Few categories of disease are as confusing as the histiocytic disorders. The historical origins of this confusion are readily understandable. At the time of the initial descriptions of these diseases, few reliable markers were available to determine either the lineage or the stage of differentiation of the cells involved. Moreover, malignancy as applied to the histiocytic diseases was an operational definition founded on an aggressive clinical course or aberrant morphology rather than on knowledge of clonality and altered cellular differentiation. These uncertainties stimulated a proliferation of multiple names for similar clinical syndromes, further adding to the confusion. Fortunately, this situation has now begun to change. With the techniques of modern cellular and molecular biology it is now possible to reevaluate and catalogue the histiocytic disorders by less ambiguous criteria than those used previously.

The Cellular Origins of Histiocytes

The term histiocyte was originally used to designate a large cell normally found in lymph nodes and spleen that was morphologically nonspecific, but had voluminous, granulated cytoplasm, sometimes containing ingested particles, and one or more round to irregularly shaped pale nuclei. Subsequently, the term histiocyte was taken as synonymous with the fully differentiated end cells of the monocyte/macrophage lineage including sinusoidal macrophages in the spleen, alveolar macrophages in the lung, and Kupffer cells in the liver.

Still more recently, the term has been extended to include another group of cells comprised of Langerhans cells of the skin, interdigitating dendritic cells of the lymph nodes, thymus, and spleen, and dendritic reticulum cells found principally in the germinal centers of lymph nodes. Consequently, the term histiocyte, as currently applied to the histiocytic diseases was an operational definition of the cells involved. Moreover, malignancy as defined on the basis of cellular differentiation. These uncertainties stimulated a proliferation of multiple names for similar clinical syndromes, further adding to the confusion. Fortunately, this situation has now begun to change. With the techniques of modern cellular and molecular biology it is now possible to reevaluate and catalogue the histiocytic disorders by less ambiguous criteria than those used previously.

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The current concept of lineage derivation of macrophages and dendritic cells is summarized in Fig 1A. Both macrophages and Langerhans/dendritic cells arise from bone marrow (BM) CD34+ stem cells, probably under the influence of granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-3 (IL-3), and tumor necrosis factor α (TNFα).1,2 Macrophages develop from the stem cell, designated colony-forming unit granulocyte-macrophage (CFU-GM), committed to granulocyte and macrophage differentiation. These stem cells give rise to promonocytes that mature in the BM to monocytes, which then circulate in the blood before entering the tissues to complete the maturation process. The Langerhans cell also develops from a blood cell that originates in the BM. Its maturation commences in the epidermis, but may not be completed before these cells migrate into the lymphatics of the dermis and are swept along to lymph nodes. There, in regions rich in T cells, they complete the process of maturation into dendritic cells. Whether the Langerhans cell is an obligatory intermediate in the maturation of an interdigitating dendritic cell or whether these antigen-presenting cells can also develop more directly from blood borne cells is not known. Langerhans cells contain distinctive Birbeck granules that are not found in macrophages or other cell types. These are rod- and occasionally, tennis-racquet-shaped organelles with a central zipper-like striation.

Functionally, monocytes and macrophages are "professional phagocytes" that defend against microorganisms and rid the body of unwanted organic and inorganic particles by means of their phagocytic prowess. The Langerhans and dendritic cells are poor phagocytes, but are highly evolved for the efficient presentation of new antigens to CD4+ T lymphocytes in the initiation of the immune response. They present antigen in conjunction with their rich array of surface MHC class II and CD1a antigens. The Langerhans cells develop from a population of CD4+ and CD5+ blood cells. With continued maturation in vitro, and presumably in vivo, they develop into dendritic cells. In the process of maturation, Birbeck granules and cytoplasmic endosomes that are abundant in the Langerhans cell become less abundant and may be sparse or absent in the mature dendritic cells. CD1a antigen density also diminishes.

Macrophages and dendritic cells share certain characteristics, and it is probable, but not certain, that they belong to the same cell lineage. The evidence for a common lineage is as follows. Both cell lines arise from blood cells that originate in BM stem cells bearing CD34 surface antigen. Differentiated macrophages and dendritic cells have many antigens in common including CD1a, CD18, CD45, CD54, and surface receptors for some Ig and complement molecules, but each also has unique antigens (Table I). Both types of cells respond to the growth stimulatory signals of GM-CSF, IL-3, and TNFα.3,4 and both synthesize certain biologically active molecules including IL-1β, macrophage inflammatory protein (MIP-1α), and MIP-2.4,37 The fact that they differ in certain morphologic features and in phagocytic and antigen-presenting abilities does not argue against a common lineage, for it has long been known that macrophages from different anatomic sites differ structurally and that environmental conditions have profound influences on whether the cell develops the characteristics of a tissue or of an alveolar macrophage. The only strong argument against a common cellular origin of macrophages and dendritic cells is the observation that in osteopetrotic mice congenitally deficient in CSF-I production, tissue macrophages are decreased in numbers, but dendritic cells are not.44 Balanced against this are observations, both in fetal murine development and in differentiation of human cord blood cells in vitro, that there are phenotypic transitions between macrophages and dendritic cells in the display of antigens such as CD1a, CD14, CD33, and receptors for Ig and C3b complement component. Two other observations, which admittedly may have alternative explanations than a common lineage, are also pertinent. First, in the Chediak-Higashi syndrome, giant lysosomes are seen in Langerhans cells as well as granulocytes and macrophages, suggesting that these cells arise from the same abnormal stem cell. Second, diseases of Langerhans cells have occasionally been reported to evolve to acute malignancies of monocytic cells. Among the antigenic, structural, and functional markers that are helpful in identifying macrophages and Langerhans cells in disease states are CD1a and CD3, CD15, CD30, CD45, CD68, acid phosphatase, and lysozyme (Table I). Two features are particularly useful for personal use only. on October 21, 2014. For personal use only.
Fig 1. The origin of histiocytes and the histiocytic disorders. (A) The cellular origin of macrophages, Langerhans cells, and dendritic cells from CD34+ stem cell (SC). Langerhans cells and, to a lesser extent, dendritic cells have distinctive intracytoplasmic Birbeck granules. The direct pathway between Langerhans cells and the common granulocyte/macrophage stem cell (CFU-GM) is not certain. (B) Macrophages and Langerhans cells play prominent roles in four categories of disease: reactive and malignant macrophage disorders and reactive and malignant Langerhans cell disorders.

in distinguishing these cells from other cell types and from each other: the distinctive Birbeck granules in Langerhans cells and the phagocytosis by macrophages of large particles such as blood cells. Macrophages lack Birbeck granules, and Langerhans cells are only weakly phagocytic. Although a variety of tumor cells, including rhabdomyosarcoma cells and myeloma cells, may occasionally exhibit phagocytosis, the phenomenon is not common and these cells are readily distinguished from mononuclear phagocytes.

CRITERIA FOR CLASSIFICATION OF HISTIOCYTIC DISORDERS

With current knowledge of the developmental biology of the histiocytic cell lineages, it is now possible to formulate a reasonable catalogue of histiocytic diseases based on ultrastructural and phenotypic markers of lineage (Table 1) and molecular or chromosomal markers of malignancy. In the
past, it was not always easy to determine whether a proliferating cell was reactive or neoplastic, and several histiocytic diseases that were thought to be malignant have, in fact, never been shown to involve a clonal expansion of abnormally differentiated cells. In view of these uncertainties, it is important to precisely define cell lineage and to use objective criteria for defining malignancy. I suggest the following criteria for defining malignancy:

Definite. Definite histiocytic malignancy is a clonal disease with proliferation of cells with enzymatic, functional and/or immunophenotypic characteristics unique to macrophages or Langerhans cells. Because there are no known clonal markers unique to the histiocytic system, other markers such as chromosomal rearrangements must sometimes be used to define clonality.

Probable. Probable histiocytic malignancy is (1) proliferation of cells with enzymatic, functional, and/or immunophenotypic characteristics of macrophages or Langerhans cells, and disease progression to monoblastic leukemia and/or generation of a monoblastic leukemic cell line, or (2) a clonal proliferation of cells, usually defined by a chromosomal marker, with expression of phenotypic markers of more than one lineage, but including macrophage or Langerhans cell markers.

Possible. Possible histiocytic malignancy is a proliferation of cells with enzymatic, functional, and/or unique immunophenotypic characteristics of macrophages and a clonal rearrangement of Ig or T-cell receptor (TCR) genes.

The criteria listed as probable and possible take cognizance of the fact that there is considerable ‘lineage infidelity’ in acute leukemic hematopoiesis. Biphenotypic markers are a common event, and lineage conversion is a well-documented phenomenon, and Ig and TCR gene rearrangements are excellent markers of clonality but occur frequently in myeloid as well as lymphoid leukemias. Using the above criteria, one can reasonably conclude that true malignancies of macrophages and Langerhans cells are uncommon, but do exist.

Classification of Histiocytic Disorders

A logical approach to the classification of the histiocytic disorders divides them into diseases of macrophages and those of Langerhans/dendritic cells and then further subdivides these according to whether the proliferating cells are malignant or ‘reactive,’ i.e., neoplastic or proliferating in response to an inflammatory stimulus. Considered in this way, there are four major categories of histiocytic disease:

1. reactive macrophage histiocytoses, (2) malignant macrophage histiocytoses, (3) reactive Langerhans cell histiocytoses, and (4) malignant Langerhans cell histiocytoses. In the text that follows, I have attempted to distinguish between the reactive and malignant disorders based upon the criteria of malignancy described above. Where there is uncertainty with regard to the malignant nature of a given disorder, I have so indicated.

Each of these categories can then be further subdivided according to the characteristics of the proliferating cells or by clinical manifestation. For example, hemophagocytic histiocytoses encompasses several disorders with the common feature of morphologically dramatic phagocytosis of blood cells by large macrophages. Figure 1B presents a schematic summary of the histiocytic diseases based upon cell lineage and whether or not cell proliferation is neoplastic or reactive. Fig 1C and Table 2 present an expanded version of this classification of histiocytic diseases. In Table 2, six major categories of macrophage disease (types M-I to M-VI) and
Table 1. Markers for Macrophages, Langerhans Cells, and Dendritic Cells

<table>
<thead>
<tr>
<th>Antigens</th>
<th>Macrophage</th>
<th>Langerhans Cell</th>
<th>Dendritic Cell</th>
<th>Histiocytoses</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LHCH</td>
<td>MH-PH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-100</td>
<td>± +</td>
<td>+ +</td>
<td>+ +</td>
<td>–</td>
<td>8, 10-14, 16</td>
</tr>
<tr>
<td>MHC class II</td>
<td>+ +</td>
<td>+</td>
<td>+ +</td>
<td>+</td>
<td>10, 11, 14</td>
</tr>
<tr>
<td>CD1a,c</td>
<td>+ +</td>
<td>+</td>
<td>+ +</td>
<td>+</td>
<td>10, 17-19</td>
</tr>
<tr>
<td>CD4</td>
<td>± ±</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>8, 10, 20</td>
</tr>
<tr>
<td>CD11b,c</td>
<td>++ +</td>
<td>+</td>
<td>+</td>
<td>8, 10</td>
<td></td>
</tr>
<tr>
<td>CD14 [My4]</td>
<td>++ ±</td>
<td>± ±</td>
<td>–</td>
<td>– +</td>
<td>8, 10, 17, 21</td>
</tr>
<tr>
<td>CD15A</td>
<td>++ +</td>
<td>–</td>
<td>–</td>
<td>+ –</td>
<td>10, 13, 21</td>
</tr>
<tr>
<td>CD18</td>
<td>++ +</td>
<td>–</td>
<td>+</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>CD25 [IL-2R]</td>
<td>+ ±</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>10, 22, 23</td>
</tr>
<tr>
<td>CD30 [Ki-1]</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>± +</td>
<td>13, 15, 16, 21, 23</td>
</tr>
<tr>
<td>CD33 [My9]</td>
<td>+ +</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>24</td>
</tr>
<tr>
<td>CD35 [C3bR]</td>
<td>+ ±</td>
<td>–</td>
<td>+</td>
<td>+ +</td>
<td>10, 24, 25</td>
</tr>
<tr>
<td>CD45 [LCA]</td>
<td>++ +</td>
<td>+</td>
<td>+</td>
<td>+ +</td>
<td>13, 16, 21, 25, 26</td>
</tr>
<tr>
<td>CD54 [ICAM-1]</td>
<td>++ +</td>
<td>+</td>
<td>+</td>
<td>+ +</td>
<td>10, 26, 27</td>
</tr>
<tr>
<td>ICAM-2</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>10, 28</td>
<td></td>
</tr>
<tr>
<td>CD68 [KP-1]</td>
<td>+ –</td>
<td>–</td>
<td>–</td>
<td>± +</td>
<td>16, 17, 23, 28, 29</td>
</tr>
<tr>
<td>CD71 [Transf R]</td>
<td>++ ±</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>4</td>
</tr>
<tr>
<td>FCr [CD16, 32]</td>
<td>+ ±</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>10, 22</td>
</tr>
<tr>
<td>MAC 387</td>
<td>++ ±</td>
<td>–</td>
<td>± ±</td>
<td>– +</td>
<td>8, 14, 18, 16</td>
</tr>
<tr>
<td>HB15</td>
<td>– +</td>
<td>+</td>
<td>+</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>GM-CSFR</td>
<td>++ +</td>
<td>+</td>
<td>+</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>IgER</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>PNAR</td>
<td>diffuse halo &amp; dot</td>
<td>halo &amp; dot</td>
<td>halo &amp; dot</td>
<td>8</td>
<td></td>
</tr>
</tbody>
</table>

Morphology
- Birbeck granules: – + + + + + + + + + 11, 22, 32
- Lysosomes: + + + + + + + + + 2

Enzymes
- Lysozyme: ++ – – – ± + + 13, 16, 17, 21
- Acid phosphatase: ++ ± – – + + 8, 16, 23
- ATPase: – + + + + 8, 15, 33, 34
- α-naphthyl esterase: ++ + ± + 34
- Antitrypsin: ++ – – – ± + ± 8, 16
- Antichymotrypsin: ++ – + – ± + 8, 23
- Cathepsin E: – + + + + + 35
- α-mannosidase: – + + ± 8

Biologic
- TNFα: + – ± + 37
- IL-1β: + + + + + 36, 37
- IL-6: + – ± + 36
- Factor XIlia: – + + ± + 14, 38
- MIP-1α: + + ± + + 36
- MIP-2: + + ± + 29

Function
- Phagocytosis: ++ ± – – – 2, 6
- Antigen presentation: + + + + + 3, 7

Abbreviations: LHCH, Langerhans cell histiocytosis; MH-PH, macrophage hemophagocytic histiocytosis; R, receptor; LCA, leukocyte common antigen; PNA, peanut agglutinin; ICAM-1, intercellular adhesion molecule 1; MHC, major histocompatibility complex.

four categories of diseases of Langerhans cells (types L-I to L-IV) are listed. This can be compared with a working classification proposed by the Histiocyte Society in 1987 that has many of the same features, but does not distinguish among the reactive Langerhans cell disorders and groups together malignant disorders of macrophages and Langerhans cells.8

Nomenclature
A large number of clinical syndromes involving the proliferation of cells presumed or known to be histiocytes have been described. As noted above, true malignancies have often not been distinguished from a reactive proliferation of cells responding to antigenic or microbial stimuli. Additionally, each syndrome has been given at least one and usually several names, and much of the relevant literature in the past has been confusing and often chaotic. Obviously it is desirable to use disease designations that precisely identify the cells involved and the pathogenetic mechanisms when these are known. The subsequent text presents suggested names in boldface as well as historical designations in italics.
Table 2. Histiocytic Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Cell</th>
<th>Characteristic Pathologic Features</th>
<th>Clinical Course</th>
<th>Etiology/Pathogenesis (references)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive macrophage histiocytoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M-I. Storage diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Gaucher's disease</td>
<td>MP</td>
<td>Intraacellular storage material in macrophages.</td>
<td>Chronic; infiltration and dysfunction.</td>
<td>Enzyme deficiencies</td>
</tr>
<tr>
<td>B. Niemann-Pick disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. Sphingomyelinase deficiency</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M-II. Benign proliferative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>macrophage diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xanthoma disseminata;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multicentric reticulohistiocytosis;</td>
<td></td>
<td>Macrophages with foamy cytoplasm and usually without particle phagocytosis</td>
<td>Nodules in skin ± joints and ± viscera. Self-limited; sometimes recurrent</td>
<td>Unknown (38, 53-56)</td>
</tr>
<tr>
<td>Juvenile xanthogranuloma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M-III. Nonmalignant hemophagocytic macrophage diseases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease)</td>
<td>MP</td>
<td>Lymphocytophagocytosis</td>
<td>Benign to fatal; lymphadenopathy, ± visceral disease</td>
<td>Usually unknown; rare association with herpesvirus 6 or EBV (68-74)</td>
</tr>
<tr>
<td>MIV. Malignant diseases of macrophages</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Acute monocytic leukemia</td>
<td>Monoblast</td>
<td>Proliferation of primitive hematopoietic cells in BM</td>
<td>Aggressive; usually fatal</td>
<td>Unknown, malignant</td>
</tr>
<tr>
<td>B. Chronic myelomonocytic</td>
<td>Monoblast</td>
<td>Proliferation of primitive hematopoietic cells in BM</td>
<td>Aggressive; usually fatal</td>
<td>Unknown, malignant</td>
</tr>
<tr>
<td>leukemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M-VI. Malignant 5q35 histiocytosis</td>
<td>MP</td>
<td>Proliferating MPs without cellular phagocytosis</td>
<td>Cytophenias; infiltration of soft tissues and bone</td>
<td>Probably malignant with 5q35 translocation and cell lines (23, 47, 48)</td>
</tr>
<tr>
<td>Reactive Langerhans cell histiocytoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-I. Benign Langerhans cell histiocytosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Eosinophilic granuloma (Hand-Schuller-Christian disease)</td>
<td>LHC</td>
<td>Infiltration with Langerhans cells with characteristic Birbeck granules</td>
<td>Variable; benign to aggressive. Involves bone ± lungs, pituitary &amp; rarely viscera</td>
<td>Usually unknown (92-96, 99-101)</td>
</tr>
<tr>
<td>B. Relapsing Langerhans cell histiocytosis</td>
<td>LHC</td>
<td>Infiltration with LHCs</td>
<td>Variable; benign to aggressive; rarely fatal. Relapsing</td>
<td>Unknown (97, 98, 102-108)</td>
</tr>
<tr>
<td>C. Self-healing histiocytosis</td>
<td>LHC</td>
<td>Infiltration with LHCs</td>
<td>Skin involvement. Benign</td>
<td>Unknown (88-91)</td>
</tr>
<tr>
<td>Presumptively malignant Langerhans cell histiocytoses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L-II. Progressive Langerhans cell histiocytosis (Letter-Siwe disease)</td>
<td>LHC</td>
<td>Infiltration with LHCs</td>
<td>Fatal. Infiltration of skin, marrow, and viscera</td>
<td>Possibly malignant, but monoclonality not proven; some progress to AMoL (46, 111-128)</td>
</tr>
<tr>
<td>L-III. Langerhans cell lymphoma</td>
<td>LHC</td>
<td>Infiltration with LHCs with Birbeck granules</td>
<td>Aggressive lymphoma</td>
<td>Probably malignant; only 2 cases reported (34, 35)</td>
</tr>
<tr>
<td>L-IV. Dendritic cell lymphoma</td>
<td>DC</td>
<td>Node replacement by cells with complex interdigitating processes</td>
<td>Generally limited to lymph nodes</td>
<td>Probably malignant; some have aneuploidy (128-134); 13 cases reported</td>
</tr>
</tbody>
</table>

Historical designation of disease is given in italics.

Abbreviations: MP, macrophage; LHC, Langerhans cell; DC, dendritic cell; SLE, systemic lupus erythematosus; AMoL, acute monocytic leukemia.
Where the historical designation is unambiguous, it has been retained.

**CATEGORIES OF DISEASE**

**Storage diseases involving macrophages.** The storage diseases (Table 2, Reactive Macrophage Histioctyes, type M-I) are a diverse group of heritable disorders that have the common feature of macrophages filled with nondigestible organic material. Almost all involve an enzyme defect in a normal degradative or catabolic pathway that leads to intracellular accumulation of material in phagocytes. These disorders are best considered under the inborn errors of metabolism rather than as histiocytic disorders and are not further reviewed here. However, it should be noted that enzymatically normal macrophages can sometimes be overwhelmed by excessive tissue breakdown and mimic in appearance the cells found in the inherited enzyme deficiencies. For example, "sea blue" histiocytes may be seen in acquired idiopathic thrombocytopenic purpura as well as inherited sphingomyelinase deficiency.

**Benign proliferative macrophage diseases.** The benign proliferative macrophage diseases encompass a range of disorders with the common feature of skin nodules with macrophage infiltration (Table 2, Reactive Macrophage Histioctyes, type M-II). Most studies suggest that in diseases such as juvenile xanthogranuloma, xanthoma disseminata, and multicentric reticulohistiocytosis, the predominant cells are unequivocally macrophages, as evidenced by absence of Birbeck granules and reactivity with antimacrophage serum such as M-387. In juvenile xanthogranuloma, multinucleate giant cells called Touton cells are characteristic. Phagocytosis in these cells is not prominent. Therefore, these disorders might be designated simply as benign proliferative macrophage diseases.

The clinical course of the benign proliferative macrophage disorders varies from a self-limited disorder to an aggressive disease with complications of tissue destruction and infection. In juvenile xanthogranuloma and xanthoma disseminata, nodules are widespread in the skin and mucous membranes. Characteristically, the nodules in juvenile xanthogranuloma are 0.5 to 1 cm in diameter, are yellow to red in color and are prominent on the scalp and face; however, they can occur in the mesentery and viscera as well. The lesions usually appear in infancy, but may be present at birth or may be delayed until adult life. They usually involute spontaneously.

**Multicentric histiocytosis** is another rare multisystem disorder characterized by frequent joint involvement with a destructive synovitis, as well as visceral and muscle involvement, and may present problems in the differential diagnosis of dermatomyositis. It is a disease of adults and is sometimes associated with tuberculosis or with a concomitant malignancy. In one study of multicentric histiocytosis, the cells were described as dermal dendrocytes on the basis of factor XIIIa reactivity. In individual cases, the issue of cell lineage clearly can only be resolved by electron microscopy.

These benign proliferative macrophage disorders may all be clinical variants of the same process; however, because the inciting agents are unknown, one cannot draw a firm conclusion. There is no evidence for malignancy, but chemotherapy is sometimes indicated to interrupt the cycle of cell proliferation and prevent a destructive arthropathy or a disfiguring skin lesion. These disorders should be distinguished from the reactive histiocytic proliferations occurring in the setting of an immunodeficiency syndrome, such as X-linked lymphoproliferative syndrome, or in a phagocyte dysfunction syndrome such as chronic granulomatous disease. More familiar clinical disorders such as sarcoidosis may also share some of the pathogenetic events leading to proliferation and accumulation of mononuclear phagocytes.

**Nonmalignant hemophagocytic macrophage disorders.** Several clinically distinctive hemophagocytic syndromes have been described (Table 2, Reactive Macrophage Histioctyes, type M-III). They are all characterized by the proliferation within lymph nodes and sometimes other tissues of large macrophages phagocytizing and digesting blood cells including red blood cells, lymphocytes, neutrophils, and platelets. In all these syndromes, the predominant cell is defined by the absence of Birbeck granules and the presence of macrophage markers. In most cases, these macrophages are normal cells that appear to be reacting to an inciting stimulus. The nonmalignant hemophagocytic disorders include the following:

The **fulminant hemophagocytic syndromes** are aggressive and often fatal disorders most frequent in children and characterized by fever, systemic symptoms, jaundice, multiple organ failure, coagulopathy, and phagocytosis of blood elements with cytopenias. It may be fatal in up to 40% of cases, or recovery can occur in 1 to 8 weeks. The cells are macrophages that have S-100, CD11c, CD14, CD33, CD68, and receptors for Ig, complement and IL-2, and react with antibodies to lysozyme and with M-387.

The etiology is usually not known, but some cases appear to be a reaction to drugs or infection with bacteria or with viruses such as Epstein-Barr virus (EBV) and dengue virus. Sometimes a cluster of cases is observed suggesting transmission of a viral agent. In sporadic cases the clinical setting is often associated with immunodeficiency. A few cases have been associated with T-cell lymphoma and rarely with systemic lupus. It is uncertain in the T-cell lymphoma cases whether viral infection, possibly with EBV, is the inciting event to hemophagocytosis or whether in a subset of these cases it is the malignant nature of the process that is associated with hemophagocytosis. There is no evidence suggesting that the involved macrophages are neoplastic.

The largest series of cases of **fulminant hemophagocytic syndrome** have been reported from Asia, where virus infection is the usual inciting stimulus. Because of the frequency of associated viral infections, some authors have used the designation **viral-associated hemophagocytic syndrome** for this disorder.

Familial forms of hemophagocytic syndrome known as familial lymphophagocytic lymphadenopathy or familial erythrophagocytic lymphohistiocytosis have also been described. They are often associated with defects in humoral and cellular immunity. The clinical and histopathologic features of the familial form of this disorder are similar to those
of sporadic cases of hemophagocytic syndrome. A few cases have been associated with T-cell lymphoma. The familial disease can be an aggressive and sometimes fatal illness. Response to therapy is poor and allogeneic BM transplantation has been used in treatment.

Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease) is another of the hemophagocytic syndromes in which macrophages are the main protagonists. Lymphocytes inside of proliferating macrophages within the sinuses of lymph nodes is the predominant histologic feature. The macrophages are clearly defined by enzymatic and antigenic analyses. The internalized lymphocytes are frequently intact, suggesting that they have entered the macrophages by emperipolesis rather than by phagocytosis (ie, by particle ingestion); however, the two processes may be difficult to distinguish by light microscopy alone unless digestive degradation of phagocytized cells has already begun.

Whereas massive lymphadenopathy usually dominates the clinical picture, some cases may involve the genitourinary tract, upper veins, bone, or extranodal soft tissues. Fever, systemic symptoms, and evidence of inflammation including elevated erythrocyte sedimentation rate and granulocytosis are common. The outcome is usually benign, but prognosis correlates with the number of disseminated nodal groups and with involvement of extranodal tissues. Over 400 cases have been described. Some cases have been associated with EBV or herpesvirus 6 infection and one case with a malignant lymphoma, but usually the etiology is not defined. Most cases do not require treatment, but corticosteroids, vinca alkaloids, and alkylating agents have been used in severe cases.

Additional hemophagocytic disorders with names such as hemophagocytic lymphohistiocytosis, and cytophagic histiocytic panniculitis have been described, but it is unclear whether they are distinctive disease entities requiring separate terminology.

A variety of names has been applied to still another rare aggressive illness characterized by fever, systemic symptoms, abdominal and pleural effusions, and infiltration of skin, liver, lymph nodes, spleen, and BM by large multinucleate macrophages with ingested blood cells. The skin lesions are polymorphous and vary from macular eruptions resembling those seen in vasculitis to skin lesions are polymorphous and vary from macular eruptions resembling those seen in vasculitis to skin lesions are polymorphous and vary from macular eruptions resembling those seen in vasculitis to skin lesions are polymorphous and vary from macular eruptions resembling those seen in vasculitis to skin lesions are polymorphous and vary from macular eruptions resembling those seen in vasculitis to skin lesions are polymorphous and vary from macular eruptions resembling those seen in vasculitis to skin lesions are polymorphous and vary from macular eruptions resembling those seen in vasculitis to skin lesions are polymorphous and vary from macular eruptions resembling those seen in vasculitis to skin lesions are polymorphous and vary from macular eruptions resembling those seen in vasculitis to skin lesions are polymorphous and vary from macular eruptions resembling those seen in 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HISTIOCYTES AND HISTIOCYTOSIS

Drawing on the observations of earlier scholars that several disease syndromes had similar histologic features, coined the generic term histiocytosis X to encompass eosinophilic granuloma of bone, Hand-Schuller-Christian disease, and Letterer-Siwe disease. Many disorders that were classified under this rubric are now known to involve proliferation of Langerhans cell precursors and it has been proposed that the generic term be changed to Langerhans cell histiocytoses. It is convenient to divide these histiocytoses into two categories: nonmalignant disorders that are generally characterized by chronicity and granulomatous lesions, and the progressive and neoplastic diseases that are usually clinically acute and characterized by lesions in which cell proliferation is prominent. The former include the many variants of unifocal and multifocal eosinophilic granuloma and relapsing Langerhans cell histiocytosis. The presumptively malignant disorders include the childhood and adult variants of what was formerly called Letterer-Siwe disease and the Langerhans/dendritic cell variants of true histiocytic lymphoma. Problems frequently arise in the differential diagnosis of the Langerhans cell histiocytoses if only conventional histologic examination is used without ultrastructural or phenotypic analysis. Most often the confusion arises between histiocytosis and high-grade lymphomas.

Benign Langerhans cell histiocytosis. There are several nonmalignant diseases of Langerhans cells (Table 2, Reactive Langerhans Cell Histiocytosis, types L-1, A through C). Perhaps the rarest is so-called congenital self-healing histiocytosis which, as the name implies, is generally a benign disorder diagnosed at birth. The skin is the predominant organ involved and lesions may be widespread, prompting the designation of a “blueberry muffin baby.” Most cases resolve spontaneously, but occasionally, patients die from pulmonary involvement by the proliferating cells. There is little doubt that this is a disorder of Langerhans cells based on the presence of Birbeck granules and other phenotypic markers.

The term Hashimoto-Pritzker-type Langerhans cell histiocytosis has been applied to this disorder when it is characterized by deep subcutaneous skin nodules, but there is little rationale for retaining this designation.

The various disorders characterized by eosinophilic granuloma of bone and/or soft tissues are not uncommon. This term, which is widely used, is a misnomer because the lesions are polymorphous with a variable mixture of Langerhans cells, lymphocytes, foamy macrophages, fibroblasts, and eosinophils. Macrophages with appropriate markers are present in the lesions but the predominant cells are clearly Langerhans cells. Although it has been proposed, based on the composition of the cellular infiltrate, that the granulomata may be a part of an immunologic reaction, the granulomata are thought to be part of a benign reactive process with an unknown inciting stimulus. Occasional cases may be associated with reaction to drugs. The disease usually starts in childhood or adolescence as a solitary bone lesion. This is usually curable by curettage, excision, or irradiation, and the single bone lesion is considered to have an excellent prognosis. However, unless the solitary lesion is cured, the disease often spreads and continues to wax and wane throughout life. Sometimes multifocal bone lesions occur early. In its most benign form, the disease remains restricted to bone; however, in about 50% of patients, the pituitary is involved and diabetes insipidus occurs. Loss of other pituitary hormones is an occasional occurrence, and one must be aware of the possibility of hypothyroidism and estrogen deficiency as complications of this disease.

The clinical distinctions between the clinically benign form of eosinophilic granuloma and other nonmalignant diseases of Langerhans cells, such as Hand-Schuller-Christian disease, is often blurred. The latter disorder is also characterized by polymorphous lesions in bone and soft tissues with diabetes insipidus and exophthalmos being a frequent finding (Fig 4).
are frequently used in treatment, there is no definitive evidence that the cells are neoplastic.

To emphasize the blurred margins between these reactive Langerhans cell histiocytoses, it is not uncommon for localized eosinophilic granuloma to begin in childhood or adolescence and for the more widespread and aggressive disease to appear later in life. For this reason, these disorders have been provisionally grouped under a single disease category in Table 2 (type L-1).

Localized disease is treated and often cured by local excision or radiotherapy, but systemic disease is often treated by chemotherapy including vinblastine and etoposide. A few of these cases end in leukemia, Hodgkin’s disease, or other lymphomas; however, the contribution of years of chemotherapy to this evolution is difficult to evaluate.

Progressive and malignant Langerhans cell histiocytoses. Acute proliferative forms of Langerhans cell histiocytosis are more common in children, but also occur in adults. The common disease variant with involvement of the blood, BM, and viscera as well as skin was, in the past, usually called Letterer-Siwe disease or simply histiocytosis X, but the term progressive Langerhans cell histiocytosis is, for the moment, preferable (Table 2, Malignant Langerhans Cell Histiocytosis, type L-II). Cases have been reported in monozygotic infants and as a congenital disorder beginning in utero. The evidence for the neoplastic nature of these disorders is weak and is not based upon proven clonality, but upon the weaker evidence of occasional progression to monocyctic leukemia. The rare reported associations with mediastinal germ cell tumors may reflect observations of the tissue phase of acute monocyctic leukemia. The data on aneuploidy of the Langerhans cells determined by flow cytometry have been conflicting. There are reports suggesting that abnormalities of chromosome 17p13, the site

In the most aggressive form of Langerhans cell histiocytosis, which I have designated as relapsing Langerhans cell histiocytosis (Table 2, type L-1B), the granulomata occur throughout the skin, in the mucous membranes of the mouth and female genital tract, and in the lungs, bone, spleen, and lymph nodes. The viscera are occasionally involved, but the central nervous system outside of the pituitary is usually spared.

The disease often begins in adolescence, but continues throughout life. I have seen a case with onset at menarche followed by a long remission and then recurrence with pregnancy. This disease can be disfiguring, and lung involvement can be life threatening. In rare cases, lung transplantation has been attempted. As the name suggests, the disease often pursues a relapsing and remitting course. There is a poor correlation between the histologic appearance of the Langerhans cells and clinical behavior of disease. Although the disease may be very aggressive and anticancer agents

Fig 3. (A) Maculo-papular skin lesion in a patient with hemophagocytic histiocytosis. (B) Nodular skin lesion in a patient with hemophagocytic histiocytosis.

Fig 4. A child with Langerhans cell histiocytosis with prominent exophthalmos. She also had defects of membranous bone and diabetes insipidus.
of the p53 gene, are common in this disease.\textsuperscript{117} For now, progressive Langerhans cell histiocytosis is listed as a malignant disorder, but the reader should be aware that this designation is uncertain.

The clinical and histologic borders that divide aggressive relapsing Langerhans cell histiocytosis from progressive Langerhans cell histiocytosis are often indistinct. The course of progressive Langerhans cell histiocytosis is often acute and frequently fatal with visceral and hematopoietic involvement. Skin lesions are prominent on the back, buttocks, and postauricular areas, and often resemble seborrheic dermatitis. Lytic bone lesions have a predilection for the skull and proximal appendages, and are a result of orbital involvement. These are common features. Lymphadenopathy may be massive. Other organs involved may include thymus, spleen, BM, kidney, gastrointestinal tract, and muscle.\textsuperscript{118} The lungs often have a honeycomb appearance on roentgenograms. The pituitary is commonly infiltrated by tumor, but only rarely is the rest of the central nervous system involved.\textsuperscript{119} The proliferating cells in the bone and visceral lesions have the morphologic and phenotypic characteristics of Langerhans cells, and the finding of Birbeck granules confirms the diagnosis; however, there is a poor correlation between histologic appearance of the lesions and clinical behavior of disease.\textsuperscript{12}

A variety of drugs have been used to treat these histiocytoses. The published reports do not always distinguish between the different categories of histiocytic disease, so one is uncertain as to whether malignancies of macrophages or of Langerhans cells are being described. The drugs include vinca alkaloids, doxorubicin, corticosteroids, etoposide, and interferons given alone or in combination.\textsuperscript{120-122} Although the rationale for using the drug was its toxicity for monocytes, 2-chlorodeoxyadenosine was reported to be effective in a case that appears to have been typical Langerhans cell histiocytosis.\textsuperscript{123}

Eleven patients in a series of 90 children with Langerhans cell histiocytosis were considered to have a poor prognosis based on organ dysfunction. They were treated with aggressive multiagent chemotherapy, but six died and three have recurrent disease. In contrast, in good-prognosis patients, the response to single chemotherapeutic agents is good, with between 63% and 90% entering complete remission.\textsuperscript{124} Recently there have been several reports of BM transplantation for malignant histiocytosis. At least some with Langerhans cell histiocytosis have prolonged disease-free survival after autologous or allogeneic BM transplantation.\textsuperscript{125,126} Good results with liver transplantation\textsuperscript{127} and poor results with lung transplantation have also been reported.\textsuperscript{128}

Malignant Langerhans cell and dendritic cell lymphomas. There is some evidence for a localized form of malignant Langerhans cell histiocytosis that could reasonably be called Langerhans cell lymphoma. Two cases have been described that were clinically aggressive neoplasms with involvement of several organs. The tumor cells had prominent mitoses, Birbeck granules, and Langerhans cell markers such as adenosine triphosphatase (ATPase). They also had some markers found in macrophages including KP-1 and nonspecific esterase.\textsuperscript{33,24} Like other malignant Langerhans cell histiocytoses, they were negative for CD30.

There is more evidence for the existence of lymphomas that appear to be neoplasms of interdigitating dendritic cells. Thirteen cases have been described\textsuperscript{129-134} and recently reviewed.\textsuperscript{135} The cell type is identified by ultrastructural analysis that shows long processes with complex interdigitations. These are distinct from the proliferating cells involved in the other forms of presumptively malignant histiocytoses.\textsuperscript{8,15,13,136} The cells generally lack definitive macrophage markers, but may stain weakly for acid phosphatase and strongly for ATPase and C3b receptors. They react with antibody CR4,\textsuperscript{23} which is said to be specific for dendritic cells.\textsuperscript{136} Although the cells are predominantly mononuclear, some tumors have aneuploidy by DNA analysis, suggesting that these tumors are probably truly malignant.\textsuperscript{135} The clinical course of these dendritic cell lymphomas may be relatively benign or aggressive.\textsuperscript{136}

HISTORICAL LANDMARKS IN THE HISTIOCYTIC DISORDERS

In 1893, a 25-year-old medical resident by the name of Alfred Hand, Jr, presented a paper to the Philadelphia Pathological Society entitled Polyuria and Tuberculosis. In it he described the autopsy of a patient that showed several defects in cranial bone.\textsuperscript{137} Hand reviewed the subject again, 28 years later,\textsuperscript{138} but by that time several others had claimed a piece of the action. In 1905, Kay described a similar case with bone lesions, exophthalmos, and polyuria and presented the patient to the Pennsylvania Medical Society.\textsuperscript{139} In 1915, Artur Schuller in Germany and, in 1920, Henry Christian of the Peter Bent Brigham Hospital (Boston, MA), respectively, described similar cases. Christian’s case was described in Defects in Membrane Bone, Exophthalmos and Diabetes Insipidus, An Unusual Syndrome of Dyspituitarism.\textsuperscript{140}

In 1924, Eurch Letterer described a 6-month-old child with a fulminant nonleukemic proliferation of cells of the reticuloendothelial system.\textsuperscript{141} Nine years later, Stern Siwe put Letterer’s case together with two other cases to describe ein neues Krankheitsbild unter den Hepatosplenomenagen.\textsuperscript{142} Like Hand before him, Siwe persevered in his interest and reviewed the histiocytic disorder again, 16 years later.\textsuperscript{143}

In 1940 Lichtenstein and Jaffe\textsuperscript{144} and Olani and Ehrlich\textsuperscript{145} simultaneously described eosinophilic granuloma of bone, and in 1941, Dr Sidney Farber at a meeting of the American Association of Pathologists and Bacteriologists drew attention to the histologic similarities of Hand-Schuller-Christian disease, Letterer-Siwe disease and eosinophilic granuloma of bone.\textsuperscript{146} In 1953, Lichtenstein coined the term histiocytosis X to describe these entities. In 1966, Bassett and Nezeloff, working in Paris, identified the Langerhans cell as being a characteristic cellular feature of histiocytosis X.\textsuperscript{147} Nezelof continues to work on this disease at present.\textsuperscript{148,47}
molecular or chromosomal markers of malignancy. The catalogue includes the following groups of diseases.

Nonmalignant reactive macrophage disorders include (1) macrophage storage diseases, (2) several benign proliferative macrophage disorders that predominantly involve skin and bone, and (3) several hemophagocytic syndromes that vary from indolent and benign to fulminant and fatal. In some of the latter disorders, viruses have been identified as the inciting stimulus.

The malignant macrophage disorders include (1) acute monocytic leukemia and (2) chronic myelomonocytic leukemia. A rare disorder that gave rise to a permanent cell line with an anomaly of chromosomal segment 5q35 may also be an example of a histiocytic malignancy. The existence of a separate category of true histiocytic lymphoma of macrophage type is uncertain.

Reactive Langerhans cell disorders include (1) congenital self-healing histiocytosis, (2) the many variants of eosinophilic granuloma, and (3) a related disorder designated as relapsing Langerhans cell histiocytosis that is characterized by a relapsing course and infiltration of bone and soft tissues by Langerhans cells.

Presumptively neoplastic diseases of Langerhans and dendritic cells include (1) progressive Langerhans cell histiocytosis, a disease with prominent involvement of blood and BM as well as skin and viscera; (2) Langerhans cell lymphoma, and (3) dendritic cell lymphoma. However, clonality as a marker of malignancy has not been proven in these disorders.

NOTE ADDED IN PROOF

A recent report148 provides strong evidence that all forms of Langerhans cell histiocytosis are clonal. This means that eosinophilic granuloma and relapsing Langerhans cell histiocytosis should be classified among the malignant disorders of histiocytes.

ACKNOWLEDGMENT

I am grateful to a reviewer of this manuscript for pointing out the correct sequence of historical events in defining the diseases encompassed by the term histiocytosis X.

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