

# THE HISTIOCYTOSSES

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The histiocytoses, systemic disorders largely confined to childhood, have attracted inordinate attention because they do not easily fit into the usual categories of biological behavior. Is there an underlying genetic defect? Are the disorders purely reactive to dysregulated inflammatory mediators, or are they neoplastic? How is their biological progression to be predicted, and most important, how are they to be treated? This article does not provide answers to the fundamental questions but attempts to put the diagnosis of these disorders on a more rational basis. Systemic histiocytoses are the focus of this article, and consideration of the malignant disorders is omitted.

## Classification of Histiocytic Disorders

The Histiocyte Society met for the first time in Philadelphia in 1985 and set itself the task of trying to bring some order to a field bedeviled by terminologic disarray. This group of clinicians, pathologists, and scientists pooled their expertise to produce a classification of the histiocytic disorders with some definitions and diagnostic criteria.<sup>72</sup> A major first step was to separate the Langerhans cell disorders from those of the mononuclear phagocytes and the true malignancies. Advances over the following decade were incorporated into a followup document. The Reclassification Working Group of the Histiocyte Society, together with members of the World Health Organization (WHO) Committee on Histiocytic/Reticulum Cell Proliferations took the classification one step further in 1997.<sup>15</sup> See Table 1.

In recognizing that the biological behavior of many of the histiocytoses is unpredictable and that their true nature, neoplastic or reactive, is not clear, the classification divides the histiocytoses into two broad groups—those of varied biological behavior and those that are truly malignant. Within each of the two biological categories, the classification then separates the entities by their affiliation with dendritic cells, macrophages, and, in the malignant category, monocytes.

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In recent years, there has been an increase in the amount of interest devoted to the dendritic cell and an explosion in the amount of information related to their origin and function.<sup>26</sup> In the first classification, Langerhans cells were the only recognized dendritic cell. The new classification had to be broadened to include lesions and disorders that appeared to involve the numerous other forms of dendritic cells, as listed in Table 2.

**Table 1. CONTEMPORARY CLASSIFICATION OF HISTIOCYTIC DISORDERS**

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Disorders of varied biological behavior	
Dendritic cell-related	
Langerhans cell histiocytosis	
Secondary dendritic cell processes	
Juvenile xanthogranuloma and related disorders	
Solitary histiocytomas of various dendritic cell phenotypes	
Macrophage-related	
Hemophagocytic syndromes	
Primary hemophagocytic lymphohistiocytosis	
(Familial and sporadic; commonly elicited by viral infections)	
Secondary hemophagocytic syndromes	
Infection-associated	
Malignancy-associated	
Other	
Rosai-Dorfman disease (sinus histiocytosis with massive lymphadenopathy)	
Solitary histiocytoma with macrophage phenotype	
Malignant disorders	
Monocyte-related	
Leukemias [French-American-British (FAB) and revised FAB classifications]	
Monocytic leukemia M5A and B	
Acute myelomonocytic leukemias M4	
Chronic myelomonocytic leukemias	
Extramedullary monocytic tumor or sarcoma (monocytic counterpart of granulocytic sarcoma)	
Dendritic cell-related histiocytic sarcoma (localized or disseminated)	
Specify phenotype, follicular dendritic cell, interdigitating dendritic cell, etc.	
Macrophage-related histiocytic sarcoma (localized or disseminated)	

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*From Favara BE, Feller AC, Pauli M, et al: Contemporary Classification of Histiocytic Disorders. The WHO Committee on Histiocytic/Reticulum Cell Proliferations. Reclassification Working Group of the Histiocyte Society. Med Pediatr Oncol 29:157, 1997; with permission.*

## **Brief Ontogeny of Macrophages and Dendritic Cells**

The relation between dendritic cells and macrophages is close, and there may be continuing modulation of precursor forms between one and the other, explaining why it is hard to pin down the phenotypes of some of their lesions.<sup>7</sup> Much of the current knowledge about the origin of these cells stems from the techniques now available to isolate and culture populations of macrophages and dendritic cells in vitro, and it is not yet clear how much of the information derived from the culture systems is applicable to the histiocytic disorders in vivo.

**Table 2. DENDRITIC CELLS AND THEIR DISORDERS**

<b>Dendritic Cell</b>	<b>Phenotype</b>	<b>Disorder</b>
Langerhans cell	CD 1a, S100, LCG, Lag	LCH
Indeterminate cell	CD 1a, S100, fascin	Dendritic cell histiocytoma, indeterminate
Interdigitating DC	S100, fascin	Dendritic cell histiocytoma, IDC type
Dermal dendrocytes (and subtypes)	Factor XIIIa, fascin, CD 68	Xanthogranuloma family Dermal dendrocytomas
Follicular dendritic cell	CD 21, CD 35, Ki-M4, S100±, fascin	Dendritic cell histiocytoma, FDC type
Sinus dendritic cell	Si-M9, fascin, CD 68, S100	?Rosai-Dorfman disease

*Abbreviations:* Lag, Lag antigen; LCH, Langerhans (Birbeck) granules of the Langerhans granule; LCG, Langerhans cell (Birbeck) granule; IDC, interdigitating dendritic cell; FDC, follicular dendritic cell.

Dendritic cell lines are currently thought to be derived from a CD 34+ precursor that can be modulated to produce a wide variety of cells. Stimulation gives rise to a CD 45RA cell, and in turn to CD 10+ and CD 10- lines. The CD 10+ line gives rise to lymphoid cells, including lymphoid dendritic cells.<sup>20</sup> The CD 10- line produces myeloid cells, including the myeloid dendritic cells. The myeloid dendritic cells develop from a precursor that is common to the monocyte-macrophage line, and modulation between monocytes and dendritic cells is probably likely until an advanced stage of differentiation. The follicular dendritic cells—and it is likely that more than one population exists—develop from different sources.<sup>41</sup> The predominant cell that binds antigen for long periods is not bone marrow derived but develops from local mesenchyme. Other follicular dendritic cell subpopulations may indeed be from bone marrow.<sup>41</sup>

CD 34+ precursors in the blood, bone marrow, or cord blood can give rise either to granulocytic colonies or to cells that generate dendritic cells and macrophages. Under the influence of granulocyte macrophage colony stimulating factor (GM-CSF) and Flt3 ligand, two populations emerge in culture, CD 1a+ and CD 14+. Langerhans-type cells can be induced under the influence of GM-CSF and tumor necrosis factor alpha (TNF $\alpha$ ) from the CD 1a+ line. Under the same stimuli, non-Langerhans, CD 1a+ dendritic cells expressing Factor XIII emerge from the CD 14+ precursors. Addition of macrophage colony stimulating factor (M-CSF) to the CD 14+ line produces macrophages. CD 14+ monocytes in the blood can also be used as a starting point; under the influence of GM-CSF and interleukin-4 (IL-4), an immature CD 1a+ dendritic cell is generated that can mature with application of TNF $\alpha$ . Both the monocyte population and the immature dendritic population can be driven in the direction of macrophages by M-CSF, reminding us once again that similar modulations may occur in histiocytic lesions and account for some of their heterogeneity.

# Dendritic Cell Markers in Situ

The demonstration of dendritic cells in situ has been bedeviled by the twin problems of lack of sensitivity and lack of specificity of the putative dendritic cell markers. They lack specificity in that cells other than dendritic cells stain with markers such as the human leukocyte antigen II (HLA-II) antibodies, LN3 (DR subregion),<sup>43</sup> RFD-1 (HLA-DQ), and RFDR1 (HLA-DR, DQ, and DP).<sup>55</sup> Lack of sensitivity is seen with those antibodies that mark only subsets of dendritic cells, such as protein S100.<sup>65</sup> S100 is widely used as an indicator of dendritic cells, and it can be shown to reveal only some of the dendritic cells when other dendritic cell markers, such as fascin, are used.

CD 1a is a marker of Langerhans cells and the indeterminate cell but not other dendritic cells. Follicular dendritic cells can be demonstrated with CD 21, CD 35, or Ki-M4 antibodies. Dermal and interstitial dendritic cells mark with Factor XIIIa, a coagulation transglutaminase.<sup>8</sup>

More widely applicable antibodies to molecules of interest in the dendritic cell system are being described. CD 83 appears to be unique to dendritic cells in the blood, and in tissues it marks interdigitating cells, some B cells and Hodgkin cells.<sup>78</sup> Fascin, an actin-bundling protein, can be demonstrated in follicular and interdigitating dendritic cells and splenic and thymic dendritic cells but not in Langerhans cells. Hodgkin cells also react.<sup>54</sup> Antibody CMRF-44 can identify dendritic cells cultured from the blood, dendritic cells in tissue, B cells in tissue, and Hodgkin cells.<sup>26,61</sup>

## Dendritic-Cell-Related Disorders

### Langerhans Cell Histiocytosis

Langerhans cell diseases can occur in a wide variety of clinical forms, affecting different sites and ages and with widely disparate clinical outcomes. Nezelof et al<sup>48</sup> provided the contribution in which the Langerhans cell was recognized as the common thread that tied this group together. The dermal Langerhans cell and the cells of Langerhans cell histiocytosis (LCH) were both shown to express CD 1a, giving the pathologist a convenient handle for recognizing and labeling the cells. Willman et al,<sup>70</sup> using a human androgen receptor (HUMARA) assay on lesional tissues, demonstrated that the lesions of LCH were clonal in a variety of clinical forms and that multiple lesions were probably of the same clone. This was confirmed for isolated CD 1a+ cells and showed that the CD 1a+ population was clonal and that the CD 1a- inflammatory lymphoid component was polyclonal.<sup>73</sup>

Causation is still mysterious; no consistent genetic or viral association has held up. An epidemiologic case-control study of children who had LCH (1.8 years, range 0.1 to 14.6 years of age), 208 with multisystem disease and 198 with single-system LCH, found associations with

infection in the neonatal period, solvent exposure, childhood vaccinations, and a family history of thyroid disease.<sup>5</sup>

Clinical stratification for the more common clinical forms of disease has emerged from the Histiocyte Society's International Treatment Protocols for LCH. Patients are categorized as having single-system disease at a single site or multiple sites or as having multisystem disease.<sup>36</sup> Congenital papular skin disease is self-limiting, and single-system disease at one or more sites is amenable to current therapy. There is still an excessive mortality for young children who have multisystem disease.

There appears to be an increasing incidence of Langerhans cell disease in adults. The clinical forms tend to be those of single-system disease in children with localized but multifocal disease. The multifocal disease, and especially pulmonary disease, have serious functional and prognostic consequences.<sup>4</sup>

The histopathology of Langerhans cell disease has been extensively described.<sup>16,39</sup> There have been some changes in the diagnostic criteria, first elaborated by the Histiocyte Society. The gold standard of diagnosis has been the identification of the ultrastructural Birbeck or Langerhans cell granule, because none of the other tissue or cell markers is unique to LCH. However, at the practical level, the demonstration of CD 1a molecules on the surface of cells that appear to be LCH cells in the appropriate clinical setting is sufficient to consolidate a diagnosis. The other cells and lesions on which CD 1a can be demonstrated, thymocytes and some instances of Rosai-Dorfman disease or deep xanthogranulomas, can be excluded by site or by other histopathologic features. Fascin, an actin-bundling protein, is demonstrable in most histiocytic lesions, including the two just mentioned but is not expressed in LCH.<sup>34</sup>

There are several sites in which the diagnosis of Langerhans cell disease can, on occasion, be difficult to make. It is not uncommon for a bone lesion to be identified in a child (sometimes more than one lesion) in which the differential diagnosis on imaging includes LCH versus osteomyelitis, infectious or chronic relapsing forms. The difficulty arises when the lesion is sampled and does not contain the sheets of LCH cells so typical of the usual lesion. Involuting LCH lesions are filled in by fibrosis and inflammatory cells as the pathognomonic LCH cells disappear (Fig. 1). To prove a diagnosis of LCH, it would be necessary to exclude osteomyelitis by microbiological culture and to demonstrate at least some LCH cells. Rare Langerhans cells and other dendritic cells may be a part of the complex inflammatory process of bone healing. However, the demonstration of *clusters* of LCH cells, revealed by CD 1a staining with the 010 anti-CD 1a antibody in situ, is diagnostic. In their absence, a differential diagnosis between culture-negative, chronic relapsing osteomyelitis, and LCH may not be possible. Osteomyelitis is usually rich in plasma cells, whereas LCH most typically is deficient. Fractures through the lesions with attendant callus formation may make the diagnosis even more difficult, and rebiopsy of a more recent lesion may be required.

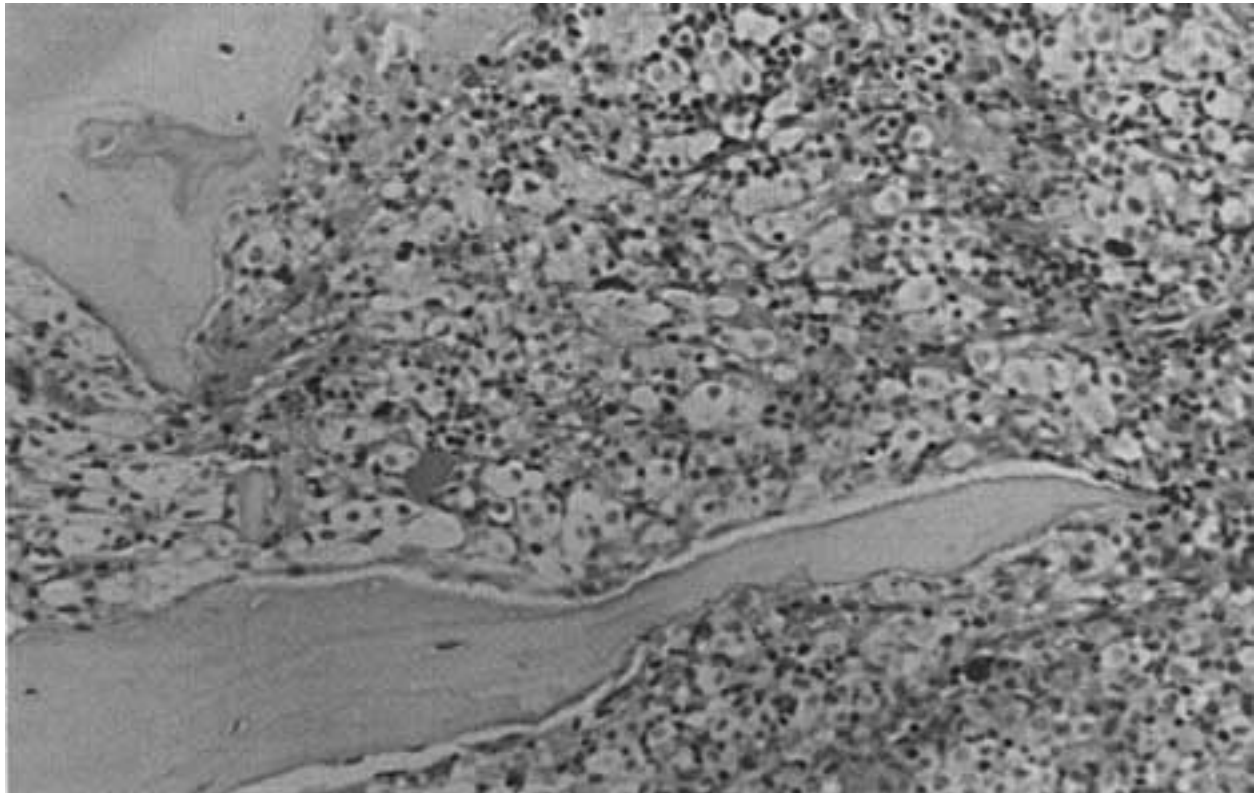


**Figure 1.** Bone with Langerhans cell histiocytosis, S100 immunostain. Note the dispersed aggregates of dark-staining LCH cells in an involuting lesion. Despite their dendritic cell affiliation, LCH cells are oval, not dendritic. (Original magnification x75)

The normal bone marrow contains a very small number of CD 1a+ cells; these cells are so few that CD 1a is not normally demonstrable in the bone marrow biopsy.<sup>59</sup> The diagnosis of bone marrow involvement in systemic LCH is another difficult area. The diagnosis of LCH involvement can be assumed when flow cytometry reveals that the number of CD 1a+ cells is substantially increased, but flow cytometry will not identify very rare events. The diagnosis remains unproved until LCH cells can be visualized on bone marrow biopsy or aspirate. Also, in this situation, the demonstration of morphologically probable LCH cells in situ with the 010 antibody to CD 1a is confirmatory. The diagnosis of bone marrow involvement in LCH is confounded further by the observation in some LCH patients of extensive activation of the macrophage system, including the marrow macrophages<sup>14</sup> (Fig.2). This unusual prominence of the marrow histiocytes does not constitute LCH infiltration, since CD 1a cannot be demonstrated.

LCH involvement may be hard to document in the liver. In children who have multifocal disease, there may be hepatomegaly and hypoalbuminemia but without evidence of direct liver infiltration. With therapy, the liver signs may remit without further consequence. The cause of the hepatomegaly and hypoalbuminemia is obscure.<sup>14</sup> LCH involvement in the liver appears to be exquisitely directed to the biliary epithelium, and the long-term consequences of liver involvement are those of sclerosing cholangitis.<sup>38</sup> Because major bile ducts are involved, needle biopsy of the liver may not demonstrate the LCH, only the consequences of biliary obstruction. If gamma glutamyl transpeptidase ( $\gamma$ GT) is added to the panel of liver function tests in these

children, early hepatic involvement may be identified by the rising levels, even where biopsy fails to document any infiltrate.



**Figure 2.** Bone marrow, patient with LCH. Diffuse activation of the macrophage system is occasionally present in LCH, seen in the marrow as a striking increase of large marrow macrophages. No LCH cells were demonstrable in this marrow. (Original magnification x125)

Brain involvement is another site where LCH may be difficult to document. LCH has been seen in the hypothalamic-pituitary axis, the choroid plexus, and the meninges.<sup>25</sup> There are instances in which children who have active or even inactive LCH develop cerebellar signs and progressive disease. Repeated biopsy of these sites in some patients has failed to reveal LCH cells, even in lesions documented to be of recent onset by magnetic resonance imaging. This leads to the suggestion that the cerebellar disease may be a paraneoplastic phenomenon and that biopsy is not appropriate.

The accuracy of diagnosis of lymph node involvement in LCH has improved with the advent of additional markers. The use of S100 antibody does not distinguish between interdigitating and Langerhans cells, but CD 1a antibodies that react with LCH cells, combined with antifascin antibodies that react with interdigitating (but not with LCH) cells, now offer a good discriminatory panel. The histologic spectrum of nodal LCH has recently been broadened by the description of an epithelioid granulomatous variant and a pattern of total nodal effacement with aneuploidy and fatal outcome.<sup>17</sup>

To the best of this author's knowledge, there is currently no way to predict the prognosis for dissemination at the time of presentation of initial lesion. Geissmann et al<sup>21</sup> have suggested that loss of E-cadherin, normally demonstrable on LCH cells, signifies loss of adhesion and a more aggressive phenotype. This has yet to be validated prospectively.

## **Secondary Dendritic Cell Processes**

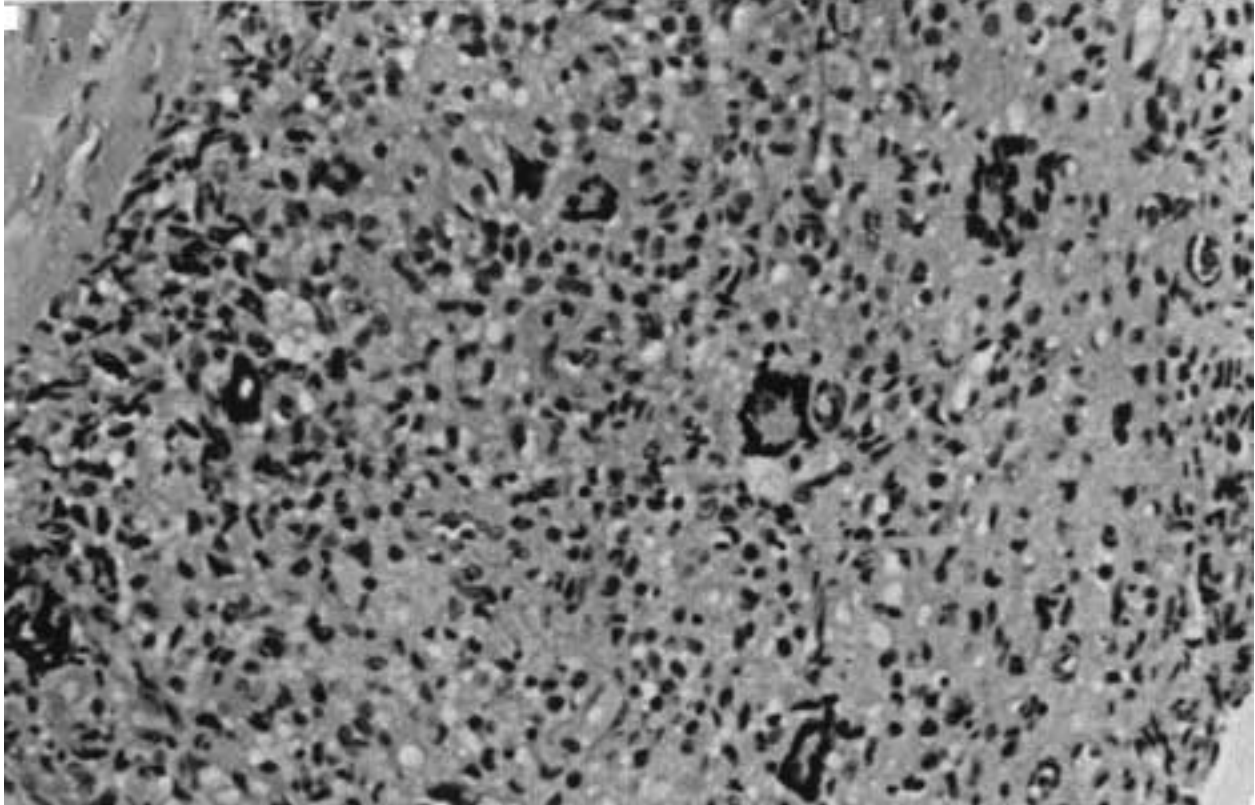
Not all proliferations of dendritic cells, particularly Langerhans cells, are LCH. Reactive collections of Langerhans cells have been described in lymph nodes afflicted with malignant lymphomas,<sup>69</sup> in thymus with myasthenia gravis,<sup>22</sup> and in association with other tumors.<sup>12</sup> Rather than being considered as the coincidence of Langerhans cell disease with these other conditions, it may be better to think of these as reactive dendritic cell accumulations.<sup>15</sup> There does not appear to be any clinical relevance to this observation, the prognosis is entirely that of the underlying condition, and no instances of the spread of the dendritic cell component are recorded.

## **Juvenile Xanthogranuloma and Related Disorders**

The simple cutaneous juvenile xanthogranuloma (JXG) is a familiar self-healing lesion of the skin in infants and young children; it is not associated with serum lipid disorders. The histopathology is characterized by an admixture in varying proportions of histiocytes—some of which are xanthomatous—and Touton giant cells. Cellular monomorphous lesions with only rare Touton cells and without lipidization cause concern, but they behave like other JXGs.<sup>47</sup> But even at its most banal, the lesion piques our interest because of the fascinating clinical associations. JXG has been associated with neurofibromatosis, juvenile chronic myeloid leukemia, and the combination of both,<sup>79</sup> Langerhans cell disease, and rarely, Rosai-Dorfman disease.

It has become evident that a host of dermal lesions share the clinical and phenotypic characteristics of JXG, including benign cephalic histiocytosis, papular xanthoma, progressive nodular histiocytosis, and xanthoma disseminatum. They vary in the site and the distribution of the lesions, but the phenotype of the constituent cells appears to be identical.<sup>75</sup> The lesions all have a preponderance of dendritic-type cells that lipidize with time, and typical Touton cells may be a feature. The phenotype is generally S100-, fascin+, Factor XIIIa+, CD 68+ (especially the PG-M1 antibody), Ki-M1P+, and CD 1a-.<sup>58</sup>

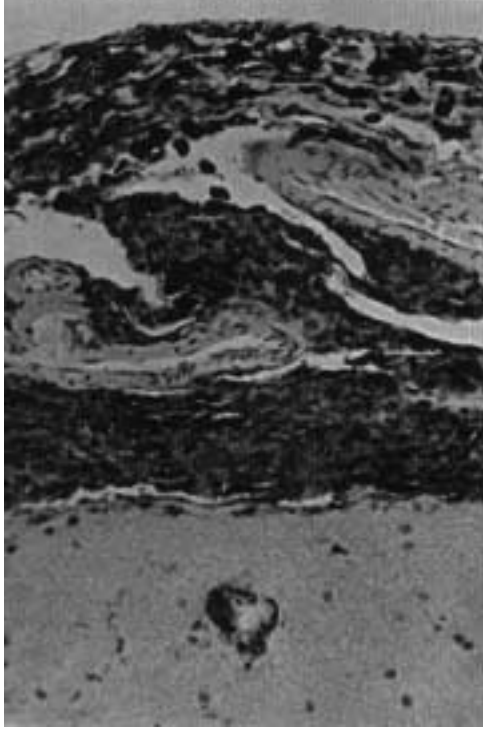
Recent reviews provide evidence that JXG can occur also as a deep-seated lesion in subcutaneous and various deep tissues<sup>46</sup> (Fig. 3) and as a more systemic disorder involving multiple sites, including viscera.<sup>19,30</sup> No matter where they occur, deep JXGs can be diagnosed by their histopathologic features and confirmed by the characteristic phenotype of Factor XIIIa+, fascin+, CD 68+, and S100-. Deep-seated lesions have the same histologic appearance as dermal JXG (though Touton cells may be sparse) and share the JXG phenotype, but there are claims that some may express CD 1a.<sup>10</sup> Diagnosis is important because the natural history of the JXG is to regress over time, and this has been the experience with the deep forms, too.<sup>30</sup>



**Figure 3.** Juvenile xanthogranuloma. Newborn (one of twins) with an extramedullary spinal cord mass but no skin lesions. Phenotype was FXIIIa+, CD68+, fascin+, CD1a-, S100-. (Original magnification x285) (Photo courtesy of Dr. V. Tobias, Sydney, Australia)

Systemic forms of JXG have been described that involve virtually all organs of the body. Such cases were recently collated and reviewed by Freyer et al.<sup>19</sup> Cutaneous lesions were absent in approximately half the patients, and the most frequent organ site involved was the central nervous system. Beyond the subcutaneous tissues, lesions were found in the liver, the spleen, the lung, and, rarely, the bone. Lesions that were not resected generally regressed, but they did so slowly, over months to years. The central nervous system involvement consisted of multiple discrete lesions with involvement of cerebrum, cerebellum, and periventricular and brain stem regions. Leptomeningeal and spinal canal lesions are also described (Fig. 4). As in the deep JXG, diagnosis relies on thinking of the condition and recognizing the typical histopathologic features in unusual sites. Classical Touton cells are a tipoff, but they may be sparse. Phenotyping confirms the diagnosis. The biological behavior has been benign with regression of lesions, and some of the repeated morbidity is ascribed to radiation or chemotherapy given to these children. However, two patients who had central nervous system involvement died of progressive disease.<sup>19</sup>

Xanthoma disseminatum appears to be a normolipemic mucocutaneous clinical variant and member of the JXG family. The disorder is characterized by many, even hundreds, of dermal papules with prominent involvement of mucous membranes, most often of the upper airways.



**Figure 4.** Juvenile xanthogranuloma; 14-year-old girl with diffuse and ultimately fatal leptomeningeal infiltration. The histology was that of a juvenile xanthogranuloma, including Touton cells. Fascin immunostain is striking. (Original magnification x125)

The disorder is more common in adults than in the very young. Like JXG, brain involvement is described, and bone involvement is rare.. Curiously, diabetes insipidus, a hallmark of LCH, is seen—albeit transiently—in as many as 40% of patients.<sup>6,68</sup> The histopathology is that of JXG, including the Touton cells, and the phenotype is also congruent, Factor XIIIa+, S100-, CD 68+, fascin+.

Zelger et al<sup>76</sup> proposed a unifying concept for the non-LCH that includes the clinical disorders being described here. Differences in their histopathology are related to admixtures of histiocytes in different functional and morphologic phases. The natural history is for the lesions to persist, progress slowly, or involute. Mortality has been described with severe glottic involvement and with central nervous system involvement (the same patient described as dying of systemic JXG, sited above).<sup>19</sup>

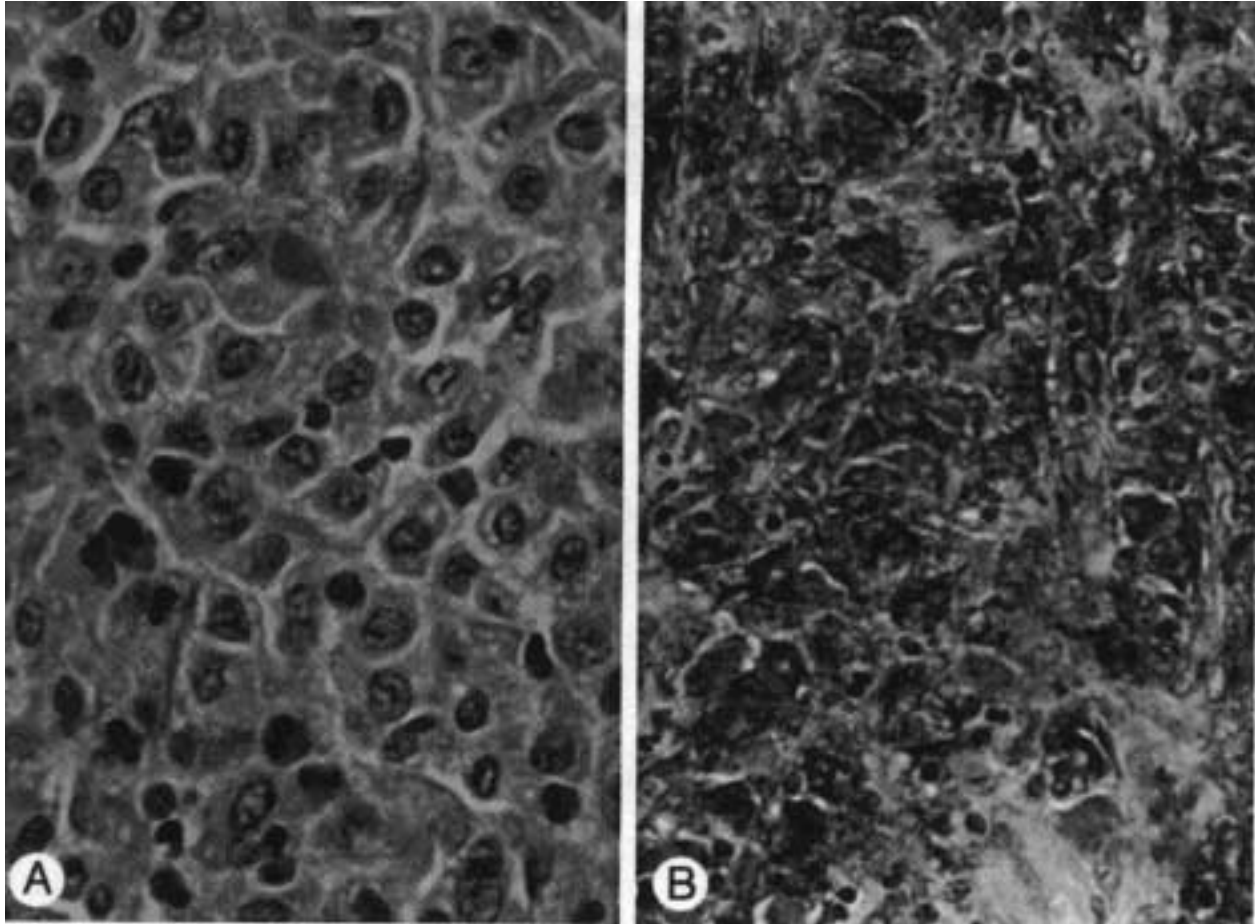
Erdheim-Chester disease has a similar xanthomatous histopathology, but it is characterized and diagnosed by radiographic metaphyseal and diaphyseal symmetrical osteosclerosis of long bones.<sup>66</sup> Central nervous system involvement is described,<sup>1,3</sup> and diabetes insipidus occurs in approximately 30% of cases.<sup>66</sup> The lesions are xanthogranulomatous with Touton cells in some cases. S100 and CD 1a are absent on lesional cells. Langerhans

cell lesions are also described in some of these same children,<sup>1,35</sup> emphasizing the close relation between various clinical forms of the dendritic histiocytoses.

## Histiocytomas of Various Dendritic Cell Phenotypes, Dendrocytomas

We have seen cases that fit the description and phenotype of the indeterminate cell lesion or dendritic cell histiocytoma generally described in adults.<sup>71</sup> Two clinical forms are apparent. The first is a localized lesion of the subcutaneous tissues that is cured by excision. The second is a less circumscribed lesion or, alternatively, multiple nodules that may progress with serious consequences. The latter has been encountered mainly around the head and the neck and intracranially.

The lesions look very much like LCH at first glance (Fig. 5A), but the phenotype is different. The cells are CD 1a+ but lack Langerhans granules and are variably S100+, CD 68+, and variably Factor XIIIa+, but express fascin strongly (fig. 5B). Adults who have multiple cutaneous lesions and who have a similar phenotype (though more usually Factor XIIIa+) are



**Figure 5.** Dendritic cell histiocytoma. A subcutaneous mass was present on the chest wall of a 7-month-old boy, attached to the pectoralis muscle. Phenotype was CD1a+, Birbeck granules absent, fascin+, S100±, CD68-. *A*, The H/E appearance simulates LCH, even with eosinophils. *B*, Fascin stain reveals strong cytoplasmic staining. (Original magnification x400)

described.<sup>42,60</sup> Similar lesions that do not meet the morphologic criteria for the JXG may be confined to the skin in both adults and children and have been referred to as dermal dendrocytomas.<sup>9,49</sup> The so-called epithelioid cell histiocytoma may also belong in this category.<sup>23</sup>

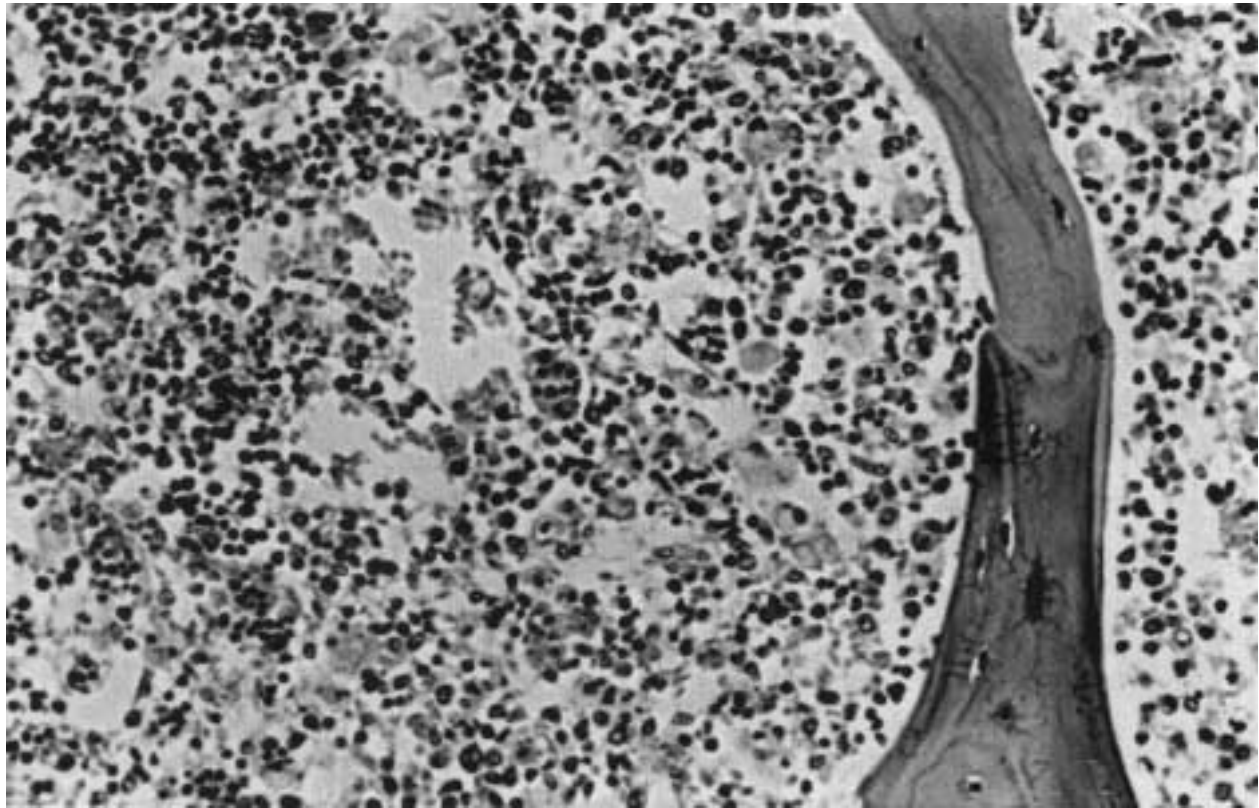
There are so few cases in children that their biological behavior cannot be reliably predicted. In our series, three localized lesions in subcutaneous tissues were excised and did not recur five to ten years later. However, two intracranial lesions and one cervical-mediastinal lesion recurred within months.

## Macrophage-Related Disorders

### Hemophagocytic Syndromes

Hemophagocytosis is not a reaction that is unique to the histiocytoses, and the erythrophagocytosis that is commonly found after blood transfusion<sup>63</sup> or locally after surgery<sup>40</sup>

should not lead to a mistaken diagnosis of a hemophagocytic syndrome. Conversely, the hemophagocytic syndromes, particularly the familial form, may at times have little active hemophagocytosis, and this should not negate the diagnosis. Tissue diagnosis should rest on the bone marrow features (Fig.6). Because of the difficulties in the diagnosis, the Histiocyte Society has drawn up a set of clinicopathologic criteria by which the diagnosis can be reliably established (Table 3).<sup>27</sup>



**Figure 6.** Hemophagocytic lymphohistiocytosis, bacteria-induced. This 18-month-old boy had chronic granulomatous disease and developed overwhelming *Pseudomonas cepacia* sepsis associated with a clinical picture of hemophagocytosis. (Giemsa, original magnification x 75)

Recent reviews of the combined experience of large centers or collaborative information from the Hemophagocytic Lymphohistiocytosis (HLH) Registry has led to a more clear delineation of the syndromes.<sup>2, 31, 33</sup>

Primary HLH manifests as a familial disease that presents early in life, familial HLH (FHLH). Consanguinity in the parents is not uncommon in FHLH, and a nature killer (NK) cell defect is present in most.<sup>2</sup> When the disease presents in an infant who does not have a prior affected sibling, the differential diagnosis rests between infantile virus-associated lymphohistiocytosis and FHLH, and the presence of consanguinity and an NK cell defect helps make the diagnosis. This is especially important because it is often infection, usually viral, that can trigger the disorder even in FHLH.

**Table 3.** DIAGNOSTIC GUIDELINES FOR HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Clinical and laboratory criteria

Fever {(duration  $\geq$  7 days, with peaks  $\geq$  38.5° C) (101.3° F)}

Splenomegaly ( $\geq$  3 cm below the costal arch)

Cytopenia (affecting  $\geq$  2 to 3 lineages in the peripheral blood and not caused by a hypocellular or dysplastic bone marrow):

Hemoglobin ( $<$  90 g/L)

Platelets ( $<$  100  $\times$  10<sup>9</sup>)

Neutrophils ( $<$  1.0  $\times$  10<sup>9</sup>/L)

Hypertriglyceridemia and/or hypofibrinogenemia (fasting triglycerides  $\geq$  2.0 mmol/L or  $\geq$  3 SD of the normal value for age, fibrinogen  $\leq$  1.5 g/L or  $\leq$  3 SD)

Histopathological criteria

Hemophagocytosis in bone marrow or spleen or lymph nodes. No evidence of malignancy

Hemophagocytic lymphohistiocytosis (HLH)

All the above criteria are required for the diagnosis of HLH.

Familial hemophagocytic lymphohistiocytosis (FHLH)

The diagnosis FHLH is justified in the presence of a family history of HLH and all criteria listed above.

Parental consanguinity is suggestive of FHLH.

Comments:

1. If hemophagocytic activity is not proved at the time of presentation, further search for hemophagocytosis is encouraged. If the bone marrow specimen is not conclusive, material should be obtained from other organs, especially the lymph nodes or the spleen. Serial marrow aspirates, over time, may also be helpful.
2. The following findings may provide strong supportive evidence for the diagnosis:
  - (a) Spinal fluid pleocytosis (frequently  $<$ 50  $\times$  10<sup>6</sup> cells/L; mainly mononuclear cells);
  - (b) Histological picture in the liver resembling chronic persistent hepatitis; and
  - (c) Low natural killer cell activity.
3. Other abnormal clinical and laboratory findings in HLH, not listed above, may be lymph node enlargement, skin rash, cerebromeningeal symptoms, jaundice, edema—especially periorbital, increased spinal fluid protein content, elevated levels of transaminases, hypoproteinemia, hyponatremia, increased very low-density lipoproteins, and decreased high-density lipoproteins. Hyperferritinemia and increased number of soluble IL-2 receptors have recently been reported.

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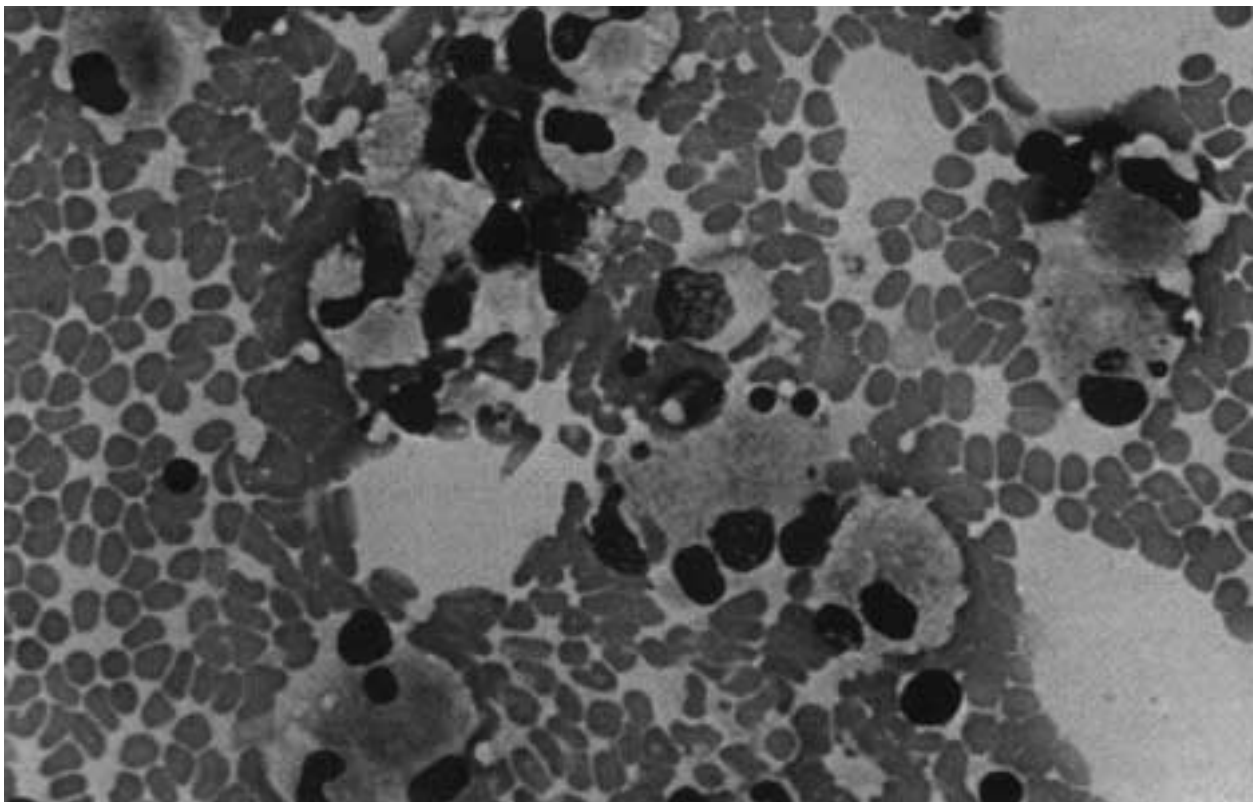
*From Henter JJ, Elinder G, Ost A: Diagnostic Guidelines for Hemophagocytic Lymphohistiocytosis. The FHL Study Group of the Histiocyte Society. Semin Oncol 18:29, 1991; with permission.*

Secondary HLH appears to be a cytokine-mediated disorder, triggered by many events. Many of these are infection associated, although it is not known if the disorder occurs in genetically predisposed patients. By the usual tests of immune competence, these patients are intact. Viral-associated lymphohistiocytosis is the most common, with Epstein-Barr virus (EBV) and cytomegalovirus being the most common virus implicated in the Orient<sup>33</sup> and in the West,<sup>2</sup> respectively. The differential diagnosis of EBV-associated lymphohistiocytosis occurring in a young boy from the X-linked lymphoproliferative syndrome (Duncan disease) can be problematical.<sup>50</sup> Infection-associated hemophagocytic syndrome can also complicate bacterial or protozoal infections.

Secondary hemophagocytic syndromes may complicate various immune disorders, inherited and acquired. Immune deficiencies, such as Chédiak-Higashi syndrome,<sup>56</sup> and human

immunodeficiency virus (HIV),<sup>24</sup> can be followed by hemophagocytic syndrome, sometimes viral induced. The systemic dendritic histiocytoses, LCH and JXG, may be accompanied or followed by a diffuse activation of the macrophage system not unlike a hemophagocytic syndrome<sup>14</sup> and account for the bone marrow changes sometimes seen in these conditions. A similar diffuse activation of the macrophage system is described in juvenile rheumatoid arthritis.<sup>44</sup>

Hemophagocytic syndrome is a feature of some malignant lymphomas, EBV-associated peripheral T-cell lymphomas<sup>62</sup> (Fig. 7), or NK-cell lymphomas with or without EBV.<sup>11,32</sup> The clear implication is that in all hemophagocytic syndromes in which EBV is found, an underlying lymphoma must first be excluded.



**Figure 7.** EBV-related peripheral T-cell lymphoma with hemophagocytic syndrome. The marrow aspirate reveals large numbers of histiocytes; hemophagocytosis is not prominent. EBV was demonstrated in neoplastic T lymphocytes in the marrow (Wright-Giemsa, original magnification x 400)

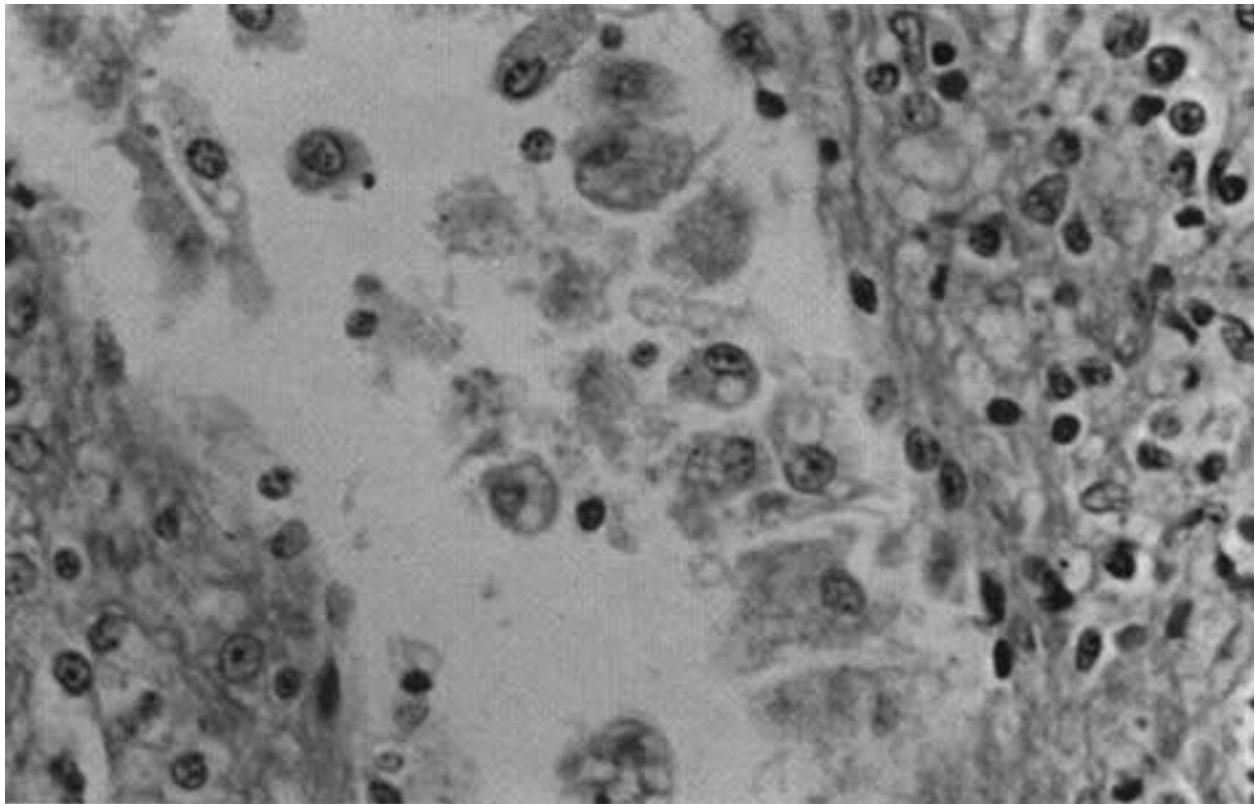
The criteria for the diagnosis of the hemophagocytic syndromes are quite explicit, but it bears repeating that the tissue diagnosis is best made on the bone marrow, not on the lymph node appearance in the absence of bone marrow confirmation. The marrow stroma is often edematous, so-called pink fat. Cellularity is variable, depending on the stage of the disease. The large, cytoplasm-rich macrophages that are so obvious in depleted marrows may be quite inconspicuous in cellular marrows. Hemophagocytosis by the macrophages is variable, extensive in most, but minimal in others. The diagnosis can be made in the absence of hemophagocytosis. Lymph nodes are variably populated by large macrophages and confined to sinuses early on, but the paracortex can be filled when the disease is extensive. The same caveats regarding

hemophagocytosis apply to the lymph node, but the diagnosis should not be made on a node alone, because severely depleted nodes from many causes, following radiation or postchemotherapy, may have the same appearance.

The hepatic features can be distinctive enough to suggest the diagnosis, pending bone marrow confirmation.<sup>14</sup> The liver reveals portal infiltration by lymphocytes and large cytoplasmic macrophages, extensive sinusoidal activation, and hemophagocytosis most prominent in sinusoidal cells. A characteristic feature is the presence of large macrophages apparently lying free in the portal or the central veins with venulitis<sup>14</sup> (Fig. 8). Because the macrophages are activated, they are clearly marked in tissues by the use of CD 68 antibodies, such as KP-1, in a cytoplasmic vacuolar pattern. The presence of some S100 staining, especially in the liver infiltrates, should not deflect from the morphologic diagnosis.

Spleen involvement is diffuse, with involvement of red pulp cords and sinuses, and splenic puncture has been used to confirm a diagnosis. Lung involvement can occur.<sup>77</sup> Neurologic symptoms are usual, and cerebrospinal involvement with large cytoplasmic macrophages is found.<sup>29</sup>

The hemophagocytic syndrome is considered a result of excess cytokine release from lymphocytes and macrophages, particularly the T helper 1 (TH1) mediators TNF $\alpha$ , interferon  $\gamma$



**Figure 8** Liver, familial hemophagocytic lymphohistiocytosis. The appearance of floating hemophagocytic macrophages in portal veins and central veins is a helpful diagnostic feature. (Original magnification X 400)

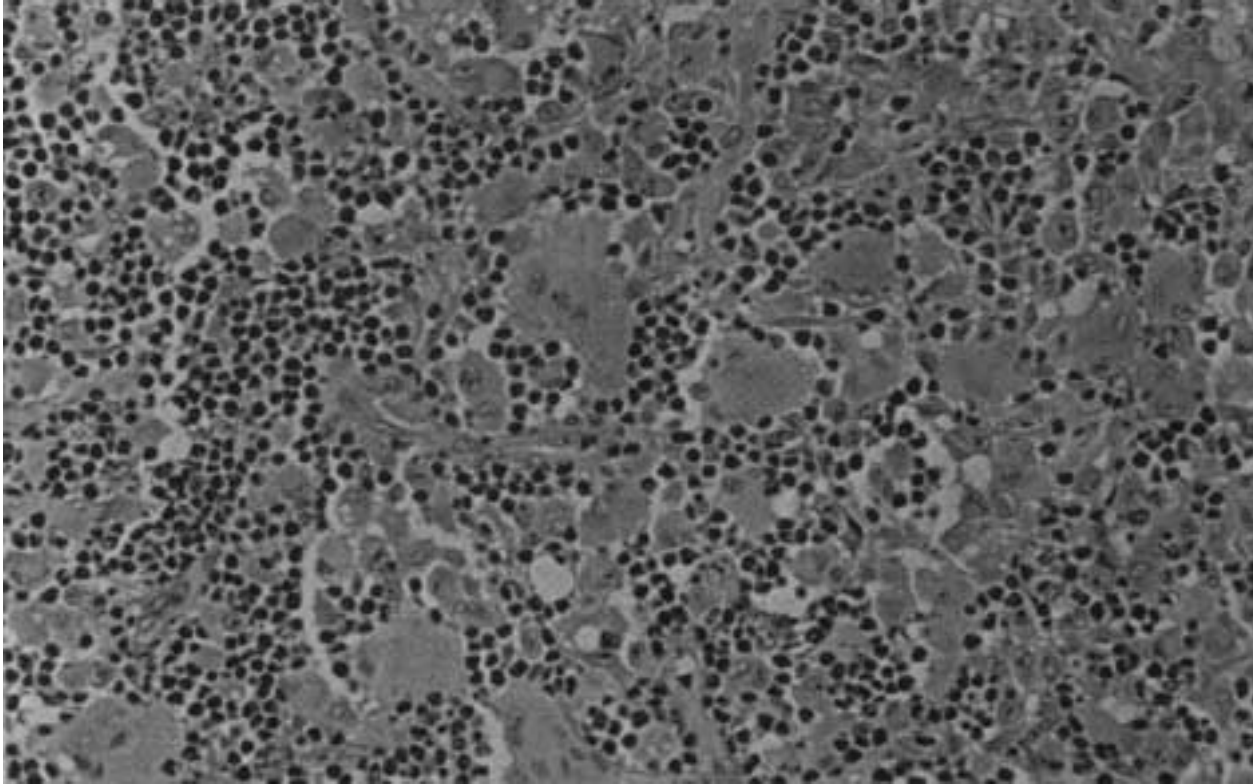
(IF $\gamma$ ), IL-1 $\alpha$ , IL-2, and IL-6.<sup>28</sup> Levels of cytokine regulators reveal an increase in IL-12 in the acute phase, which is consistent with the TH1 pattern; an absence of IL-4, which confirms TH2 inactivation; and an increase in the levels of IL-10, which indicate that the pathway for TH1 inactivation is intact, though ineffective.<sup>51</sup> EBV infection of T cells, but not B cells, has been shown to upregulate the expression of TNF $\alpha$  selectively, leading to macrophage activation.<sup>37</sup>

## **Reticulohistiocytoma and Multicentric Reticulohistiocytosis**

Solitary and multiple dermal reticulohistiocytomas are unusual lesions that have been seen in the newborn period but more commonly in young adult males at any site on the body. Multicentric reticulohistiocytosis is an adult disease that involves skin, bones, and joints but rarely lymph nodes,<sup>64</sup> and it can occur in the acral areas of older females.<sup>74</sup> What the childhood and adult forms have in common is the histologic appearance of the constituent cells: very large cells that are rich in glassy, homogenous cytoplasm that stains lightly with PAS (Fig. 9). Immunohistochemical studies confirm the macrophage nature of the cells,<sup>57</sup> but Zelger et al<sup>74</sup> claim that there are differences between constituent cells in solitary versus multicentric lesions. Specifically, they found that the cells of the solitary lesions were larger and stained for Factor XIIIa and muscle-specific actin HHF35, whereas the smaller cells of the multicentric lesions did not. Fascin does not stain the cells, so that there is insufficient reason at this stage to assign these cells to the dendritic family,<sup>34</sup> although some overlap would not be unexpected.

## **Rosai-Dorfman Disease**

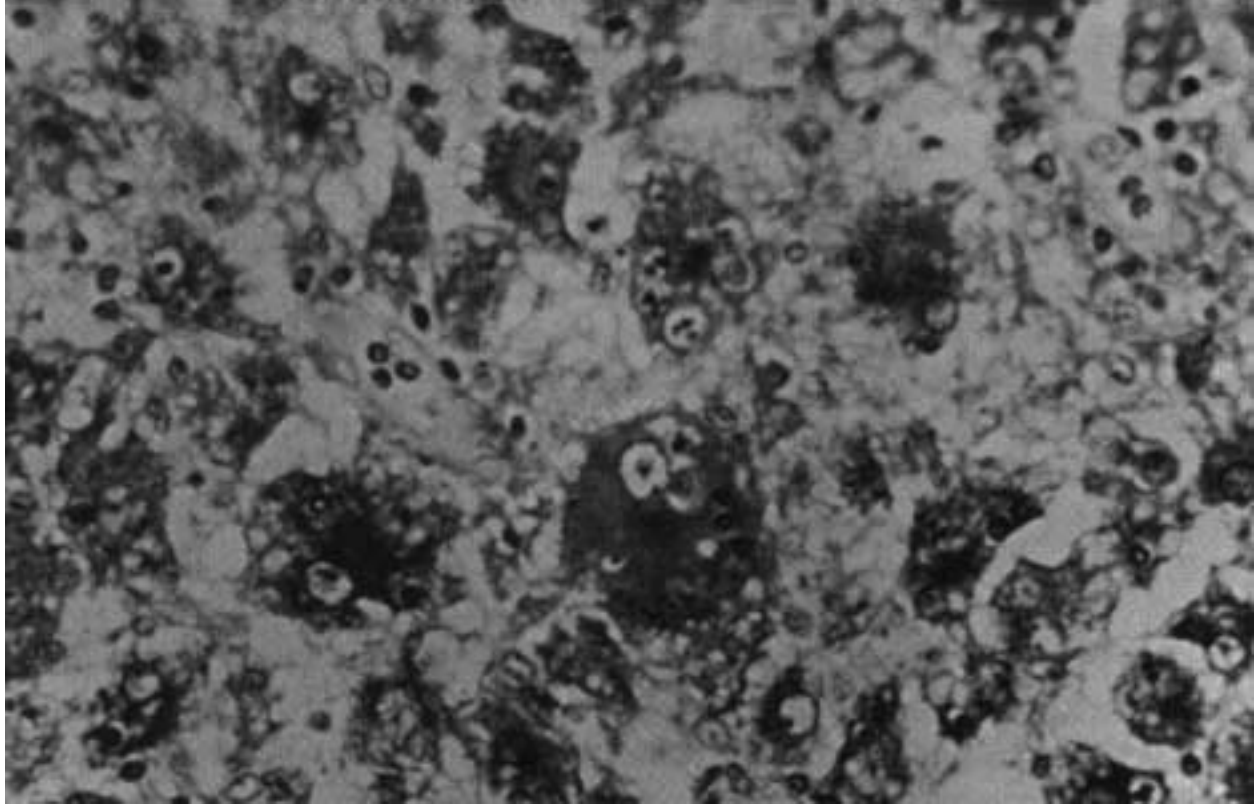
Rosai-Dorfman disease is an idiopathic and generally self-limiting condition when localized, but it has a worse prognosis when extranodal sites such as lung or liver are involved.<sup>18</sup> Cervical nodes are most commonly involved in children, though other sites, notably bone, have been involved in this age group. The large characteristic Rosai-Dorfman cells, with their pale, water-clear cytoplasm and leukocyte emperipolesis, are unique. Diagnosis is generally made on the histologic or cytologic features alone. HUMARA assay shows the process to be nonclonal.<sup>52</sup> Although the condition is listed as a macrophage disorder in the recent classification, immunophenotyping and enzyme histochemistry are more complicated. The cells have the histochemical apparatus of the macrophage; esterases and acid phosphatases are present in large amounts. The cells also have phenotypic features of the macrophages; specifically, they have CD 68 and  $\alpha$ -1-antitrypsin positivity.<sup>13</sup> The cells, however, also show some of the phenotypic characteristics of the dendritic cell series, expressing S100 and cathepsin E,<sup>53</sup> fascin<sup>34</sup> (Fig. 10), and on occasion CD 1a. The pattern is that of a cell with features of both macrophage and dendritic cell lineages, most closely resembling the newly described sinus dendritic cell.<sup>67</sup> No known phenotypic differences exist between intranodal and extranodal disease, and the phenotype is confirmatory when the lesion is found at unexpected sites.



**Figure 9.** Reticulohistiocytoma. A newborn had a papular lesion on the chest. The very large cells with glassy cytoplasm are diagnostic. The phenotype was CD68+, PNA+, CD1a-, S100-, fascin-. (Original magnification x75)

## SUMMARY

The histiocytoses, systemic disorders of the dendritic or macrophage lines, are an enigmatic group of disorders. It is hoped that by better understanding and identification of the responsible cells in each of the various conditions, their biological nature will become apparent. Because they are unusual, only multi-institutional groups, such as the Histiocyte Society, will be able to collect enough examples and bring a standardized approach to their evaluation. Those interested in joining the Histiocyte Society are invited to apply by contacting the Histiocyte Society, 302 N. Broadway, Pitman, NJ, 08071.



**Figure 10.** Rosai-Dorfman disease, soft tissue. The very large Rosai-Dorfman cells have emperipolesis of leukocytes. The phenotype was CD68+, S100+, fascin+, CD1a-. (Fascin immunostain, original magnification x125).

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