cortex of the shaft just above the condyle. There is also an indistinct, small, soft tissue mass overlying the cortex above the condyle, the faint radiopacity representing periosteal new bone apposition. Although the picture suggests that the lesion might be a malignant tumor, there is nothing in it to justify the specific conclusion that it represents Ewing's sarcoma. The limb was disarticulated a week later, and Figure 9, showing the femur in coronal section, reveals how much greater was the actual involvement than was apparent roentgenographically. The patient, a male of 19 years, died 5 months after admission to the hospital, and an autopsy was done.

FIG. 2. Roentgenograph showing irregular rarefaction of the neck of a femur. The cortex is relatively unmodified and there appears to be no soft tissue mass overlying it. It would hardly be suspected from this picture that the lesion was a neoplasm. On a clinical basis, it was thought to be tuberculosis. Surgical intervention undertaken on this premise revealed Ewing's sarcoma. The patient, a boy of 14 years, died at another hospital 4 months after admission to our hospital, and no autopsy was done.

FIG. 3. Roentgenograph showing rarefaction and disruption of the lateral cortical outline of an iliac bone—a picture pointing clearly to the presence of a malignant tumor, although not necessarily Ewing's sarcoma. This was the picture of the presenting bone lesion on admission, and, although local clinical complaints were of only several days' standing, a tumor mass of the size of a neonate head could already be felt attached to the iliac fossa and the lateral aspect of the ilium. Pulmonary metastases were already present. The patient, a girl of 16 years, died 4 months after admission to the hospital, and an autopsy was done. Figure 11 shows the removed affected innominate bone in longitudinal section through the region of the acetabulum.

FIG. 4. Roentgenograph showing an extensive, destructive, rarefying lesion, involving the body and ascending ramus of a pubic bone and definitely suggesting a malignant neoplasm. This was the picture of the presenting bone lesion on admission, and the clinical complaints referable to the ipsilateral hip joint were already of 8 months' duration. At this time, lesions were evident in some other bones also and in the lungs. The patient, a girl of 17 years, died at another hospital about 8 months after admission to our hospital, and no autopsy was done.



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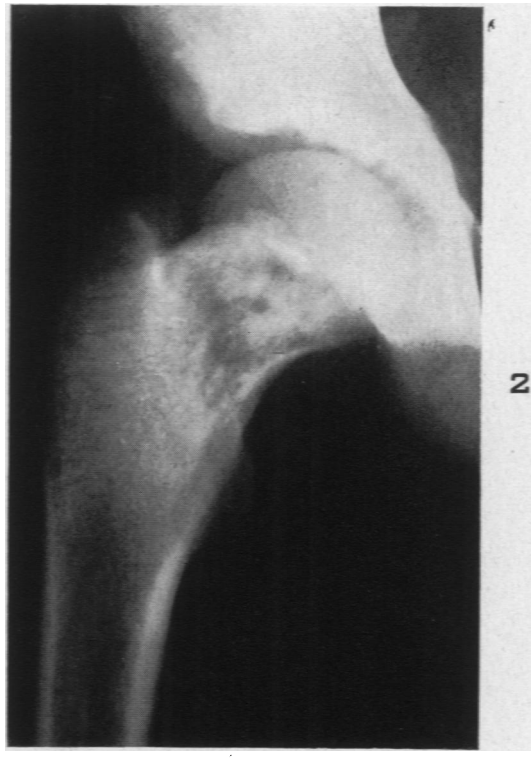

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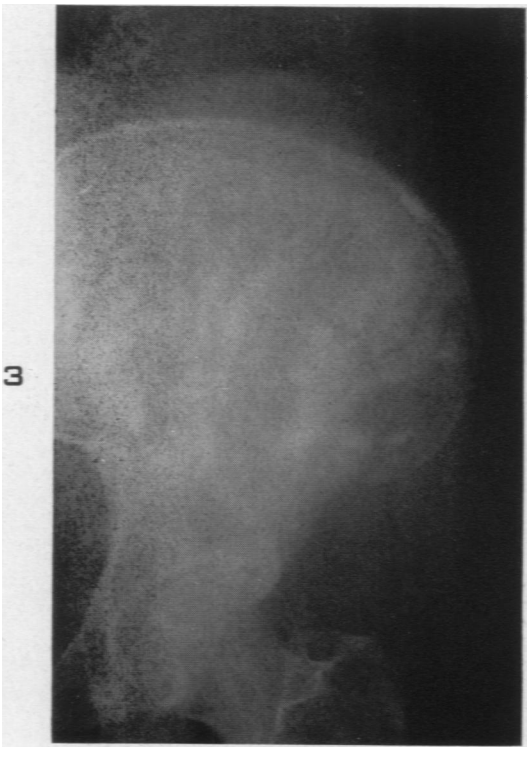

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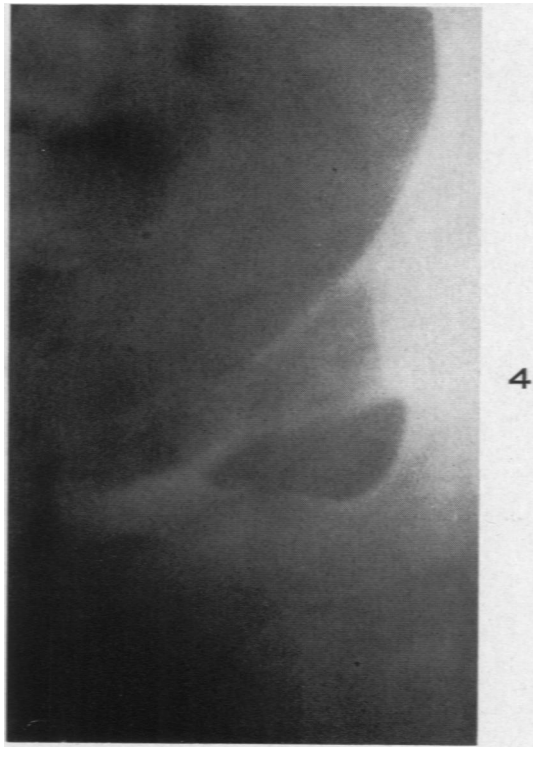

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Lichtenstein and Jaffe

Ewing's Sarcoma of Bone

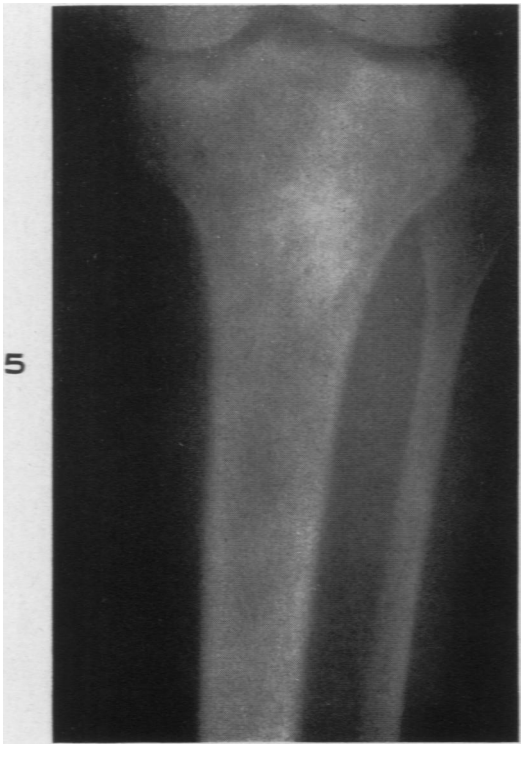
PLATE 9

FIG. 5. Roentgenogram showing extensive mottled rarefaction of the upper half of a tibia without any significant deposition of new bone by the periosteum. Although the picture of this presenting lesion could suggest a malignant tumor, there is nothing in it to justify, by itself, the conclusion that the lesion represents Ewing's sarcoma. Clinically it was suspected that it had an inflammatory basis. However, it was a Ewing's sarcoma and the patient, a girl of 18 years, died 11 months after admission to the hospital. An autopsy was done at Montefiore Hospital.

FIG. 6. Roentgenograph showing extensive destructive rarefaction of the shaft of a humerus, associated with onion-skin-like periosteal new bone deposition in the lateral side and a thick mass of neoplastic tissue overlying the bone on its medial side. This mass, in its upper region, presented some transverse radiopacities. The picture is clearly that of a malignant tumor, but if one had to be guided by the roentgenograph alone one would say that the lesion was an "osteolytic" osteogenic sarcoma rather than a Ewing's sarcoma. The patient was a girl, 8 years old, who died at home 7 months after admission to the hospital, and no autopsy was obtained.

FIG. 7. Roentgenograph of the upper portion of the shaft of a humerus. The cortex is not thickened but presents an irregular, moth-eaten appearance, while the soft tissue tumor mass overlying it shows more or less transverse streaks of radiopacity. This picture, too, suggests an osteogenic rather than a Ewing's sarcoma. The patient was a male, 24 years of age, who died at home 5½ years after admission to the hospital, and no autopsy was obtained. (See also Fig. 8.)

FIG. 8. Punched-out rarefactions in the calvarium of the patient referred to in the legend for Figure 7, representing lytic destruction of the bone by neoplastic tissue. This was the appearance of the calvarium 6 months before the patient died. It is a nondescript appearance which could have been created also by plasmatocytic myeloma or metastatic carcinoma.



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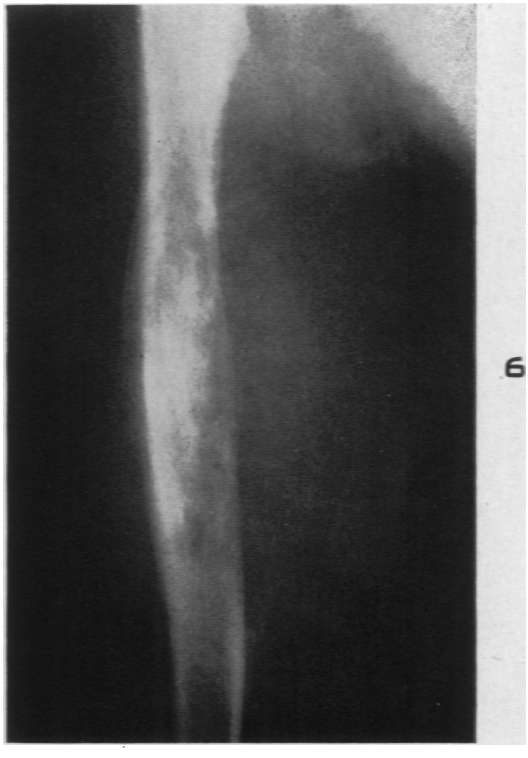

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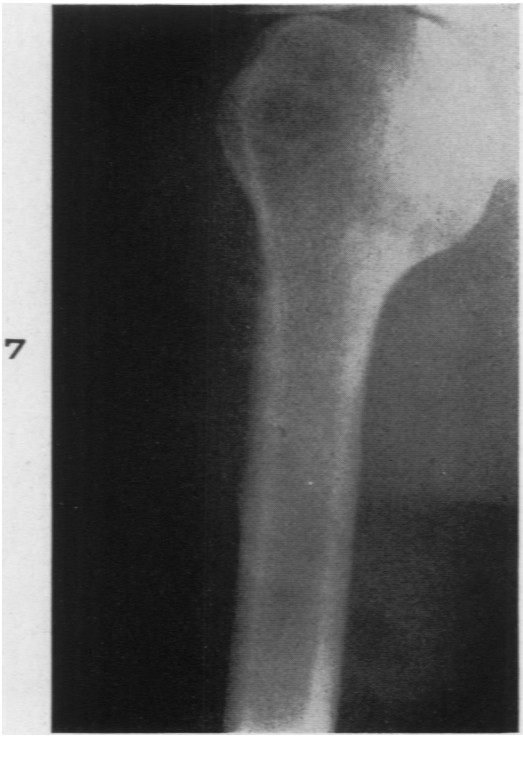

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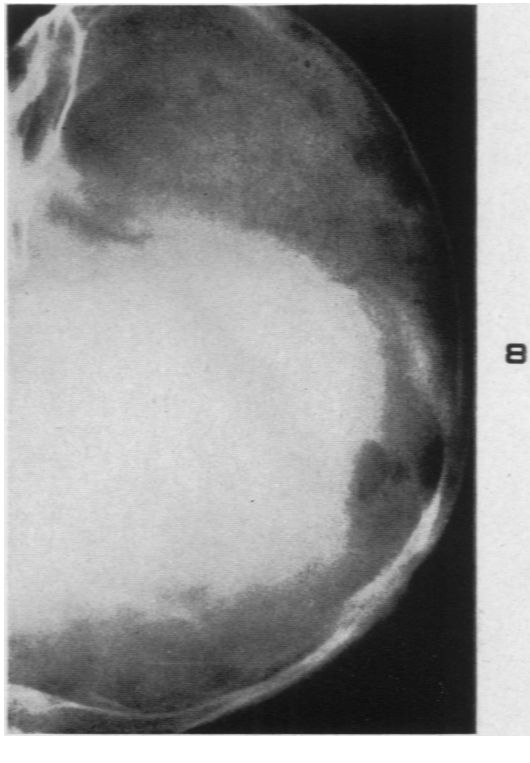

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Lichtenstein and Jaffe

Ewing's Sarcoma of Bone

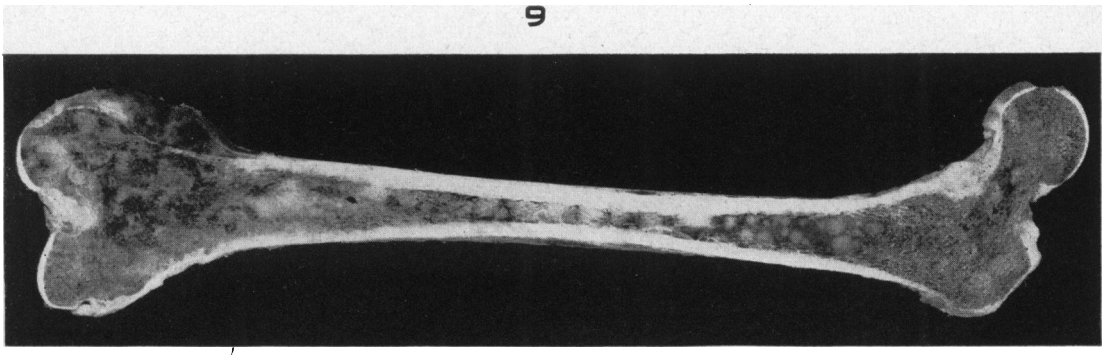
PLATE 10

FIG. 9. Photograph showing sagittally cut surface of the femur of which Figure 1 is the preoperative clinical roentgenograph. This picture shows clearly that the extent of tumorous involvement of the bone is far greater than could have been suspected from the preoperative roentgenograph. Of note are the nodules of neoplastic tissue at the upper end of the major marrow cavity.

FIG. 10. Roentgenograph of a thin slice of the bone, including the lower end, cut in the sagittal plane from the femur illustrated in Figure 9. Even here the actual extent of the involvement is not reflected roentgenographically.

FIG. 11. Photograph of the cut surface of the affected innominate bone, and the neoplastic tissue adherent to it, from the case illustrated in Figure 3. The bone is cut in the longitudinal plane, through the region of the iliac fossa. The iliac portion of the bone has been largely destroyed and replaced by a tumor mass visible to the left, while on the right is the tumor mass which extended into the pelvis.

FIG. 12. Photograph showing extensive tumorous involvement of part of the vertebral column in the case also illustrated in Figures 1, 9, and 10.



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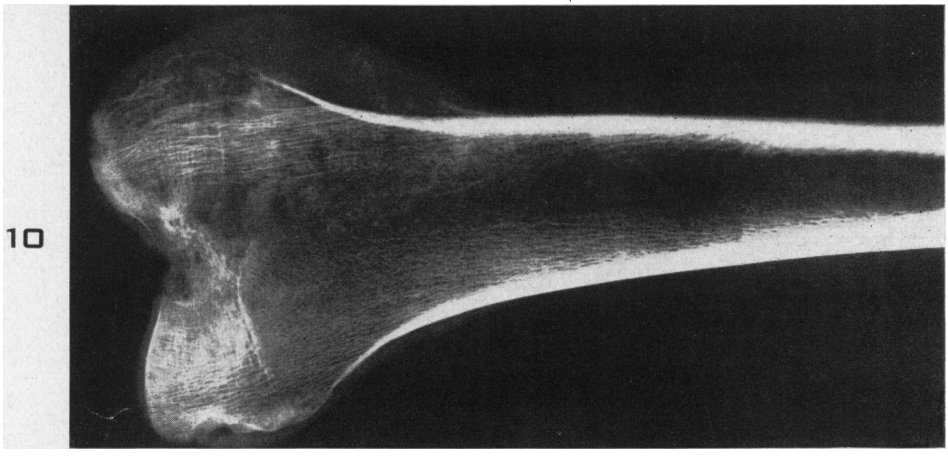

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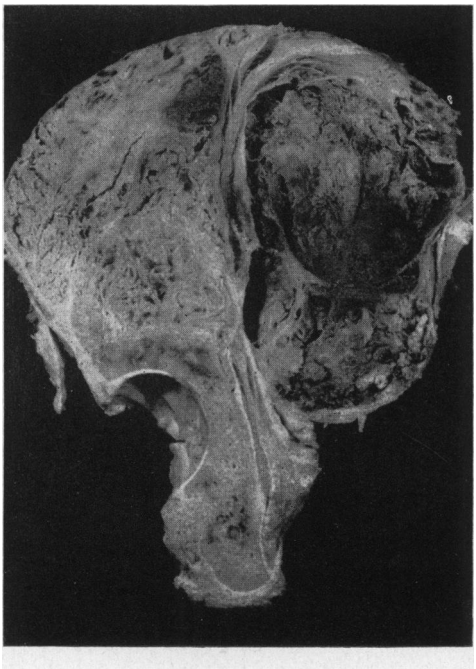

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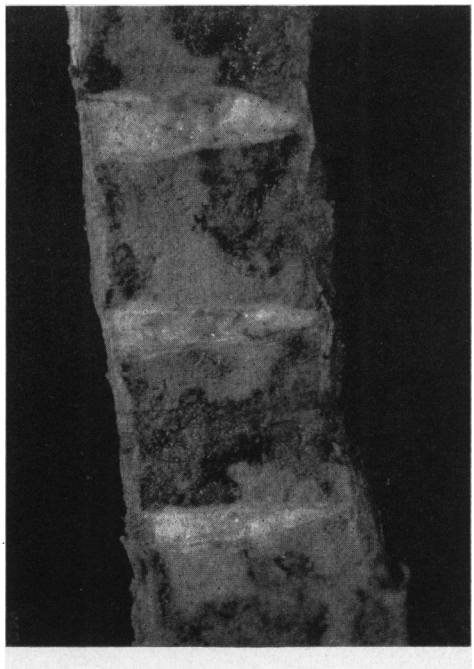

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PLATE 11

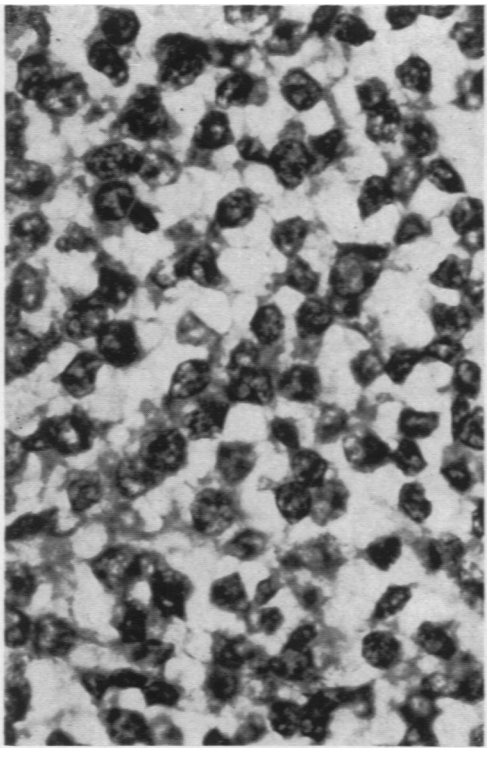
FIG. 13. Photomicrograph showing the general cytologic pattern in a cellular and relatively unmodified area of a Ewing's sarcoma. Neoplastic tissue is poor in blood vessels and the nuclei are enmeshed in a loose and more or less vacuolated cytoplasmic fabric. The tissue came from the case illustrated also in Figure 7. × 500.

FIG. 14. Photomicrograph showing the general cytologic pattern in a cellular and relatively unmodified area from a Ewing's sarcoma in another case. In this lesion, the nuclei are crowded together and the cell boundaries are not distinct. The tissue came from a male, 18 years old, in whom the presenting lesion was in a fibula and who died 3½ years after the onset of his complaints. × 500.

FIG. 15. Photomicrograph showing the cytologic pattern presented by most of the neoplastic tissue removed for biopsy, in the case illustrated also in Figure 4. From the tissue illustrated, in which small, dark, hyperchromatic nuclei are intermingled with leukocytes, it would not have been possible to tell that one was dealing with a tumor, much less a Ewing's sarcoma. It was only after many sections had been prepared from all the tissue submitted that a few microscopic fields of well preserved neoplastic tissue were found, permitting a diagnosis. × 250.

FIG. 16. Photomicrograph showing the cytologic picture presented by fields of grossly hemorrhagic neoplastic tissue in a case of Ewing's sarcoma in a male of 19 years, whose presenting lesion was in an iliac bone. It was only in the areas in which the neoplastic tissue was hemorrhagic and necrotic that one noted the pattern of tumor cells collaring capillary or larger vascular spaces. The tumor cells themselves do not make up the walls of the vascular spaces. × 250.

13



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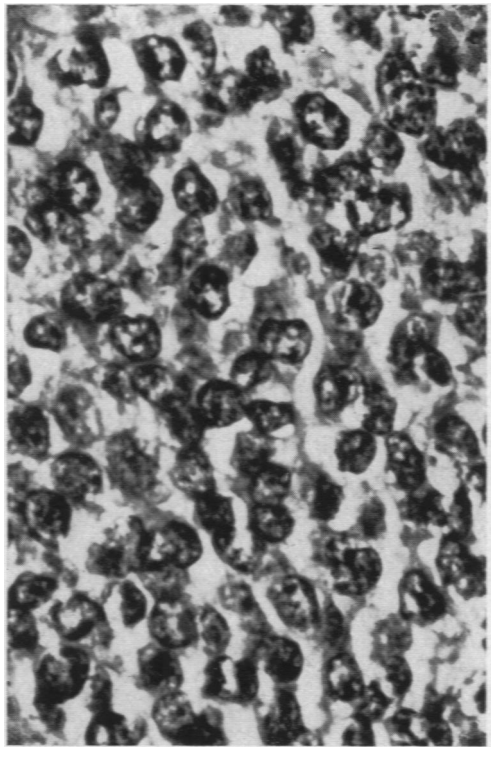

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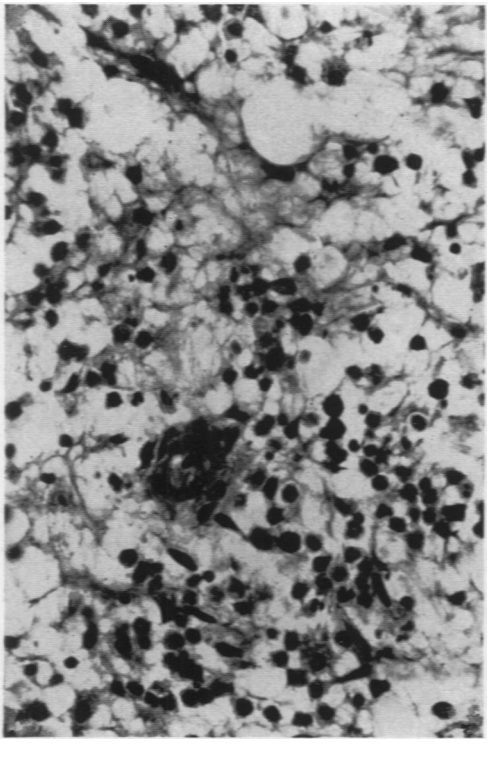

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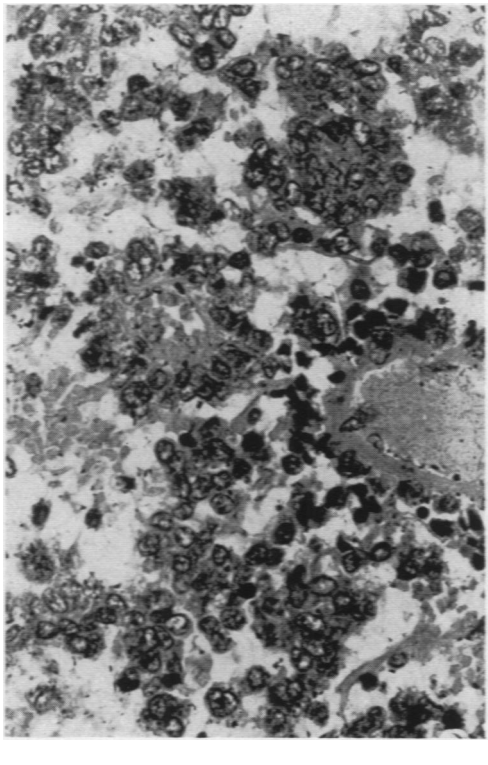

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Ewing's Sarcoma of Bone

PLATE 12

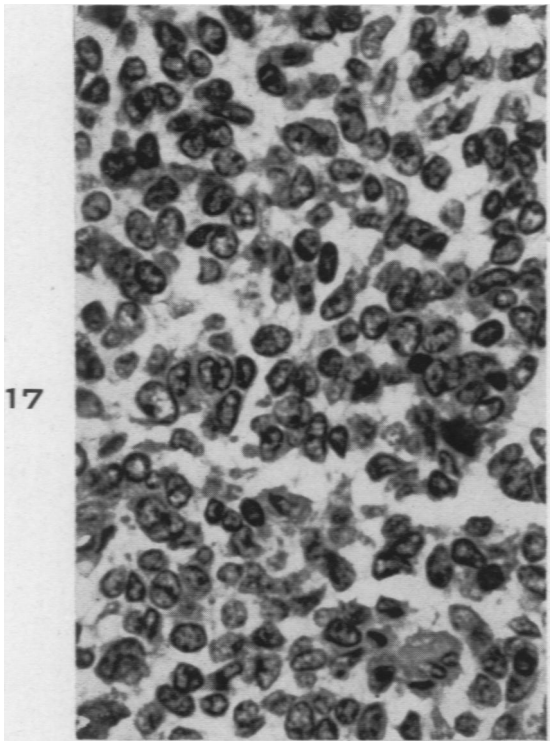
FIG. 17. Photomicrograph showing the general cytologic pattern of a tumor field in a metastatic lesion of Ewing's sarcoma in a rib in the case illustrated also in Figures 1, 9, and 12. As a result of cell degeneration in some places, there are suggestions of ring-like formations. (For comparison with Fig. 18.) × 500.

FIG. 18. Photomicrograph showing the general cytologic pattern of a Ewing's sarcoma in a fibula of a girl, 4 years of age. The "rosette-like" formations are constituted by rings of viable tumor cells surrounding cores of degenerated tumor cells, the shadows of which are still perceptible. Such spurious rosettes or pseudorosettes may be compared with the genuine ones shown in Figure 21. × 250.

FIG. 19. Roentgenograph showing a rarefying, destructive lesion in the neck of a femur, a lesion which was clinically considered to have an inflammatory basis. One could not tell from this picture that the lesion was actually a metastatic neuroblastoma. The patient was a boy of 3 years whose clinical complaints were pain in the involved hip region and limping of 3 months' duration.

FIG. 20. Photomicrograph showing the general cytologic pattern of the neoplastic tissue curetted from the femoral neck in the case illustrated in Figure 19. No more definitive diagnosis could be made from the curettings than that we were dealing with a malignant tumor. × 500.

FIG. 21. Photomicrograph showing the general cytologic pattern of an involved lymph node removed from the cervical region in the case illustrated in Figures 19 and 20. Of note are the classic rosettes, permitting a definitive diagnosis of sympathicoblastoma in this case. × 500.



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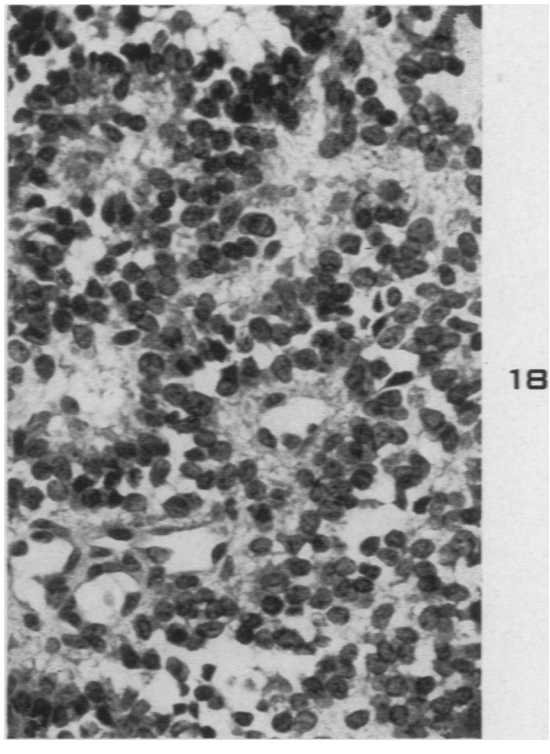

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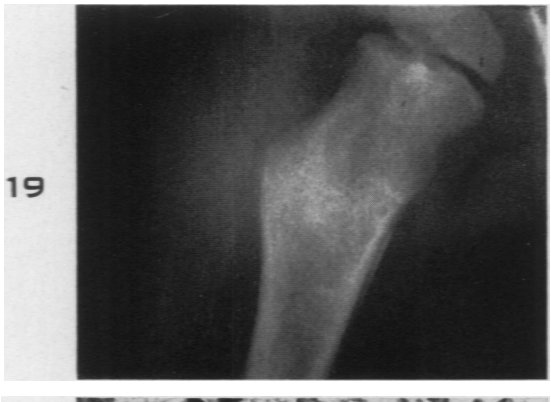

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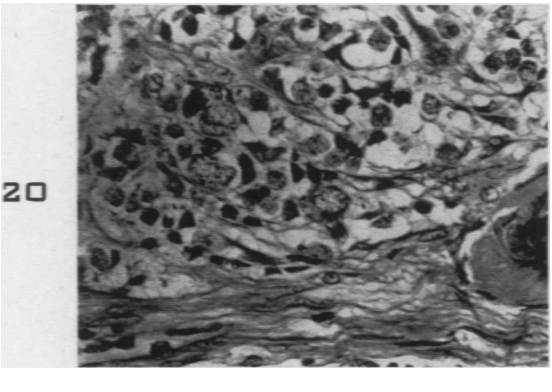

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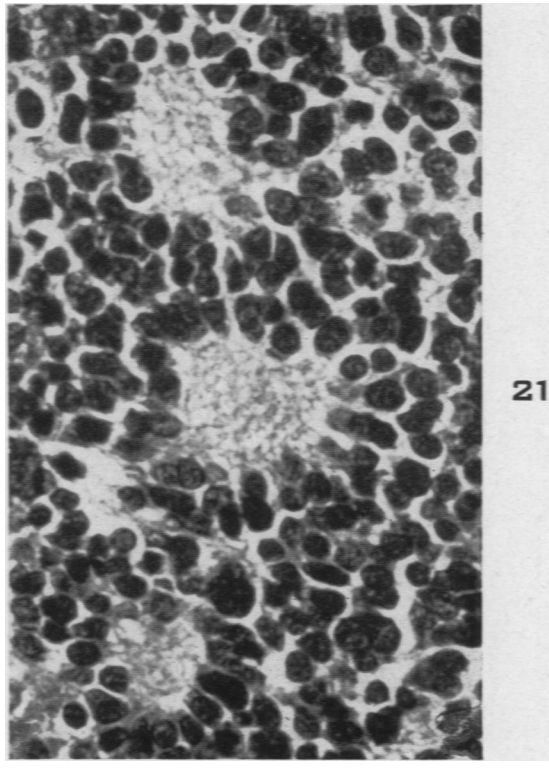

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