EOSINOPHILIC GRANULOMA OF BONE AND ITS RELATIONSHIP TO
HAND-SCHÜLLER-CHRISTIAN AND LETTERER-SIWE SYNDROMES

FRITZ SCHAJOWICZ and JORGE SLULLITEL, BUENOS AIRES, ARGENTINA

From the Latin-American Registry of Bone Pathology, Centre of Osteo-articular Pathology,
Italian Hospital, Buenos Aires

Eosinophilic granuloma was formerly mistaken for “eosinophilic myeloma” (Finzi 1929) or for “osteomyelitis with eosinophilic reaction” (Schairer 1938). It was described as a new distinct entity by Otani and Ehrlich (1940) under the denomination solitary granuloma of bone and by Jaffe and Lichtenstein (1944) as eosinophilic granuloma of bone. Farber (1941) and Green and Farber (1942) showed that eosinophilic granuloma could appear also in multiple locations and did not represent an entity but was related to Hand-Schüller-Christian’s disease and Letterer-Siwe’s disease. They introduced the term destructive granuloma of bone.

Galeotti-Flori and Parenti (1937) and Wallgren (1940) had previously suggested that Hand-Schüller-Christian disease and Letterer-Siwe’s disease were the chronic and acute manifestations of the same basic process—namely a systemic reticulo-endothelial granulomatosis: they described transitional cases.

The concept that these entities are only different clinical manifestations of a single pathological disorder has gained wide acceptance (Gross and Jacox 1942; Jaffe and Lichtenstein 1944; Engelbreth-Holm, Teilum and Christensen 1944; Schajowicz and Polak 1947; Ponsetti 1948; Nezelof and Guibert 1963; Enriquez, Dahlin, Hayles and Henderson 1967; Cheyne 1971). Schajowicz and Polak proposed the general term histiocytic granuloma for this group of disorders, which may appear without or with only isolated eosinophils (pure histiocytic granuloma), or, more commonly, with more or less numerous eosinophilic leucocytes (eosinophilic histiocytic granuloma) involving a single or several bones. On the other hand some of the histiocytes may transform themselves into lipid-bearing xanthoma cells (histiocytic xanthogranuloma). They pointed out the different modes of presentation of the histiocytic granuloma and emphasised that intermediate or transitional stages of different clinical importance might occur.

Lichtenstein, one of the most enthusiastic supporters of the unified concept, proposed in 1953 the name histiocytosis X as a broad designation under which the different types of clinical involvement could be grouped and differentiated for purposes of treatment and prognosis. He emphasised that an increasing number of lesions could start outside bone or be restricted to extraosseous sites (Lichtenstein 1964).

Yet some dissenting opinions still persist (Otani 1957, McGavran and Spady 1960, Ackerman and Spjut 1962, Fowles and Bobechko 1970). From a retrospective study of fatal and non-fatal cases Lieberman, Jones, Dargeon and Begg (1969) also considered the unifocal and multiple lesions as distinct processes with different prognostic significance. This divergence of opinion is in part due to the fact that the etiology of these entities still remains unknown, although there are several features that suggest that they represent some kind of immun allergenic process (Schajowicz and Polak 1947; Rewald 1960; Avioli, Lasersohn and Lopresti 1963) or other type of reaction to some peculiar infection, possibly viral (Lichtenstein 1964). Certain histological features and the favourable results of corticosteroids (Bass, Sapin and Hodes 1953; Avioli and colleagues 1963) and antibiotic treatment (Aronson 1951, Fisher 1953, Dargeon 1965, 1967) in some cases seem to confirm these hypotheses, supported also by earlier electron microscopic studies reporting cellular inclusions of possible viral type (Basset, Nezelof, Mallet and Turiaf 1965; Basset, Nezelof and Turiaf 1966). However, more recent investigations have likened these findings to those observed in Langerhans cells of normal skin, which
are now considered as histiocytic elements (Cancilla, Lahey and Carnes 1967; Friedman and Hanaoka 1969; Morales, Fine, Horn and Watson 1969).

The terms histiocytosis, eosinophilic granuloma, histiocytic granuloma and reticuloendotheliosis, among others, are now the ones most frequently applied to the general disease, including all variants, and it has been emphasised that the subdivisions are not sharply defined, transitional forms existing between the different entities, especially in those cases of multiple lesions, where arbitrary criteria often have to be adopted to classify them as pertaining to a determinate syndrome.

The term Hand-Schüller-Christian syndrome, which originally referred to the classic triad of skull defects, exophthalmos and diabetes insipidus, is now more broadly used to include instances of more chronic evolution, occurring generally in children older than three years, with multiple cranial lesions and sometimes involvement of other systems or with one of the other classical symptoms (exophthalmos or diabetes insipidus). The complete triad was only rarely found in the reported cases (six cases in the series of 129 cases reviewed by Cheyne) and was lacking in all but one of our cases.

The following criteria for the diagnosis of Letterer-Siwe syndrome, given by Doede and Rappaport (1967) in a long survival study, have been adopted: age of onset less than three years; clinical findings of fever, otitis media and recurrent bacterial infection; anaemia, haemorrhages, hepato-splenomegaly and diffuse non-tender lymphadenopathy; osteolytic bone lesions and, most characteristically, cutaneous manifestations often suggestive of seborrhoeic eczema. According to Lichtenstein the course is acute or subacute and the evolution commonly fatal, long survival being an exception (five instances among ninety-six adequately documented cases reviewed by Doede and Rappaport (1967)).

We want to emphasise that we consider these entities not as diseases but only as syndromes—that is, as different, often not well limited, clinical manifestations of the same basic disorder, characterised fundamentally by the proliferation of differentiated reticulo-histiocytic elements of granulomatous type, usually accompanied by more or less numerous eosinophilic granulocytes and other inflammatory cells. The histiocytes may show secondary changes such as transformation into lipid-bearing foam cells (xanthoma cells) or phagocytosis of blood pigment and cellular debris.

The purpose of this paper is to review cases classified histologically as histiocytic or eosinophilic granuloma of bone and to discuss its clinical manifestations. Our conclusions are based on the study of 106 cases filed in our laboratory during the last twenty-nine years. Since we are concerned predominantly in the study of osteoarticular pathology, only very few examples of extraskeletal lesions have been studied (five cases relating to skin, lymph nodes or mucosa). We have included only those cases with at least one biopsy of a bone lesion. Most of our material comes from orthopaedic departments and only a small number from children’s hospitals in Buenos Aires and other cities in Argentina. This explains the fact that most of our cases (seventy-six) concern solitary lesions, which disagrees with statistics from other institutions which are dealing principally with paediatric material and in which multiple or disseminated lesions with Hand-Schüller-Christian and Letterer-Siwe syndrome clearly predominate (Batson, Shapiro, Christie and Riley 1955; Avery, McAfee and Guild 1957; Oberman 1961; Fowles and Bobechko 1970).

MATERIAL AND TECHNIQUE

One hundred and six cases were studied in our laboratory during the twenty-nine years up to the end of 1969 and filed at the Latin-American Registry of Bone Pathology. All cases come from the different orthopaedic departments and children’s hospitals of our country, and only those with sufficient clinico-radiological and pathological details and followed for at least one year have been included. In eighty-five cases the material was obtained by open biopsy.
or curettage and in fifteen cases the complete resection specimen was available (rib in nine cases, clavicle in five cases and mandible in one case). In twenty-one cases the diagnosis was made from aspiration biopsy, later confirmed by operation in most cases. In a few cases more than one biopsy was performed.

In addition to routine staining of paraffin sections, including smears or imprints on several occasions, the following special staining methods were used, whenever possible on frozen sections: Del Rio Hortega's silver stain for reticulin fibres and for reticulo-endothelial elements and specific stains for lipids (Sudan III and Sudan black).

In one case part of the tissue obtained from lesions of the skull and skin was fixed in 2 per cent glutaraldehyde buffered in sodium cacodilate at 5 degrees Celsius, post-fixed in 1 per cent osmium tetroxide, dehydrated in graded alcohols and embedded in Epon for electron microscopy. Ultra-thin sections were stained with uranyl-acetate and lead citrate and examined with a Siemens electron microscope.

**CLINICAL CHARACTERISTICS**

In order to facilitate the study we divided our material into different categories according to the classification shown in Table I. In some cases precise classification was difficult or even impossible: for these cases the denomination transitional or intermediate type was adopted.

**TABLE I**

**CLASSIFICATION OF LESIONS**

<table>
<thead>
<tr>
<th>Solitary</th>
<th>Histiocytic granuloma</th>
<th>Multiple or disseminated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Acute and subacute (Letterer-Siwe syndrome)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Intermediate or transitional</td>
<td></td>
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</tbody>
</table>

According to this classification the distribution of our 106 cases was as follows: solitary eosinophilic granuloma, seventy-six cases (72 per cent); multiple eosinophilic granuloma, nine cases (8 per cent); Hand-Schüller-Christian syndrome, fifteen cases (14 per cent); Letterer-Siwe syndrome, two cases (2 per cent); intermediate or transitional, four cases (4 per cent).

The large number of solitary bone lesions is due, as stated before, to the fact that our laboratory receives material principally from orthopaedic departments and in much less proportion from paediatric clinics, where the multiple or widely disseminated lesions generally predominate.

**Age**—The age incidence and relationship of solitary and multiple lesions is shown in Figure 1. The age of predilection for the solitary lesions was between one and fifteen years (forty-seven cases or 62 per cent) with a peak between five and ten years. The extreme limits ranged from one to fifty-three years. The number of patients over twenty years was only twenty-one (27.7 per cent). Figure 2 shows that lesions in the older patients (over twenty years) are more commonly found in ribs (67 per cent), mandible (57 per cent), clavicle and scapula (50 per cent each) and skull (30 per cent). In the cases of multiple locations, including those of the Hand-Schüller-Christian syndrome and Letterer-Siwe syndrome, there was a clear predominance of occurrence under fifteen years of age (twenty-five out of thirty cases) with a predilection for the first five years (sixteen out of thirty cases).
The age limits, according to the clinical type, are shown in Table II. In several patients the process started as a solitary lesion but multiple foci, with or without the features of Hand-Schüller-Christian or Letterer-Siwe syndromes, developed after a few months, usually before six months. In none of our cases did a new focus appear in a solitary lesion after one year, which authorises us to predict a favourable prognosis if no other lesion occurs during this period.
Sex—There was an evident predominance of males, with seventy-two cases out of a total of 106 cases, the ratio being 2:17 to 1. If we consider only the solitary lesions, the male predominance was even a little higher, with fifty-three males and twenty-three females (2.30 to 1).

Site—The most frequent sites affected by the solitary lesions and the relationship with age (under and over twenty years) are shown in Figure 2. There was a clear predominance of occurrence in ribs (67 per cent) and mandible (57 per cent) over the age of twenty years, as

<table>
<thead>
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<th>Syndrome</th>
<th>Minimum age (years)</th>
<th>Maximum age (years)</th>
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</thead>
<tbody>
<tr>
<td>Solitary eosinophilic granuloma</td>
<td>1</td>
<td>53</td>
</tr>
<tr>
<td>Multiple eosinophilic granuloma</td>
<td>3/4</td>
<td>34</td>
</tr>
<tr>
<td>Hand-Süller-Christian syndrome</td>
<td>2</td>
<td>39</td>
</tr>
<tr>
<td>Letterer-Siwe syndrome</td>
<td>1/2</td>
<td>1/2</td>
</tr>
<tr>
<td>Intermediate or transitional syndrome</td>
<td>1/4</td>
<td>24</td>
</tr>
</tbody>
</table>

TABLE II
AGE LIMITS FOR THE VARIOUS SYNDROMES

Fig. 3
Multiple lesions, with one in the femoral head.

Fig. 4
Radiograph showing multiple osteolytic lesions surrounded by bone sclerosis in the right iliac bone and another small lesion in the left femoral head. Figure 4—a new lesion occurred two months later in the sixth cervical vertebra with the radiographic aspect of "vertebra plana". (Multiple eosinophilic granuloma without Hand-Süller-Christian syndrome.)

also a predominance of the skull under twenty years (70 per cent): all the long limb bones were liable to be involved in patients under twenty years of age; lesions also occurred in the vertebrae and ilium.

In multiple lesions, with and without the features of Hand-Süller-Christian or Letterer-Siwe syndromes, the bones most frequently affected were the skull and femurs. For this reason it seems to us that in every case of eosinophilic granuloma of the skull a radiograph of at least both femurs is indicated, or vice versa.

The clinical symptoms were not characteristic in solitary or multiple lesions without an accompanying syndrome. Pain, with increased local tenderness, was the most common initial complaint, followed by swelling or a tumour nodule, especially in the skull, but rarely by limping when located in a long limb bone or in the pelvis.
In two cases, located in ribs, a pathological fracture occurred. The laboratory findings were usually negative, though there was leucocytosis in six cases, with a slight eosinophilia (over 4 per cent) in four of them, as also in two other cases without leucocytosis.

In twenty cases (two of them multiple) the sedimentation rate was moderately elevated, usually with a Katz index around 25. In one of the few cases in which a sternal marrow puncture was performed 15 per cent eosinophilic leucocytes were found.

**Radiographic features**—Radiographically the lesions appeared usually as ovoid or rounded, well-limited, translucent defects generally within the medullary cavity and surrounded by slightly denser, often scalloped edges. In long limb bones the lesion was usually located in the diaphysis, and less commonly in the metaphysis, and in only one case in an upper femoral epiphysis (Fig. 3). The cortex was often eroded, but generally only slightly distended, and an evident periosteal reaction with new bone formation of onion skin type was a frequent finding, simulating osteomyelitis or a Ewing’s sarcoma (Figs. 5 and 6).

In the spine the vertebral body was usually partly or completely collapsed (Fig. 7), so that finally a flat disc of bone very similar to “vertebra plana” was produced. This was described by Calvé as an osteochondrosis analogous to Perthes’ disease, and was first identified with eosinophilic granuloma by Compere, Johnson and Coventry (1954).

The skull lesions were of a characteristic punched-out appearance of variable size, frequently multiple and often confluent in Hand-Schüller-Christian syndrome (Figs. 8 and 9). In Letterer-Siwe syndrome the osteolytic defects of the skull, as also in other bones, were usually not so conspicuous and generally smaller, the extra-skeletal manifestations predominating (Figs. 10 to 13).
Boy 11 years old. Antero-posterior and lateral radiographs showing cuneiform compression fracture of the anterior portion of the first lumbar vertebra (early stage of "vertebra plana").

Lesions on the skull of a boy. Figure 8—At the age of 12 years. Radiograph showing the typical "geographic map" aspect of the skull. The patient had several lesions in other bones (ribs, pelvic girdle, femur, humerus, clavicle), and had exophthalmos but not diabetes insipidus. Figure 9—Fourteen years later. Note the total disappearance of the bone defects after radiotherapy. Three years later there was a small recurrence in the skull, which responded to radiotherapy. The patient was alive and free of symptoms seventeen years later.

PATHOLOGICAL FINDINGS

Gross pathology—In most cases the material was obtained by curettage and consisted of numerous small, irregular fragments of greyish-pink material, sometimes brownish in colour, alternating with haemorrhagic or yellowish zones. These last are normally scanty but occasionally may predominate, such as in the extensive osteolytic lesions of the skull, especially
The evolution of a case of Letterer-Siwe syndrome. Figure 10—Boy aged 9 months, with anaemia, adenopathy, hepatosplenomegaly and cutaneous and pulmonary lesions. Radiograph shows multiple transradiant lesions in the skull. Figures 11 and 12—Three years later. Figure 13—After another three years. After treatment with steroids and x-rays the lesions have regressed.
Figure 14—Photomicrograph of a solitary lesion in clavicle, showing numerous histiocytes with pale ovoid nuclei alternating with (dark) eosinophil leucocytes. Note the small blood vessel with prominent endothelium (a). (Haematoxylin and eosin, ×400.) Figure 15—Photomicrograph of a lesion in a case of multiple bone lesions, without Hand-Schüller-Christian syndrome. There is a mixture of predominating eosinophils, histiocytes and several multinucleated giant cells with peripheral nuclei. (Haematoxylin and eosin, ×400.)

Figure 16
Photomicrograph of a smear of the lesion in the same case, showing details of the eosinophils (a) and histiocytes, with one (b) or two (c) nuclei. (May Grünwald-Giemsa, ×900.)
in the multiple lesions with Hand-Schüller-Christian syndrome—that is, in processes of apparently long evolution. In these cases wide areas of frankly fibrous appearance have also been observed.

In addition to this fragmented material, we had the opportunity of studying several complete resection specimens, especially of ribs (eight) and clavicles (five) which permitted us to observe more clearly the gross aspects. In these cases the process was usually located centrally, the cavity being occupied by a haemorrhagic, friable, granulation-like tissue, often showing necrotic, puriform zones, frequently well limited towards the neighbouring spongiosa by a scalloped sclerotic border, but sometimes without a clear limit. The cortex was thinned or broken in some cases with infiltration of the soft tissue by a friable, partly puriform material, simulating occasionally a suppurative process. In three cases reactive periosteal bone formation was observed.

![Photomicrograph of a lesion in a case with an initial solitary lesion of the femur which became disseminated after four months, presenting later the complete Hand-Schüller-Christian triad (case illustrated in Figure 27). There is intense proliferation of differentiated reticulo-histiocytic cells with only a few isolated eosinophils, simulating a reticulo-sarcoma. (× 600.)](image)

**Microscopic pathology**—The histological sections showed a mixture of palely stained reticulo-histiocytic elements (histiocytes), often forming more or less compact areas or cords, with a variable number of eosinophil leucocytes and lymphocytes, plasma cells, neutrophil granulocytes and fibroblasts. The reticulo-histiocytic cells have large ovoid, indented or reniform pale nuclei, with inconspicuous nucleoli, and usually well limited cytoplasmic borders (Figs. 14 to 16). Mitotic figures are very rare. The structure, however, is not uniform, varying in different cases, as also in different fields in the same case. In many cases eosinophils were so abundant that the diagnosis could be made without any difficulty, but in others they were very scarce or completely lacking in many fields, the intense histiocytic proliferation predominating (Fig. 17), thus producing problems of differential diagnosis with reticulo-sarcoma. This mistake was made in the case of a lesion in a rib after examination of a specimen obtained by aspiration biopsy. Later examination of the resected rib revealed the true diagnosis. Most of the histiocytes are mononucleated, but all transitions to multinucleated giant cells with few or several nuclei, sometimes disposed peripherally, were observed (Fig. 15). With special fat stains abundant droplets of Sudanophilic fat in the middle or periphery of the cytoplasm could be demonstrated in several giant cells ("Touton cells") (Fig. 18).
Photomicrographs from different zones of the same case of a solitary lesion of a rib, showing eosinophils and other inflammatory cells intermingled with histiocytes; some of them present a conspicuous cytoplasm, in part vacuolated, indicating beginning of lipoid storage. (Xanthoma cells, \( \times 125 \).) In Figure 20 the lipoid-bearing foam cells are more abundant.

**FIG. 18**
Photomicrograph of case shown in Figures 19 and 20, showing numerous histiocytic mono- and multinucleated cells with abundant cytoplasmatic lipids, often forming in the multinucleated giant cells a peripheral rim of dark staining granules ("Touton" cells). (Sudan black stain, \( \times 400 \).)
Microphotographs of lesion in the case shown in Figure 27. Intense histiocytic proliferation of follicular aspect with only scarce eosinophilic and inflammatory elements. (Figure 21: $\times 60$; Figure 22: $\times 200$.)

The same case. Biopsy specimen taken two years later from the same lesion. Photomicrographs showing numerous lipid-bearing foam cells with single or multiple nuclei ("Touton cells"). ($\times 400$.)
Patchy zones of haemorrhage and necrosis were usually present with phagocytosis of blood pigment (haemosiderin) or lipids by the histiocytes which became transformed into typical lipid-bearing foam cells (xanthomatous cells) (Figs. 19 and 20). Foam cells are more abundant in the vicinity of necrotic areas which are more extensive in the older and more widespread lesions, possibly because of deficient circulation from hyperplasia of the arterial endothelium with evident narrowing of the vessel's lumen (Fig. 14).

However, foam cells were not found only in the vicinity of necrotic zones but also independently of them and also in solitary lesions; but it was evident that they were more abundant in cases of Hand-Schüller-Christian syndrome, especially in the extensive skull lesions. Thus we observed in several cases a predominance of xanthomatous areas in the skull and only scarce foam cells in other more recent foci, where the histiocytes and eosinophils predominated. The histiocytes are replaced later by fibroblastic elements with formation of connective tissue intermingled or not with foam cells which substitutes the granulomatous tissue, as we could observe in some cases in which repeated biopsies were performed (Figs. 21 to 24).

However, in Letterer-Siwe's syndrome, which is almost always of acute evolution, the histiocytic proliferation, accompanied by a variable number of eosinophils and other inflammatory elements predominates, either lacking foam cells or these being very scarce, apparently due to the rapid evolution of this process.

With Rio Hortega's silver stain a dense net of reticular fibres surrounding individual or small groups of histiocytes was observed, but sometimes only large nests of these, originating a follicle-like pattern (Fig. 25). The Rio Hortega technique, specific for reticulo-endothelial
elements confirmed the histiocytic nature of the basic cell, showing its characteristic ramified or amoeboid aspect (Fig. 26).

In the periphery of the lesion reactive bone formation was frequently found, as also in the surface of the destroyed cortex of long limb bones, which often showed an onion skin pattern.

Our findings confirmed the fact that the histological aspect does not permit one to establish the anatomo-clinical type of any particular lesion—and so predict its future evolution—without knowing the complete clinical and radiological picture.

DISCUSSION

The comparative clinical and pathological study of our cases strongly supports the view that eosinophilic granuloma, Hand-Schüller-Christian syndrome and Letterer-Siwe syndrome represent only different clinical and anatomical manifestations of a single pathological disorder, occurring frequently in transitional or intermediate types. Although it was generally impossible to predict from the histological picture what would be the evolution of a particular case, the dissemination of an initially solitary lesion occurred usually during the first months, most frequently before the sixth month, and was more common in children under five years of age. Therefore, if a bone lesion remains solitary for twelve months, it may be expected confidently that no other focus will appear in the future and cure can be said to be permanent with conservative treatment (curettage or radiotherapy in low doses). According to Enriquez and colleagues (1967) and Cheyne (1971), apart from the age of onset the main difference between the patients who died and those who recovered was in the pattern in which the disease involved...
the soft tissues. "Widespread dissemination is indicated by involvement of the liver and spleen and the presence of a rash. Where it also leads to anaemia the prognosis is grave" (Cheyne 1971). We wish also to emphasise that an evident correlation exists between age and the bone involved, with an evident predominance for the location in certain bones, especially ribs and mandible (Fig. 2) after the age of twenty years. Another important finding was the frequent presence of a variable number of lipid-bearing histiocytes (xanthomatous cells) in cases of solitary and multiple eosinophilic granuloma without Hand-Schüller-Christian syndrome, often in relation to necrotic zones, but also independently of them. They are better demonstrated with special fat stains which show lipids often also in multinucleated giant cells, forming a peripheral rim displacing the nuclei towards the periphery ("Touton cells"). Thus the presence of xanthoma cells is not diagnostic of Hand-Schüller-Christian syndrome, since they are found occasionally in Letterer-Siwe syndrome, but they are evidently...
Boy, 3 years old. Antero-posterior and lateral radiographs of the skull showing the typical "geographic map" aspect. The patient showed bilateral otitis media, exophthalmos (but not diabetes insipidus), lesions in the maxillae with ulceration of the gums, cutaneous manifestations and another focus in the right femoral diaphysis.

Biopsy of skull lesion in the case illustrated in Figure 30 (Hand-Schüller-Christian syndrome) showing the electron-microscopic aspect of the histiocytic elements. Indented single or double nuclei, pseudopods and prolongations of the cytoplasm with a certain number of lipid vacuoles. (×6,000.)
scarce or completely lacking in this process which is probably due to the short duration of this more acute disease (Wallgren).

Another feature in support of the unified concept was the presence of different histological patterns in biopsy specimens taken from different sites of multifocal lesions; thus we observed in some cranial lesions a predominance of the xanthoma cells and fibrous areas and in material obtained from other bone lesions of the same patient, apparently more recent, abundant eosinophils with only isolated xanthoma cells. One of our cases started with a femoral lesion but became rapidly generalised (in less than six months) developing finally a complete Hand-Schüller-Christian triad (Figs. 21 to 24 and 27 to 29). In the first biopsy an intense histiocytic proliferation with only a few eosinophils was found, but in a second biopsy taken two years later from the same femoral lesion, a typical fibro-xanthomatous lesion, lacking eosinophils almost completely, was observed (Figs. 23 and 24). Mercer and Duthie (1956) reported similar pathological evidence, from biopsies carried out consecutively in a patient, of the transformation from a histiocytic granulomatous stage with predominantly eosinophils to the lipid granulomatous stage with predominantly foam cells during the past six years.

The above-mentioned findings, as also the occurrence of intermediate types, especially in young children around three years of age (Fig. 30), in which the exact classification as Hand-Schüller-Christian syndrome with conspicuous extra-skeletal lesions or as a milder, less acute, form of Letterer-Siwe disease, could not be established, seem to confirm the unifocal concept and induced Rewald (1960) to apply to both entities the denomination "Letterer-Christian's disease".

The basic pathological process constitutes the proliferation of non-neoplastic reticulo-histiocytic elements (Fig. 31) with a varying number of eosinophilic leucocytes, lymphocytes, plasma cells and multinucleated giant cells. Scarce or numerous lipid-bearing phagocytes (xanthomatous cells) may occur in either of the different clinical manifestations, but are definitely rare in Letterer-Siwe syndrome. There are many features which suggest that the entities represent some type of immuno-allergic (hypersensitive) reaction to a still unknown peculiar infection, possibly viral. This may explain the histological picture (follicle-like structures and intense eosinophilia), as also the favourable therapeutic effects of corticosteroids or antibiotics in some of the multiple lesions. This hypothesis would explain the well known fact that the earlier the age of onset of the disease (under three years) the more acute is its evolution and less favourable its prognosis (Enriquez and colleagues 1967, Cheyne 1971). We disagree with those authors who try to divide the cases into fatal and non-fatal entities (Lieberman and colleagues 1969), which can be done only retrospectively after knowing the complete evolution of the disease.

TREATMENT AND PROGNOSIS

The type of treatment varied according to the different clinical manifestations of the disease. It is summarised in Table III for the solitary and multiple lesions, limited to bone, without any determinate syndrome.

In most cases curettage was the treatment of choice in easily accessible unifocal lesions, especially in long bones (Figs. 32 and 33), followed in eleven cases by insertion of bone chips in osteolytic lesions of large size (Figs. 34 to 36) and less frequently by radiotherapy in low doses (less than 1,200 rads). In seven cases located in the rib and in five located in the clavicle a segmental resection was performed. Most of our patients were young children and in order to avoid damage to the growth cartilage, radiotherapy alone or combined with curettage was done only in a small number of cases, especially in those deeply located (vertebrae) or in some extensive solitary or multiple cranial lesions. The evolution was uniformly favourable in all unifocal bone lesions with any kind of conservative treatment mentioned above.

The treatment performed in our series of multiple and widely disseminated lesions, with and without Hand-Schüller-Christian or Letterer-Siwe syndrome, as also in the transitional cases, was much more variable than in the unifocal lesions, because the type of treatment
changed in the different periods of observation. In the earliest cases only radiotherapy was used, occasionally accompanied by curettage or resection of one focus (in a rib) or administration of hypophysial extracts or Metaclorpropamide (Diabenese) in the cases of diabetes insipidus, with a moderate improvement of the urine density and diminution of excretion. In the more
recent cases of Hand-Schüller-Christian and intermediate syndromes, corticosteroids in variable doses were used, alone (one case) or accompanied by radiotherapy with good results in only some of them. For this reason in the more severe and widely disseminated or acute cases (intermediate and Letterer-Siwe syndrome, or those which did not respond to corticosteroids)

TABLE III
 METHODS OF TREATMENT

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<thead>
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<th>Type of treatment</th>
<th>Number of cases</th>
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<tr>
<td></td>
<td>Solitary</td>
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<tr>
<td>Curettage</td>
<td>32</td>
</tr>
<tr>
<td>Curettage and radiotherapy</td>
<td>7</td>
</tr>
<tr>
<td>Curettage and bone chips</td>
<td>11</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>7</td>
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<tr>
<td>Radiotherapy and antibiotics</td>
<td>2</td>
</tr>
<tr>
<td>Resection: Rib</td>
<td>7</td>
</tr>
<tr>
<td>Clavicle</td>
<td>5</td>
</tr>
<tr>
<td>Maxilla</td>
<td>1</td>
</tr>
<tr>
<td>Radiotherapy followed by resection of rib</td>
<td>1</td>
</tr>
<tr>
<td>Curettage, excision of gums and radiotherapy</td>
<td>1</td>
</tr>
<tr>
<td>Not known</td>
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</table>

chemotherapy was used (nitrogen mustard in one case and methotrexate in another case) with improvement of the process.

In three more recent cases of disseminated lesions, after the failure of radiotherapy, or as primary treatment, Dr Derqui of the Buenos Aires Children's Hospital employed an antimitotic agent, Velve (vinblastine sulphate) in low doses with excellent results and complete disappearance or diminution in size of the osteolytic lesions. These cases, together with several others not included in this paper, will be reported later.

In our two cases of Letterer-Siwe syndrome, accompanied by severe anaemia, besides chemotherapy (nitrogen mustard, antibiotics or corticosteroids and vitamin A respectively) periodic blood transfusions were performed. Both patients were alive three and eight years respectively after onset.

SUMMARY

1. The clinical, radiological and pathological features of 106 cases of eosinophilic granuloma of bone (solitary and multiple) are reported.
2. Our findings support strongly the concept that eosinophilic granuloma, Hand-Schüller-Christian and Letterer-Siwe syndrome are closely related manifestations of a single pathological disorder, characterised fundamentally by the proliferation of non-neoplastic histiocytes, intermingled with a variable amount of eosinophilic leucocytes and other inflammatory elements.
3. Lipid-bearing histiocytes (xanthoma cells) may be found in variable amounts in solitary and multiple lesions but are more abundant in the more extensive or chronic lesions of Hand-Schüller-Christian syndrome.
4. These entities may perhaps represent some type of immuno-allergic (hypersensitive) reaction to a still unknown infection, possibly viral.
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