EOSINOPHILIC GRANULOMA OF BONE *

WITH REPORT OF A CASE

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This report concerns a peculiar lesion of bone that has apparently escaped general recognition. It is true that a few pertinent cases have been described in the literature, under one heading or another. Thus, Finzi [1] describes under the heading of "myeloma with prevalence of eosinophile cells," a case in which the lesion was in the frontal bone of a boy of 15 years. Mignon,[2] under the heading of "a granulation tumor of the frontal bone," gives a clinical and roentgenographic description of another case which may well be one in point but in which adequate anatomical confirmation is lacking. In this case the lesion also was in the frontal bone, and the patient was a boy of 12 years. Schairer [3] described 2 cases of a benign disease of the child skull (osteomyelitis with eosinophil reaction). In each of these cases the lesion was in a parietal bone, and in each again the patients were boys, of whom one was 9 and the other 10 years old. Schairer makes no mention of Finzi's case, and Mignon makes none either. Furthermore, these various case reports do not leave one with the impression of a clearly defined entity such as we consider the lesion to represent.

This lesion is designated "eosinophilic granuloma of bone" for reasons to be indicated presently. Our experience includes 1 case treated during 1938 in our hospital, and followed since, in which the lesion was in the femur of a 4 year old girl. We have also seen material from a case treated at another hospital in which the lesion was in the frontal bone of a 21 year old man, and from another case, in still a different hospital, with involvement of a rib of an 11 year old boy. These last 2 cases, seen in consultation, supplement the information gleaned from our own case. It is the latter case, however, that substantially provides the basis for the ensuing discussion, which will also take cognizance of the cases already

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reported under various headings in the literature and previously mentioned.

Eosinophilic granuloma of bone presents itself as a rather well localized, single lesion starting in the medullary cavity and tending to erode, expand and perforate the cortex in the bony site affected. When first observed the lesion may already have perforated the cortex and extended into the neighboring soft tissues. Indeed, the roentgenographic and clinical findings may lead one to suspect the presence of a malignant bone tumor. Surgical exploration shows that the affected portion of the bone has been extensively replaced by a more or less soft, yellowish or brownish tissue. In its microscopic appearance the latter is characterized essentially by the presence of compacted, tumor-like aggregates of large phagocytic cells, with conspicuous collections of eosinophilic leukocytes interspersed.

The interpretation of this picture is perplexing, for it does not suggest any classified disease of bone, either inflammatory or neoplastic, with which we are familiar. It seems to us that the condition in question may be regarded provisionally as a peculiar, inflammatory granulomatous lesion of indeterminate nature. We appreciate that the term proposed for this lesion is not altogether above criticism. It is true that we know nothing of the etiology of this granuloma. Nevertheless, the name we have given to this lesion at least serves to call attention to the heavy infiltration with eosinophilic leukocytes which is generally such a prominent and consistent histological feature.

Report of Case

Clinical History: The patient was a white female child, 4 years of age, who was admitted to the hospital on Nov. 7, 1938, because of pain and swelling of the left thigh of about 2 weeks duration. The past history was not significant except for the occurrence of whooping cough in 1936, and otitis media in 1937. The family history was irrelevant except for contact with two aunts who had had pulmonary tuberculosis.

Three weeks before admission the child began to cry at night and complain of pain and discomfort. At this time also the mother noted a limp. The following week the child began to localize the pain in the region of the left thigh and became plaintive and subdued, whereas formerly she had been quite active. During the week prior to admission these symptoms became more pronounced. No history of trauma was elicited.

Physical Examination: This revealed a fairly well nourished and well developed child who appeared ill and listless. The temperature ranged between

99 and 100.6° F. by rectum. The patient walked with a slight limp, holding the left leg abducted 10–15°. There was a slight, ill-defined swelling of the upper portion of the left thigh, the circumference of which was about 5/8 inches greater than that of the right thigh. Motion of the left hip was somewhat limited in all directions. There was definite tenderness over the anterior and lateral portions of the thigh, 3 inches below Poupart's ligament, corresponding to the area of maximal swelling. The superficial veins in the left groin appeared slightly dilated. The left inguinal lymph nodes were not enlarged.

Laboratory Examinations: A blood count gave the following values: hemoglobin 12.2 gm. (Sahli), red blood cells 4.0 million, and white blood cells 9200, with a differential count of polymorphonuclears 49 per cent, lymphocytes 45 per cent, eosinophils 4 per cent, basophils 1 per cent, and monocytes 1 per cent. Serum chemical estimations, including those of protein, sugar, nonprotein nitrogen and uric acid, were within the normal range. The Kahn test was negative.

Roentgenographs of the left femur (Fig. 1) disclosed an expanded, somewhat fusiform area of rarefaction within the proximal third of the shaft of the femur. This medullary defect extended from the intertrochanteric region down the shaft for a distance of approximately 3 inches. There was evidence of periosteal new bone deposition, which could be traced downward below the lesion to the junction of the proximal and middle thirds of the femur. The cortex at the site of the lesion was distinctly thinned in consequence of endosteal erosion, and appeared to be broken through in its proximal portion. There was suggestive trabeculation within the rarefied osseous defect. The X-ray picture was quite plausibly interpreted by the roentgenologist as probably indicating the presence of a tumor within the upper end of the femur. Roentgenographs of the other bones of the left lower extremity and of both upper extremities failed to disclose any other lesions.

Operation: A definite preoperative clinical diagnosis was not made, but the following tentative opinions were ventured: osteomyelitis, tuberculous osteitis and Ewing's tumor.

Operation was performed on Nov. 9, 1938. A 4 inch incision was made just below the trochanter on the lateral side of the femur. The periosteum was found congested and the cortex thinned. A cortical window was removed, exposing a cavity in the bone containing approximately 10–15 cc. of blood-tinged fluid and lined by a soft yellowish tissue which was thoroughly curetted. The wound was then closed tightly, without drainage.

Smears from the operative field revealed many polymorphonuclear leukocytes and a few lymphocytes, but no bacteria. Cultures of the swabbings were sterile after 48 hours. A guinea pig inoculated with tissue from the lesion showed no evidence of tuberculosis after 10 weeks.

Course of Illness: Two weeks after operation, because of the interesting picture revealed by the pathological examination of the lesion, the surgeon was advised to perform a sternal bone marrow biopsy. Microscopic study of the tissue thus obtained showed an increase in the proportion of eosinophilic myelocytes and young eosinophilic granulocytes. These cells constituted almost 15 per cent of the marrow cells. The neutrophilic polymorphonuclear leukocytes were not increased in number, nor did the other cellular elements of the sternal bone marrow appear to be significantly altered.

The postoperative course during the stay in the hospital was uneventful and the wound healed per primam. The patient was discharged from the hospital on Dec. 3, 1938.

On empirical grounds the child was given postoperative deep roentgen therapy. Subsequent roentgenographs suggested progressive filling in of the curetted bone area in the femur. When the child was last seen, about 1 year after operation, she appeared well and active, and was symptom-free. A differential white blood count done at that time still showed an eosinophilia of 5 per cent, however. This is undoubtedly an interesting observation, but its interpretation leads one into speculation.

Pathological Examination of Material from the Femur

The surgical specimen consisted of numerous fragments of soft yellowish green tissue curettings from the rarefied area in the upper end of the femur.

Sections stained with hematoxylin and eosin showed a striking histological picture, unique in our experience at that time. The non-osseous material was composed of a cellular tissue, densely infiltrated by large nests, indeed by whole sheet-like masses, of eosinophilic polymorphonuclear leukocytes which stood out vividly in the hematoxylin and eosin stain (Fig. 2). Interspersed between the collections of eosinophils were compacted, tumor-like aggregates of cells of fairly uniform type, with large, pale, oval or kidney shaped nuclei (Fig. 3). Their cytoplasm was pale staining and rather indistinctly outlined. Many of these cells had two or more nuclei. In addition there were an appreciable number of larger multinuclear (giant) cells present, not resembling megakaryocytes or osteoclasts, which had apparently resulted from coalescence of the basic proliferating stromal cells (Fig. 4). The latter had some superficial resemblance at first sight to myeloid tumor cells. Indeed, our initial impression was that the lesion might be an eosinophilic myelocytoma. Closer inspection, however, revealed that many of the cells in question contained phagocytozed eosinophils and erythrocytes, as well as eosinophilic and reddish brown granules. This feature was particularly well demonstrated by the Giemsa stain. The intracellular eosinophilic granules apparently resulted from disintegrated phagocytozed eosinophilic leukocytes, while the more brownish granules were identified as iron-containing pigment, presumably from broken-down red blood cells. Clearly then, the closely packed large cells which are so prominent a feature of the lesion represent large

phagocytes (Fig. 5). Whether these represent wandering macrophages, or histiocytes derived from the fixed tissue reticulum of the bone marrow, is difficult to decide.

In addition to the large aggregates of eosinophils there were present also plasma cells, small lymphocytes and neutrophilic polymorphonuclear leukocytes. However, there was no suggestion of abscess formation or other indication of a suppurative infection. In this connection it may also be pointed out that cultures for bacteria remained sterile. The lesion was moderately vascular, being permeated by capillaries and other thin walled blood vessels, and there were areas of extravasation and hemorrhage. The supporting connective tissue framework was delicate.

Sections of the osseous fragments showed the intertrabecular spaces to be infiltrated by the same type of tissue. The cortical bone was porotified but not at all necrotic. The enlarged vessel spaces contained fibrous tissue which was infiltrated by small round cells and a few leukocytes.

The condition was difficult to diagnose. We felt that the lesion represented a peculiar granuloma of bone of undetermined etiology. Our final diagnosis was eosinophilic granuloma of femur of undetermined etiology (possibly a virus granuloma).

Discussion

After observing this case, and appreciating its uniqueness, we were on the alert for other similar cases. In September, 1939, one of us (H. L. J.) was asked to see a case in consultation, which turned out to be pertinent. The patient was a boy 11 years of age who for several weeks had noted a swelling over one of his ribs. The X-ray picture of the lesion had been misread by everyone who saw the plate as indicating the presence of a malignant tumor, probably a Ewing's tumor.*

* This patient was seen through the courtesy of Dr. Murray H. Bass and Dr. Harold Neuhof, and he was operated upon at the Mount Sinai Hospital, New York City. A detailed written opinion on this case was submitted, drawing upon our experience with the femur lesion already discussed. This opinion included the statement that "certain features of the lesion suggest that it is some sort of a granuloma, but it does not fit into any of the well known granuloma categories." In the July issue of *The American Journal of Pathology* there appeared an article by Otani and Ehrlich entitled, "Solitary granuloma of bone, simulating primary neoplasm," which deals with a number of instances of the lesion in question here, but builds its discussion particularly upon this case. We are glad to know that

Subsequently material from a lesion in the frontal bone of a calvarium was shown to us, which was said to have broken through the inner table of the skull into the dura. This lesion had been surgically resected and the patient, a young man about 21 years of age, had been given postoperative roentgen therapy on the premise that he had a bone tumor. And yet, fully 6 years later, the patient was known to be alive and well. Examination of the microscopic sections showed that the lesion in question also resembled the one we had seen in the femur.†

With these 3 cases in mind, and appreciating that they constituted a lesion *sui generis*, we began searching in the medical literature for other similar cases. We found the 3 reports (covering 4 cases) already mentioned. These are simply case reports and present no detailed discussion of the lesion in question. It is interesting to note that in all of these cases the lesion was in the calvarium and had perforated one or both tables of the skull. While we cannot agree with the interpretations of the underlying pathology of the lesion implied in the titles chosen by the authors, their descriptions parallel our own findings rather closely. In connection with the microscopic lesions there are some slight histological variations from case to case, for instance in the degree of infiltration by eosinophilic leukocytes, the prominence of the histiocytic cells and the extent of phagocytosis, the number of giant multinuclear cells, and the vascularity of the lesion as a whole. However, the basic histological pattern remains essentially the same in all cases.

For reasons that have already been made clear in connection with the description of our pathological findings, we feel that the lesion in question represents neither a myeloma nor an osteo-

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Drs. Otani and Ehrlich have come to the same conclusion in regard to the latter.

We also wish to note in this connection the report on Case 26302 from the Case Records of the Massachusetts General Hospital, in *The New England Journal of Medicine*, July 25, 1940, 223, 149. On the basis of the pathological examination this case is reported as an instance of "eosinophilic granuloma of bone." In discussing the pathology of the lesion Dr. Tracy B. Mallory accepts our designation and interpretation of it as a specific and distinctive one.

† This case was seen through the courtesy of Dr. Herman Bolker. Since submitting our manuscript for publication we have had the opportunity of studying material from still another case which he kindly put at our disposal. In this case the patient was an infant 10 months old, in whom the lesion involved over one-third of the distal part of a radial shaft.

myelitis, as others [1, 3] have suggested, but rather some type of a granuloma. However, it does not fit into any of the recognized granuloma categories. We venture the suggestion that the lesion may conceivably represent a virus granuloma. We regret that the idea occurred to us after the surgical specimen from our principal case had been fixed in formalin, but we propose, in future, to preserve fresh tissue in 50 per cent glycerin for animal inoculation.

The finding of an increased proportion of eosinophilic myelocytes and young eosinophilic granulocytes in the sternal bone marrow in the case presented here suggests that there may be a systemic response to the etiological agent or factor. This tendency to active eosinophilic myelopoesis is also reflected by the finding in our case, and likewise in the reported cases,[1, 2, 3] of a significant eosinophilia in the blood smears, ranging between 4 and 10 per cent, and not ascribable to any other demonstrable cause.

In regard to the differential diagnosis, it should be pointed out that certain clinical features may lead one to suspect the presence of eosinophilic granuloma of bone even before surgical intervention is attempted. Among these considerations are the occurrence of the lesion in a child or a very young adult, a short history of painful localized swelling of only several weeks duration, roentgenographic evidence of a rarefied and destructive bone lesion (notably in the calvarium, but possibly in a rib or in a long bone), with perforation of the cortex and perhaps a palpable soft tissue mass overlying the affected bone. The finding of a slight or moderate eosinophilia (4–10 per cent) in the differential white blood count may also be helpful. If an aspiration needle puncture is done, examination of the tissue may reveal the presence of numerous eosinophilic leukocytes.

However, surgical exploration and pathological examination are really essential in establishing the definitive diagnosis. The microscopic sections readily enable one to rule out all types of ordinary malignant bone tumors, including Ewing's tumor, reticulum cell sarcoma, and spindle cell or osteolytic osteogenic sarcoma. Another condition, in particular, with which the lesion may conceivably be confused, namely solitary myeloma, may likewise be excluded by histological examination. Other osseous lesions from which the condition in question is to be differentiated need only be mentioned, *e.g.* the bone lesions of aggressive myeloid leu-

kemia, of Hodgkin's and of Hand-Schüller-Christian's disease, bone cyst, and posttraumatic rarefaction.[4]

Finally, one must consider the possible relationship of the condition in question to so-called eosinophilic leukemia or the clinical syndrome discussed by Bass [5, 6] under the heading, "Unusual eosinophilia with splenomegaly (eosinophilic leukemia?) in a child." This question is naturally suggested by the relatively high incidence in young individuals, and by the finding of active eosinophilic myelopoiesis and of eosinophilia in the circulating blood in cases of eosinophilic granuloma of bone. There are many essential features, however, pertaining to the clinical entity of so-called eosinophilic leukemia, which are entirely lacking in the condition with which we are dealing, namely a chronic clinical course, splenomegaly, enlargement of lymph nodes, pronounced eosinophilia (30–80 per cent), and persistent leukocytosis often reaching leukemic proportions. Moreover, in none of the case reports discussed by Bass was there any mention of the presence of focal, tumor-like bone lesions.

Treatment and Prognosis

The treatment of choice, as we see it, is wide surgical excision of the lesion. When the lesion occurs in a long bone, or in the calvarium, thorough curettage will suffice. A more radical procedure does not appear to be indicated. In regard to the value of, or necessity for, postoperative roentgen therapy, it should be mentioned that the patients in the foregoing reports did receive such treatment on empirical grounds and made a complete recovery. On the other hand, some of the published case reports previously cited state that satisfactory improvement was noted after surgery alone. This would indicate that postoperative roentgen therapy may not be essential to recovery.

Despite the rapid development of the condition and its seemingly aggressive nature, as reflected by a more or less ominous roentgenographic picture, the prognosis appears to be uniformly good. The postoperative follow-up observations, in all the cases in which this information was available, were gratifying indeed. In every instance complete relief of symptoms was noted and there was roentgenographic evidence of gradual repair of the eroded bone. The period of observation ranged from 7 months to 6 years. It seems fair to conclude that we are dealing with a benign lesion,

and that adequate surgical extirpation, with or without subsequent roentgen therapy, may be expected to effect a clinical cure.

Summary

This paper deals with a peculiar and hitherto not clearly defined lesion of bone which has apparently escaped general recognition. We propose that this lesion be designated "eosinophilic granuloma of bone." It presents itself as a rather well localized, single lesion, starting in the medullary cavity and tending to erode, expand and perforate the cortex in the bone site affected. The latter is found extensively replaced by a more or less soft yellowish or brownish tissue. In its microscopic appearance this tissue is characterized essentially by the presence of compacted, tumor-like aggregates of large phagocytic cells, with conspicuous collections of eosinophilic leukocytes interspersed. Many of these cells contain phagocytozed eosinophils and erythrocytes, as well as eosinophilic granules and brownish iron-containing particles. Some of them have two or more nuclei, and there is also a scattering of giant multinuclear cells.

We venture the suggestion that the lesion may conceivably represent a virus granuloma. The finding of a significantly increased proportion of eosinophilic myelocytes and young eosinophilic granulocytes in the sternal bone marrow in our case suggests a systemic response to the etiological factor. This tendency to active eosinophilic myelopoesis is also reflected in the finding of eosinophilia, usually ranging between 4 and 10 per cent and not ascribable to any other demonstrable cause.

The condition seems to have a predilection for children and very young adults, especially males. It has been noted most commonly in the calvarium. It pursues a rapid clinical course characterized by painful swelling and a tendency to pathological fracture or perforation of the affected bone. The duration of symptoms before the patient seeks treatment may be no more than a few weeks. Despite the rapid development of the condition and its seemingly aggressive nature, as reflected by a more or less ominous roentgenographic picture, the prognosis appears to be uniformly favorable. Our experience, and that of others, indicates that adequate surgical extirpation of the lesion, with or without subsequent roentgen therapy, may reasonably be expected to effect a clinical cure.

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DESCRIPTION OF PLATES

PLATE 117

FIG. 1. Roentgenograph of the left femur showing an expanded area of rarefaction within the proximal third of the shaft. Note the evidence of periosteal new bone deposition, extensive endosteal erosion and perforation of the cortex.

FIG. 2. Microphotograph of the lesion in the femur showing large focal collections of eosinophilic leukocytes. The deeply staining clumped cells are all eosinophils. × 150.

FIG. 3. Higher magnification showing eosinophilic polymorphonuclear leukocytes dispersed among large phagocytic cells. The leukocytes containing large granules are eosinophils. × 475.

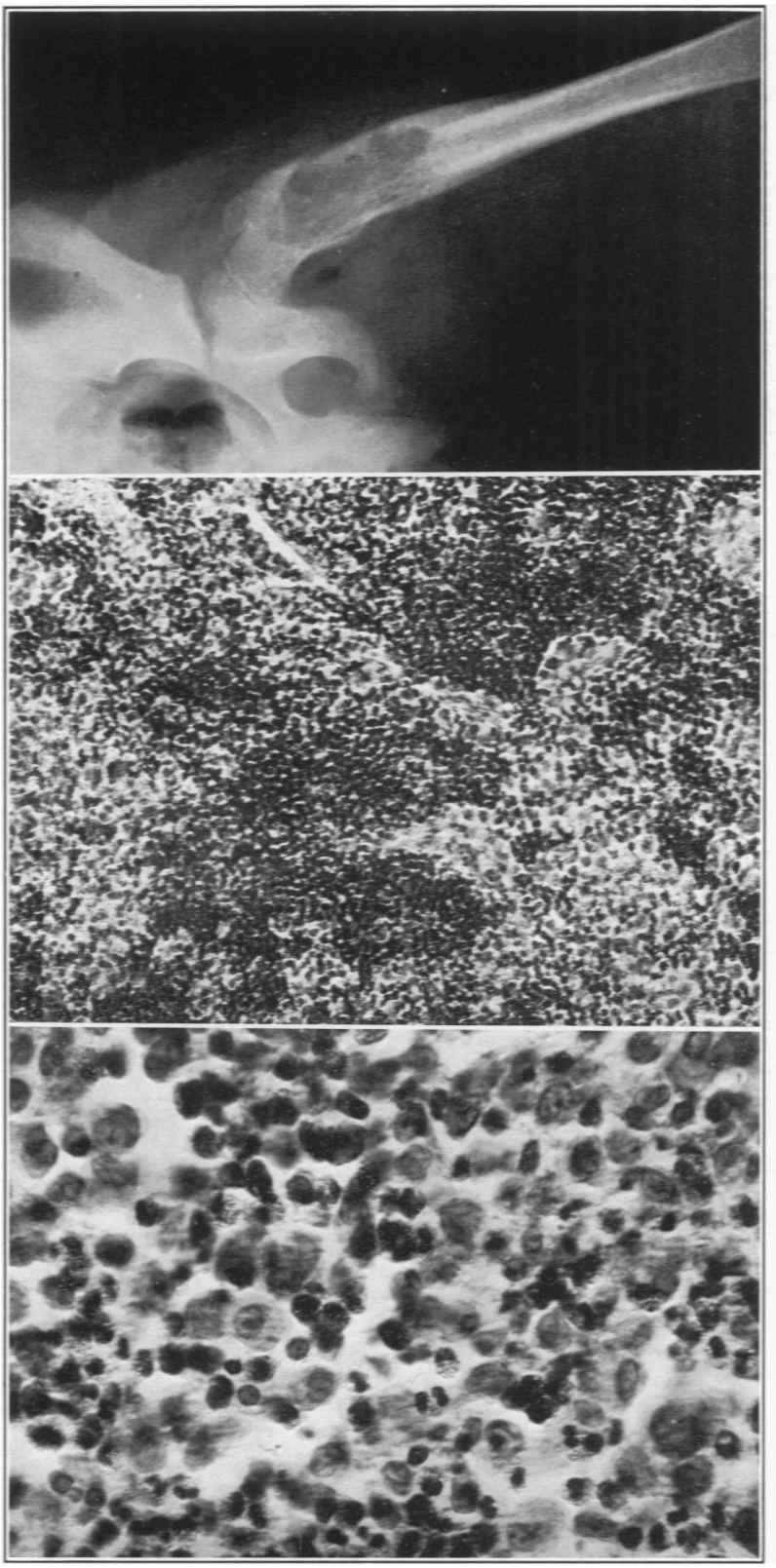
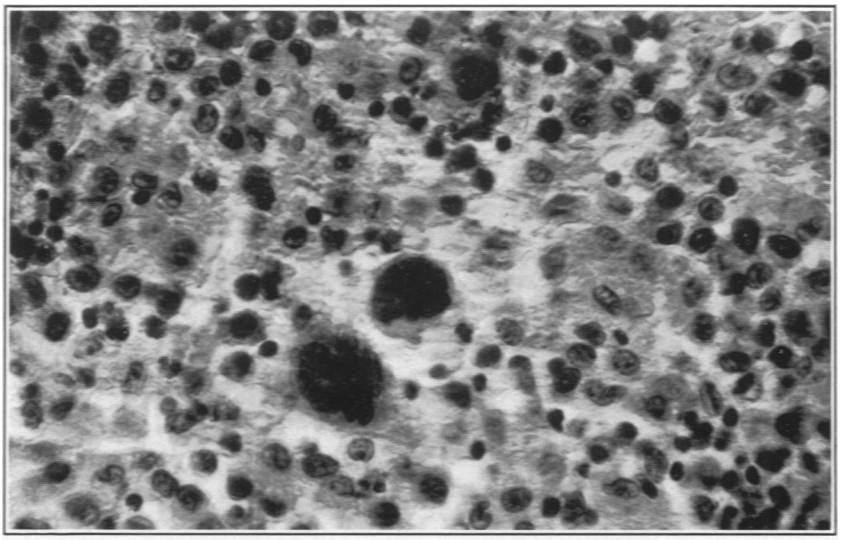


PLATE 118

FIG. 4. Microphotograph of the lesion in the femur showing a number of large multinuclear (giant) cells. Note that they resemble neither megakaryocytes nor osteoclasts. × 350.

FIG. 5. Higher magnification showing a compacted tumor-like aggregation of large phagocytic cells. Note that many of them have more than one nucleus. Some of these cells contain phagocytozed eosinophils and erythrocytes, as well as eosinophilic granules and iron-containing particles. × 700.



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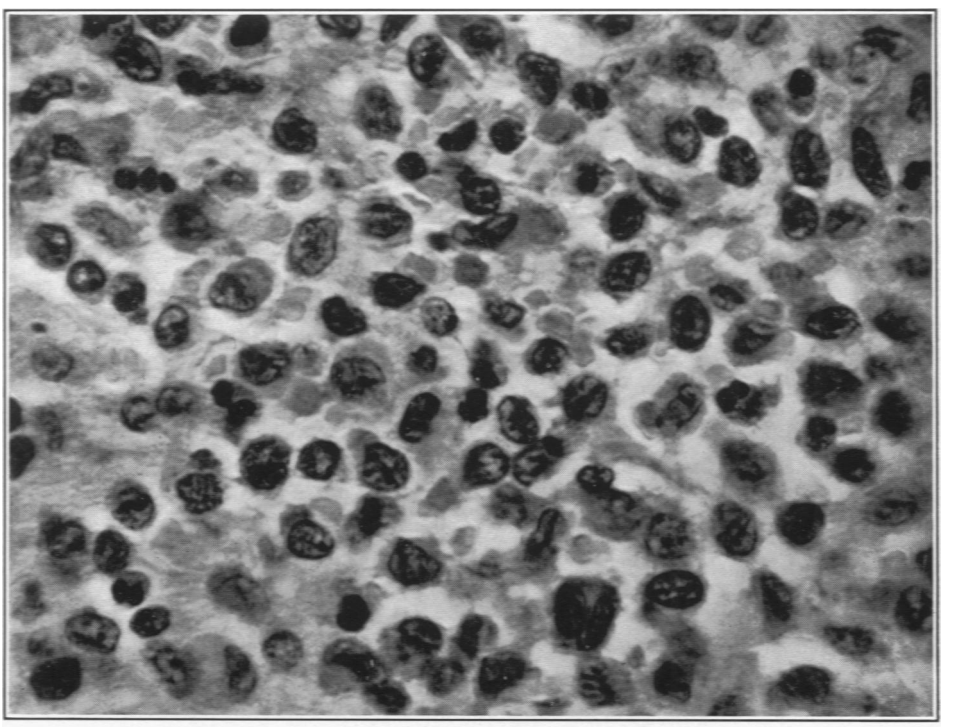

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Lichtenstein and Jaffe Eosinophilic Granuloma of Bone