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Paediatric Update

The Histiocytoses: The Fall of the Tower of Babel

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INTRODUCTION

THE HISTORY of our understanding and treatment of patients suffering from the group of diverse disorders, termed 'the histiocytoses', is characteristic of the self-correcting chain of events which often occurs in science and medicine. To this day these disorders remain enigmatic. In nearly all examples we do not understand their aetiology. There is a primitive view of their pathophysiology. Their classification continues to change and their treatment remains empirical at best [1–5]. Yet, progress has been made as evidenced both by the level of data-driven discussion and, most importantly, the fact that more patients now survive.

This update will examine: (1) some of the historical developments associated with our understanding of these disorders; (2) issues concerning their classification; (3) data upon which interpretations concerning aetiology and pathogenesis can be made; (4) the successes and failures of different treatment approaches; (5) late sequelae; and (6) future areas of challenge.

HISTORICAL NOMENCLATURE

When Metchnikov described the reaction of cells of the larval starfish to a rose thorn in the late 1800s, the first building blocks of a system which would eventually be referred to as the Tower of Babel were set [6]. Based on the observations and conceptual framework of Metchinkov's work on phagocytic cells, Aschoff introduced the term 'reticuloendothelial system' (RES) [7]. 'Reticulo' refers to the characteristic of cells comprising this compartment to form a 'lattice or reticulum by cytoplasmic extensions', while 'endothelial' refers to the fact that these cells often are situated near vascular endothelial cells. [8]

The macrophage was considered to be the central cellular player in this system because of its ability to ingest, remove or store large (hence its name 'macro' = large and 'phage' = to eat) foreign or excess and particulate materials. While such particulates were initially introduced as foreign material such as dyes, it soon became apparent that macrophages play a critical role in the ingestion and removal of invading microorganisms as well as cellular waste products and debris. Macrophages were thus easily separated from 'microphagocytic' polymorphonuclear granulocytes (PMN) by both the type of particulate material processed, as well as the often long time periods ingested material could be observed in macrophages compared with the relatively short periods in PMN.

A wide variety of terms were subsequently used to described the cellular constituents of the RES depending upon their morphology and location, as well as the type of foreign material ingested. Such terms have included peritoneal macrophages, alveolar macrophages, Kupffer cells, foam cells, synovial cells, osteoclasts and microglial cells. During this period of descriptive proliferation, the term 'histiocyte' was utilised to designate macrophages which were in tissues (either fixed or mobile) and contained somatic tissue remnants. Other terms started to proliferate which led Gall to list over 30 terms for these macrophages and refer to the RES as the 'Tower of Babel' [6]. During the late 1960s, van Furth introduced the terminology of the Mononuclear Phagocytic System (MPS) based on his conclusion that this nomenclature better described the morphological, functional and kinetic features of the RES [9]. In many respects, the terms RES or MPS fall short of describing this complex system of tissue maintenance and host defence. The system is often not necessarily 'reticular' and there would appear to be no competing 'non-mononuclear' phagocytic systems. Nevertheless, these terms, like the rather general and nondescript term, histiocyte, still persist.

Subsequent studies provided additional critical evidence that macrophages played a much more profound role in host defence than as simple scavengers. That role is now known to involve the ingestion and processing of foreign material, particularly bacteria, followed by the presentation of major histocompatibility complex (MHC)-bound peptide antigens to T lymphocytes. The activation of T lymphocytes results in a cascade of events leading to both macrophage and lymphocyte proliferation directed at eliminating the invader's threat to the host.

The discovery of the epidermal dendritic cell by the Berlin medical student, Paul Langerhans, in 1868 subsequently resulted in the addition of yet another group of cells to the RES or MPS [10]. But it took over 100 years for this to be

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fully appreciated due to the initial misclassification of this cell as neuronal and because of its distinctive morphological and functional characteristics.

Langerhans initially believed his namesake cell to be part of the nervous system because of the dendritic-like processes observed following gold chloride [10]. In a subsequent publication he retracted this view but did not provide a definitive function to this class of cells [11]. A functional role for dendritic cells and, in particular, Langerhans cells, would only become evident in the 1960s and 1970s with the discovery of their ability to process and present antigens (especially viral, cancer-associated and self-antigens) to T lymphocytes and thus profoundly activate immune responses [12, 13]. In addition to the overlapping functional characteristics of macrophages and dendritic cells including Langerhans cells, they have also been shown to share subsets of cytoplasmic and surface differentiation antigens plus a common haematopoietic cellular origin. Finally, the diseases in which macrophages and dendritic cells are involved may also share both clinical and pathophysiological characteristics.

These features have provided sufficient linkage to consider these two relatively divergent but related cell types as part of the RES or MPS involved in normal host defence and immunity. The term histiocyte has thus taken on a broader definition encompassing a wide variety of different cell types, but primarily including macrophages and dendritic cells. The term 'histiocytosis', therefore, simply refers to the increased numbers of these cell types observed in certain disease states, although the term adds little to reveal any underlying cause. Much work has been directed to refining the description and understanding of these disorders in order to provide a more rational basis for determining therapeutic interventions. This update will focus on only the major types of 'histiocytosis'.

A COMMON ORIGIN BUT SEPARATE LIVES

Much debate has occupied the search for the cell of origin of histiocytes from their initial description. Macrophages were first to arise locally from mesenchymal tissue components [8]. Blood monocytes were considered to be circulating progeny of similar tissue resident cells. Other groups believed

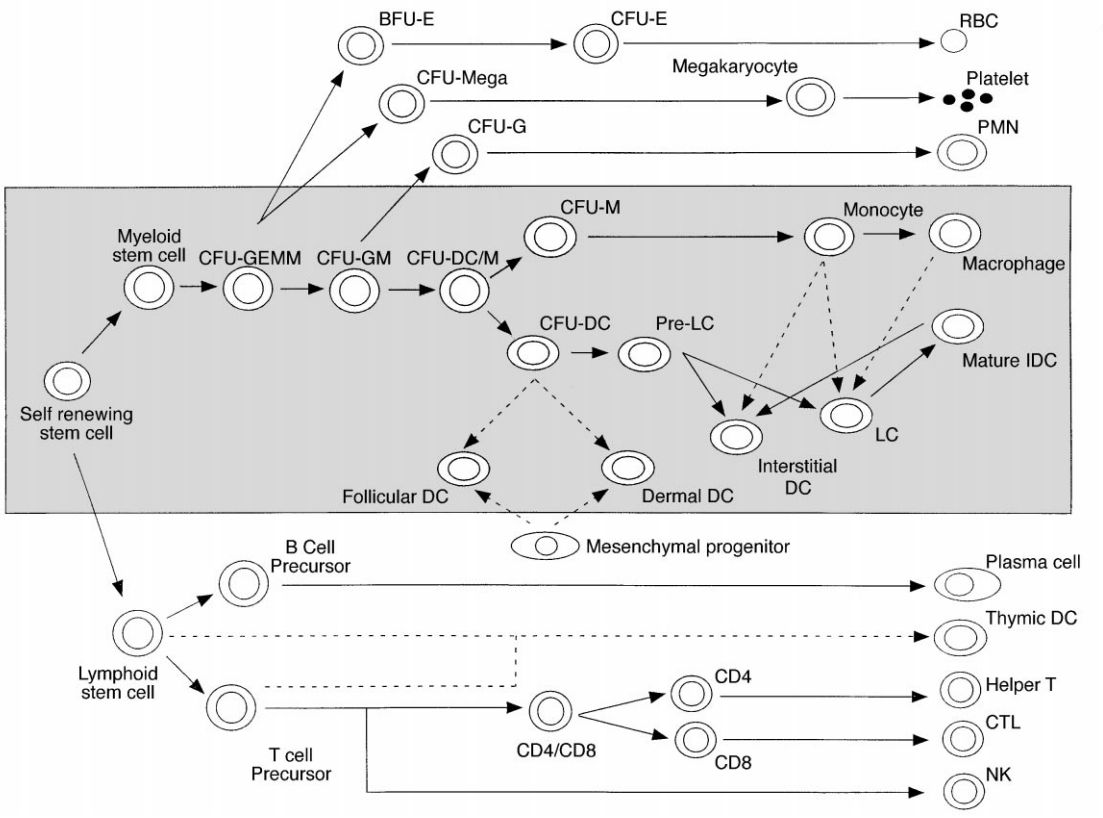

Figure 1. Possible lineage development and relationships of histiocytes. The lineage relationships shown have been determined through *in vivo* or *in vitro* studies of differentiation. The text should be consulted for references. Langerhans cell histiocytosis is believed to result from the proliferation and accumulation of clonal dendritic cells with characteristics most resembling the Langerhans cell. The 'pre-Langerhans cell' has also been referred to as an indeterminate cell in that it may express the CD1a surface antigen but lacks Birbeck granules. There are disorders involving the expansion of cells with these features which belong to the dendritic cell grouping of diseases. The interstitial dendritic cell and dermal dendrocytes have been linked as the primary cell expanding in juvenile xanthogranulomatous disease. The macrophage is a critical cellular component in the haemophagocytic lymphohistiocytosis disorders whether they be primary (i.e. inherited form), or secondary. In addition, the primary cell involved in Rosai–Dorfmann most resembles that of an activated macrophage. The solid lines suggest a more definitive assignment of lineage progression while the broken lines suggest uncertainty. CFU-GEMM, colony forming unit-granulocytic, erythroid, megakayotic, monocytic; CFU-GM, colony forming unit-granulocytic, monocytic; BFU-E, burst forming unit-erythroid; CFU-Mega, colony forming unit-megakaryocyte; CFU-G, colony forming unit-granulocytic; CFU-DC/M, colony forming unit-dendritic cell/monocyte; CFU-M, colony forming unit-monocytic; CFU-DC, colony forming unit-dendritic cell; CFU-E, colony forming unit-erythroid; PMN, polymorphonucleocyte; DC, dendritic cell; IDC, interdigitating dendritic cell; CTL, cytolytic T lymphocyte; NK, natural killer cell; RBC, red blood cell.

monocytes to be derived from endothelial precursors [8]. For many years it was not clear that blood cells had a very high turnover in the adult; thus, there was no reason to assume that a common haematopoietic progenitor needed to exist as a self-renewing source of blood components [14]. However, embryologists soon shed light on this mystery through the identification of the yolk sack, fetal liver and then bone marrow as the source of all haematopoietic lineages [14]. More recently, the fetal aorto-gonad-mesonephros (AGM) region has also been identified as a definitive source of haematopoietic stem cells (HSC) for the adult animal [15–18]. Further experimentation using gamma irradiation and bone marrow transplantation in mice, and ultimately in humans, has proven the existence of self-renewing HSC which give rise to all haematopoietic elements [19]. These, of course, include the histiocytes, which we will consider to be primarily (but not exclusively) comprised of macrophages and dendritic cells (Figure 1) [20, 21].

Many of the lineage relationships have been derived through *in vitro* culture methods under the influence of different cytokines representing survival and differentiation factors. Some of the lineage relationships also remain controversial. For example, dermal and follicular dendritic cells have been postulated to be descendents of both a haematopoietic precursor, as well as a soft tissue mesenchymal progenitor [5, 20–22]. In addition, the conversion of monocytes and macrophages into dendritic cells under the influence of specific cytokine environments has been described using *in vitro* approaches, but whether such changes in lineage differentiation occur *in vivo* remain speculative [5, 20, 21, 23–25]. Furthermore, the existence of a dendritic cell derived from a lymphoid stem cell has been described in both mice and humans [21]. While the myeloid-derived dendritic cells function in the activation of T lymphocytes, the thymic-derived dendritic cell has been proposed to serve as a downregulator of immune responses [21]. However, although macrophages and dendritic cells have retained some common characteristics, during the process of lineage determination and differentiation they have also diverged both cellular markers and functional characteristics (Table 1) [5, 20, 21]. Some of the distinguishing markers include the presence of the surface marker CD68 on macrophages but usually not seen on most dendritic cells. In contrast, dendritic cells, and particularly Langerhans cells, usually express the surface marker CD1a. Another unique feature of many dendritic and all Langerhans cells is the presence of intracytoplasmic structures called Birbeck granules or X bodies [26]. These subcellular structures are variable in length (approximately 200–400 nm) and have a uniform width of approximately 33 nm. They most likely arise by receptor-mediated endocytosis and have been shown to contain cell membrane antigens [26].

Functional analysis has demonstrated that macrophages play major roles in the phagocytosis of large particulate antigens such as bacteria. Following ingestion of particulates, macrophages become activated and increase the expression of

Table 1. *Characteristics of major RES cell types**

Marker	Macrophage	Pre-Langerhans	Langerhans	Interdigitating DC	Dermal dendrocyte
Cytoplasmic					
NSE	+	±	±	±	±
AP	+	±	±	±	±
S100	±	+	+	+	–
Birbeck granule	–	–	+	–	–
Surface					
CD1a	±	+	+	–	–
CMRF-44	±	?	+ to +++	+ to +++	?
CMRF-56	±	?	– to +++	– to +++	?
CD14	+	–	–	–	–
CD68	++	–	±	±	+
CD115 (M-CSF R)	+	–	–	–	–
CD64 (Fc R)	++				
CD32 (Fc R)	++	?	+	+	?
CD16 (Fc R)	+	?	–	–	?
CD40 (Costim.)	+	?	± to ++	± to ++	?
CD80 (Costim.)	+	?	± to ++	± to ++	?
CD86 (Costim.)	+	?	± to ++	± to ++	?
HLA-A,B,C	+ to ++	?	+ to +++	+ to +++	?
HLA-DR	+ to ++	?	+ to ++	+ to ++	?
Factor XIII	–	–	–	–	+
Fascin	–	?	–	+	+
Physiology					
Phagocytic	++++	?	++	++	?
T cell stimulation	++	?	++++	++++	?

*This table is not meant to be all inclusive, but to highlight some of the more commonly used distinguishing characteristics of several of the important cell types in the RES system related to the histiocytic diseases. The symbols + and – are shown to indicate a positive or negative reaction. ?, indicates that insufficient data are available to conclude definitively a positive or negative result. In addition, a ± sign indicates that variability may exist or that only a subpopulation may express the antigen. + to +++ or +++ to + indicates that expression is upregulated or downregulated, respectively depending upon the physiological conditions. The information is taken from references cited in the text. Fascin, as discussed in Schmitz and Favara [225]. Data on this marker require further confirmation. NSE, non-specific esterase; AP, acid phosphatase; DC, dendritic cell.

the MHC gene products on their surface, as well as costimulatory receptors (especially CD86 and CD80). Macrophages are located in lymphoid tissue, connective tissues and in most body cavities. Dendritic, and in particular Langerhans cells, have also been demonstrated to be phagocytic but tend toward the processing of viral antigens as well as tumour-associated and self-antigens [5, 20, 21, 27]. Dendritic cells usually show constitutively high levels of MHC proteins and costimulatory receptors and play a critical role in the activation of naive T lymphocytes [5, 20, 21]. Dendritic cells are primarily situated in lymphoid and connective tissues, as well as in epithelium [21].

Processing foreign antigens and their presentation in the context of MHC Class I or II products plus the expression of costimulatory receptors allows macrophages and dendritic cells to be potent stimulators of lymphocytes. During this process of antigen presentation and activation, both macrophages and lymphocytes secrete a wide range of cytokines which further augment their own activity, as well as recruit other cell types such as granulocytes and eosinophils [27].

From these normal characteristics and functions, one can start to understand the potentially multifaceted phenotypic possibilities that might result from aberrant proliferation and/or function of macrophages and/or dendritic cells. Proliferation of these cell types plus the recruitment of other cells to local areas produce swellings (tumours), erythema (from pro-inflammatory cytokines), as well as the displacement and dysfunction of normal tissue elements. The local release of certain cytokines can produce tissue damage as well. Both localised or systemic cytokines can lead to fever, skin rashes, hypotension as well as alterations of normal immune responses [28–30]. The overlapping functions of macrophages and dendritic cells may thus generate some of the same clinical signs and symptoms. However, different localisation and trafficking patterns may result in some of the differences observed in disorders of the RES.

DISCRIMINATING FEATURES AND CLASSIFICATION OF THE COMMON HISTIOCYTIC DISORDERS

The critical importance of understanding the distinguishing characteristics of the different types of disorders involving the RES is exemplified by recent improvements in outcome through directed therapeutic approaches to specific subtypes of disease class. Historically this has not always been the case [31].

In 1893 Dr Alfred Hand from Philadelphia published a case report of a 3-year-old boy with failure to thrive, exopthalmos, hepatosplenomegaly, lymphadenopathy, a scabies-like rash, diabetes insipidus and lytic skull lesions [32]. This child died from progressive disease of uncertain aetiology. In 1915, Dr Schüller in Vienna reported on 3 patients with skull defects, some of which disappeared without treatment [33]. Shortly thereafter, in 1919, Dr Christian from Boston added an additional patient who had skull defects, exopthalmos and diabetes insipidus. Dr Christian also noted gum retraction and ulceration leading to dental problems [34]. In 1924 Dr Letterer, then at the University of Würzburg in Germany, described a 6-month-old infant with a diffuse purpuric skin rash, fever, cough and tachypnoea, hepatosplenomegaly, anaemia and thrombocytopenia. This patient died from progressive disease which was felt to be due to the proliferation of large cells derived from the RES [35]. Just less than 10 years later, Dr Siwe in Sweden reported a 16-month-old girl with fever, a nodular rash, left lower leg swelling and bone destruction, lympadenopathy, hepatosplenomegaly and anaemia [36]. This patient died from progressive disease and, again, the observed cellular infiltrate was believed to be primarily due to large cells derived from the RES.

While these and other cases like them were thought to be distinct clinical entities, Dr Farber in Boston concluded that they in fact shared a similar cellular infiltrate and Dr Lichtenstein, then in Los Angeles, subsequently proposed that the so-called eosinophilic granuloma of bone, the multifocal disease referred to as Schüller–Christian or Hand–Schüller–Christian disease and the most severe systemic form, called Letterer–Siwe disease, represented different manifestations of the same disease process involving the RES [37, 38]. Dr Lichtenstein called this disease 'Histiocytosis X' [38]. Nearly 20 years later, Dr Nezelof in Paris proposed that the Langerhans cell was the cell of origin for all forms of Histiocytosis X based on the histological similarities, including the presence of Birbeck granules or X bodies, between normal Langerhans cells and the cell primarily accumulating in Histiocytosis X [39]. While this evolution of thought was important in helping to improve the definition of these disorders, it remained quite controversial how such a histologically non-malignant disease could give rise to such a pleiotropic spectrum of signs, symptoms and outcomes.

Of note is that one year before Lichtenstein suggested the unifying concept of Histiocytosis X, Farquhar and Clairveaux reported an infant with a familial and rapidly fatal form of what was believed to be Letterer–Siwe disease [40]. Owing to the prominent amount of haemophagocytosis observed, they suggested that this disorder was a variant of histiocytosis and called it 'Familial Haemophagocytic Reticulosis'. In 1961, Nelson reported prominent involvement of the central nervous system with familial haemophagocytic reticulosis but without the prominent erythrophagocytosis. They termed this variant 'lymphohistiocytosis' [41]. Two years later, MacMahon coined the term 'Familial Erythrophagocytic Lymphohistiocytosis' (FEL) and emphasised that this disorder was an entity distinct from Letterer–Siwe Disease [42]. In addition, the macrophage, and not the dendritic cell, appeared to be a significant culprit in FEL. During the mid-1960s, Miller and Nezelof noted some similarities between FEL and Graft-versus-Host Disease (also termed chronic runt disease) and suggested an underlying immune deficiency as the cause [43, 44]. Subsequent reports further defined the clinical and chemical features of FEL including hypofibrinogenaemia and hyperlipidaemia [45–47]. The existence of non-familial forms of the disease were also reported, usually associated with an older median age than the familial forms and with infections (usually viral), immunosuppression or cancer [47, 48]. This disorder was referred to as Infection Associated Haemophagocytic Syndrome (IAHS), Viral Associated Haemophagocytic Syndrome (VAHS) and also Malignancy Associated Haemophagocytic Syndrome (MAHS).

The establishment of the Histiocyte Society led to a reclassification of these disorders in 1987 [1]. The classification system delineated histiocytoses as (1) Class I or Langerhans Cell Histiocytosis (LCH) with the extent of disease delineated; (2) Class II or Non-Langerhans Cell Histiocytosis primarily consisting of Haemophagocytic Lymphohistiocytoses (HLH), such as FEL and IAHS; and (3) Class III or

Table 2. Diagnostic criteria for Langerhans cell histiocytosis

- Tentative diagnosis: Characteristic histology using routine haematoxylin and eosin staining of sections from paraffin-embedded tissue
- Definitive diagnosis: Characteristic histology plus the positive finding of CD1a staining by immunohistochemistry on frozen or paraffin sections. The presence of Birbeck granules detected by electron microscopy have in the past been used as a definitive finding for the Langerhans cell, but are also known to be found in some inflammatory disorders of the lymph node [1, 225]

Malignant Histiocytoses which included monocyte-related malignant diseases like monocytic leukaemia, dendritic- or macrophage-sarcomas. The diagnostic criteria for the different classes have been clarified as well. Diagnosis is based on both pathological, clinical and other laboratory criteria (Tables 2 and 3) [1, 1(a)]. For the next 10 years, this classification system proved to be important in defining the types of treatment which should be utilised based on the class of histiocytosis rather than just on the sometimes overlapping clinical features.

However, the half-life of a classification schema is often shorter than the time it takes to have it accepted. Based on further work classifying the varied histiocytic disorders according to the cell primarily involved in the pathogenesis, a more recent classification schema has been proposed (Table 4) [3, 20]. This system separates out all histiocytic disorders of 'varied biological behaviour' from those which are clearly 'malignant'. The latter include those disorders such as monocytic leukaemia, as well as dendritic or macrophage sarcomas. The former includes disorders which are dendritic-(not simply Langerhans cell) related compared with those which are macrophage-related based on the pathological analysis of biopsy specimens. While this type of classification system is more inclusive of some of the less common types of histiocytosis, it too will clearly undergo revision as more refined definition of the aetiologies and pathophysiology of these disorders is ascertained (see below).

Table 3. Diagnostic criteria for haemophagocytic lymphohistiocytosis (HLH) [1(a)]

Clinical
Fever*
Splenomegaly*
Lympadenopathy
Rash
Jaundice
Oedema
Positive family history
Parental consanguinity
Haematological
Cytopenias ($\geq$ 2 of 3 lineages in peripheral blood)*
Haemoglobin ($<$ 90 g/l)
Platelets ($< 100\times10^9$/l)
Neutrophils ($< 1\times10^9$/l)
CSF
Pleocytosis of mononuclear cells (macrophages and/or activated T lymphocytes
Elevated CSF protein
Laboratory
Hypertriglyceridaemia (fasting triglycerides $\geq$ 2 mmol/l or $\geq$ 3 S.D. above normal)*
Increased VLDL; decreased HDL
Hypofibrinogenaemia ($\leq$ 1.5 g/l or $\leq$ 3 S.D. below normal)*
Elevated liver function tests
Hypoproteinaemia
Hyperferritinaemia
Hyponatraemia
Immunological
Hypercytokinaemia (see Tables 6 and 7)
Soluble receptors (see Tables 6 and 7)
Decreased or absent NK function
Histopathology
Haemophagocytosis in bone marrow or spleen or lymph nodes without malignancy*

*For the diagnosis of HLH to be made at least five of the asterisked criteria must be met. A positive family history provides strong evidence in favour of familial HLH and parental consanguinity is suggestive. CSF, cerebrospinal fluid, VLDL, very low density lipoprotein; HDL, high density lipoprotein; NK, natural killer cell; S.D. standard deviation.

AETIOLOGY AND PATHOGENESIS—ARE WE READY FOR RECLASSIFICATION?

LCH–epidemiology

Although epidemiological analyses cannot define a cause, such studies often provide clues to where one should look with cellular and molecular tools. In the case of LCH, several tantalising associations have been observed.

The annual incidence of LCH has been calculated to be between 3 and 7 cases per million people with males being more frequently affected than females [49–51]. Although a Danish population based study showed no significant associations of LCH with neonatal and perinatal factors between 1975 and 1989, a U.S.A. case–control study demonstrated several potentially interesting associations [49, 52]. For example, the latter study showed that the development of

Table 4. Classification schema of histiocytoses

Disorders of varied biological behaviour
Dendritic cell or related disorders
Langerhans cell histiocytosis
Juvenile xanthogranuloma and related diseases
Solitary histiocytoma (dendritic cell phenotype)
Secondary dendritic cell disorders (e.g. association with Hodgkin's Disease)
Macrophage or related disorders
Haemophagocytic syndromes
Primary or familial haemophagocytic hymphohistiocytosis
Secondary or nonfamilial haemophagocytic hymphohistiocytosis
Infection Associated Haemophagocytic Syndrome (IAHS)
Malignancy Associated Haemophagocytic Syndrome (MAHS)
Sinus histiocytosis with massive lymphadenopathy (Rosai–Dorfman Disease)
Solitary histiocytoma (macrophage phenotype)
Multicentric reticulohistiocytosis (frequently associated with arthritis)
Generalised eruptive histiocytoma
Malignant disorders
Monocytic leukaemia (FAB classification M5)
Monocytic sarcoma
Histiocytic sarcoma
Dendritic cell phenotype
Macrophage cell phenotype

LCH was associated with maternal urinary tract infections during pregnancy and with feeding problems, medication usage and blood transfusions during the first 6 months of life [52]. A subsequent and even larger case–control study included 459 children with LCH, approximately half of whom had multisystem disease and the other half with single system disease [53]. This study demonstrated a significant odds ratio (OR) for postnatal infections, diarrhoea and vomiting, and medication usage associated with multisystem LCH. Single system LCH was associated with thyroid disease or a family history of thyroid disease [53]. However, an important and consistent finding has been that there is no seasonal variation or geographic clustering of cases of LCH, thus arguing against any obvious infectious and, in particular, viral aetiology. Clearly, these three epidemiological studies do not completely agree with one another, thus making definitive hypotheses difficult.

LCH—association with malignancies

Through reviews of the literature as well as information obtained by establishing a registry of patients in whom LCH and a malignancy have occurred, it has been strongly suggested that there exists an association of LCH and malignancies higher than would be expected by chance alone [54, 55]. Examples include acute lymphoblastic leukaemia (ALL), acute myeloid leukaemia (AML) and some solid tumours such as Hodgkin's and non-Hodgkin's lymphoma, retinoblastoma, thyroid cancer, osteosarcomas, various types of brain tumours as well as lung and other carcinomas [55]. Of note is that solid tumours more often occur following the diagnosis of LCH. They developed from 0.5 to 26 years after the LCH was diagnosed and they frequently occurred within a radiation field used as treatment for LCH. One of the issues in the analysis of such data is the misdiagnosis of true LCH in a patient with a solid tumour, rather than a Langerhans cell reaction to the solid tumour [55].

Similarly, AML was more likely to develop following treatment for LCH, suggesting the possibility of therapy-induced leukaemia. Clearly, the alkylating agents used at one time to treat patients with LCH were responsible for the development of AML in some cases and, more recently, the use of etoposide may have contributed to this observed phenomenon [55]. Nearly all types of AML, except for French–American–British (FAB) classification M0 and M6 subtypes, have been observed. Of particular interest, however, is the relatively high frequency of FAB M3 subtype (acute promyelocytic leukaemia). Approximately 47% (8 of 17 cases of AML) of the cases of AML identified were M3. APL is usually not considered to be highly associated with secondary AML [56].

The majority of cases of LCH which develop following treatment for ALL stands in contrast to the results for AML and solid tumours. In 7 of 12 cases examined, LCH occurred 6–12 months following the diagnosis of ALL. In addition, the LCH which developed included both localised and generalised forms. Most cases of ALL were FAB L1 morphologically [55].

Whether patients with LCH truly have a predisposition to developing various malignancies remains to be determined. One must also acknowledge that a systematic epidemiological analysis of incidence and prevalence of patients with LCH and malignancies with large populations of people has not been conducted. Thus, while data obtained from registries can be quite useful, there is likely to be bias built into such databases.

LCH—familial cases

Another important observation has been that of familial forms of LCH. A small number of identical twins have been reported and/or observed [57–63]. In these cases the onset of LCH is usually at a quite young age (approximately 5 months) and there is usually close co-ordinance of onset between the two twins [64]. In addition, several instances of fraternal twins or siblings of different ages have been reported. In these cases, the diagnosis of LCH is usually made at an older age than that observed with identical twins. Also, there is a wider range of onset of LCH among affected individuals [64]. The occurrence of LCH in a parent and a child or in cousins has also been observed [64, 65]. The estimated frequency of familial cases of LCH is likely to be less than 2% of all cases [64].

What do these familial cases tell us? The usually concordant onset of LCH in identical twins is like to be the result of intrauterine trafficking of LCH cells through shared placental circulation. This has been observed for both ALL and AML [66–69]. In those cases, the identity of the disease in each twin can be definitively proven by the fact that the same molecular alterations are observed in the leukaemia taken from each twin. If this does occur for LCH, then it strongly suggests that LCH cells can migrate through the circulation from local sites of disease. An alternative explanation is that the concordant development of LCH in the setting of identical twins is a result of an environmental exposure, such as a viral infection or toxic exposure. The development of LCH in multiple family members such as in fraternal twins, other siblings, parent and child or other relatives certainly suggests, but does not prove, that there is a genetic predisposition to having LCH. Certainly, a common environmental factor cannot be ruled out at this time.

However, when one combines even the low incidence of familial LCH with the strongly suggestive association with the occurrence of certain malignancies, then one is obligated to at least evaluate LCH as a disorder which should have an underlying genetic cause. This has led some investigators to propose that LCH may share some features of 'Knudson's Two Hit' model [55, 70, 71]. For example, when LCH develops very early in life, one would assume that the patient would have inherited a mutation in one of the two alleles for a specific predisposition gene and then subsequently the second allele would become abnormal. For patients who develop the disorder at a later age, both mutations would be acquired.

Thus, the association of LCH with the development of other malignancies and the familial occurrence of LCH point to the possibility of a genetic predisposition or a genetic basis for the development of this disease. Several important lines of evidence have accumulated over the past several years directed at further elucidating this issue.

LCH—clonality and genetics

Arising in part from discussions at the Nikolas Symposium, work on the genetic basis of LCH focused on the Langerhans cell from LCH lesions. Using molecular approaches to define clonality based on X chromosome inactivation, several reports have unequivocally demonstrated that the Langerhans cells from LCH lesions are clonal, i.e., derived from a common precursor [72–76]. This has been shown by sorting

CD1a-positive cells from lesions and showing that they, and not recruited lymphocytes, are clonal [74]. Other studies have demonstrated through quantitative analysis that the Langerhans cells from local or systemic disease are clonal [72]. Thus, LCH cells have been shown to be clonal from a wide variety of tissues including bone, lymph node, bone marrow, skin, soft tissue and lung. In contrast, it has also been shown that the lesional cells from Rosai–Dorfman Syndrome (also termed Sinus Histiocytosis with Massive Lymphadenopathy) or the macrophages in HLH syndromes are not of clonal origin [76, 77].

Much debate has gone on concerning whether clonality proves that LCH is a malignant disorder. Clearly, clonality does not mandate that a proliferative process be considered a cancer, as there are several examples of inflammatory processes as well as dermatological disorders which are clonal but are not considered cancerous [78, 79]. In addition, LCH does not show the cytological features of atypia observed in at least high-grade cancers. Nevertheless, LCH is an often highly proliferative process which can evolve into a life-threatening systemic disease. While these results do not yet tell us the best way to treat patients, they do put LCH into a disease class which could be termed a ''clonal proliferative neoplasm with variable clinical manifestations''. This is not dissimilar to that observed for a number of malignant or pre-malignant conditions such as observed in myelodysplastic syndromes (MDS). What is important in this discussion is not whether LCH is a cancer or not, but what does this teach us and where do such findings direct future work.

The clonality of the lesional Langerhans cell strongly points to the possibility of being able to uncover somatic (or inherited in some cases) mutations which lead to the observed phenotype. While some controversy has arisen over whether normal Langerhans cells involving large areas of skin could be derived from a single precursor, at the current time there is no compelling evidence proving that normal Langerhans cells are clonal. Therefore, one could postulate that fewer mutations would lead to a more limited form of the disease, while the acquisition of additional mutations would result in systemic forms. Alternatively, different gene defects regulating the different parts of the same molecular pathway leading to Langerhans cell proliferation could occur. Lastly, modifying genes from the different genetic backgrounds could serve to modify the clinical behaviour along with environmental and age-specific physiology. Regardless of which of these possibilities are true, the search for a genetic cause for LCH is critical.

Thus far, this search has not revealed a definitive genetic alteration. Traditional cytogenetic analyses have not demonstrated any consistent changes in karyotypes from LCH lesions [80–82]. This may be in part due to the sensitivity of such methods or to the low frequency of such chromosomal abnormalities. However, a recent report showed the presence of a t(7;12) translocation from a lesion of a patient with LCH [83]. This is particularly interesting in light of the *tel* gene being mapped to this region of chromosome 12 [84]. *Tel*, originally identified as part of a translocation involved in a child with CMML [84], has been implicated in the development and/or clinical behaviour of a variety of myeloid and lymphoid malignancies [85–88]. The observed translocation reported for LCH is, therefore, of immense interest as it may involve a gene known to be important for haematopoietic growth and differentiation, as well as in leukaemia. It is, therefore, critical to assess whether the t(7;12) abnormality or more subtle mutations of genes on chromosomes 7 or 12 are commonly described in LCH. Fluorescent *In Situ* Hybridisation (FISH) analyses have thus far not demonstrated any consistent genetic changes [76, 89]. Further studies using molecular methods need to be performed to assess more subtle changes such as has been uncovered for *tel* in ALL [88].

Markers and function of LCH cells

A significant amount of additional data points to the Langerhans cell being intrinsically abnormal in LCH. Evaluation of cytoplasmic and surface markers have demonstrated several differences between the LCH cell and the normal Langerhans cell, as well as the histiocytic component of HLH (Tables 1 and 5). For example, peanut agglutinin (PNA) staining has revealed that LCH cells usually have characteristic cell surface and strong perinuclear staining; this is in contrast to the low level of diffuse staining observed in normal Langerhans cells [90]. The LCH cell pattern of PNA staining is also seen in Reed Sternberg cells of Hodgkin's disease, as well as in some interdigitating reticulum cells [91]. Another distinguishing feature of LCH cells is their high and constitutive expression of placental alkaline phosphatase (PLAP) [90, 92]. While normal Langerhans cells can be stimulated to express PLAP transiently, LCH cells remain strongly positive; this has been proposed to represent an 'activation phenotype' of the LCH cell. The γ-interferon receptor has also been reported on LCH cells but not on normal Langerhans cells; this may represent another example of an activated phenotype for the LCH cell. Of further

Table 5. *Distinguishing surface and cytoplasmic histiocytic markers in LCH and HLH*

Markers	Comment	LCH cell	HLH
Surface			
CD1a*	Non-classical MHC	Positive	Negative
CD68*	Macrophage activation	Negative	Positive
Cytoplasmic			
S100		Positive	Usually negative
PLAP	Placental alkaline phosphatase	Positive	Negative
PNA	Peanut agglutinin	Positive†	Negative
Birbeck granule	Endocytosed trilaminar membrane structures	Positive	Negative

LCH, Langerhans cell histiocytosis; HLH, haemophagocytic lymphohistiocytosis; MHC, major histocompatibility complex. *Negative does not imply an absolute lack of expression and some cells in each disorder may express variable low levels of these markers. See Table 1; †LCH cells have a distinct cytoplasmic membrane plus perinuclear ring and dot pattern.

interest is the constitutive expression of costimulatory molecules CD86 and CD80 on LCH cells [90].

Normal Langerhans cells are potent antigen presenting cells and activators of T lymphocytes [27]. One measure of this type of activation is the mixed epidermal–lymphocyte reaction which results from allo-antigen presentation by Langerhans cells [90]. Quite surprisingly, LCH cells purified from lesions have been reported to be extremely poor inducers of T cell activation using this assay [90]. A possible explanation for this is that other cells present in the cell preparation are producing inhibitory cytokines. To address this possibility, epidermis overlying the LCH infiltrate was tested and was shown to contain Langerhans cells with normal or even enhanced stimulatory activity. These studies suggest that the observed decreased ability of LCH cells to stimulate T cells in this allo-stimulatory system is not due to the secretion of inhibitory cytokines. However, the purity of the cellular preparation was not absolute; in addition, it is possible that LCH cells would be secreting cytokines that could downregulate this specific function while allowing for the modulation of other phenotypic parameters. The reported lack of the capacity of LCH cells to activate T lymphocytes also stands in contrast to the cytokines secreted in and by the different lesional cell types.

A significant amount of work has shown that LCH lesions contain increased production of a variety of immunomodulatory cytokines (Table 6) [93–95]. *In situ* hybridisation and immunocytochemistry have demonstrated that some of these cytokines are produced by the LCH cells themselves, while others are expressed by lymphocytes within the lesion [93]. Of particular note is that the cytokines expressed are consistent with that expected to result in the local activation of T and dendritic cells, as well as for the recruitment of macrophages and granulocytes including eosinophils. In addition, the local production of these cytokines might be responsible for fever, as well as bone resorption such as would result from IL-1 and prostaglandin E_2 [96]. Thus, the cytokines produced have inflammatory, activation, mitogenic and chemotactic characteristics which could, in principle, give rise to the expansions of LCH lesions, as well as other phenotypic features. However, the local production of these cytokines does not explain the wide clinical variability of LCH including why some forms are local, some disseminated and other cases wax and wane in the same patient over time. In addition, there are very little data to support a profound systemic cytokinaemia as has been described in HLH (see below) [97, 98].

Thus, LCH would appear to be a primary, clonal proliferative disorder with the ability to effect local tissue damage by the expansion of the infiltrative cells, as well as by the cytokines produced. In this regard, LCH does represent a disorder characterised by abnormal production of cells and cytokines important for normal and abnormal regulation of immune functions. However, alterations in immune function have been observed but no consistent defects reported [28, 30, 99, 100]. These alterations would, therefore, be more likely to be a secondary result of abnormal Langerhans cells, rather than a primary defect of the immune system.

HLH—epidemiology and genetics

The incidence of familial or primary HLH has been most accurately estimated in the Swedish population with 0.12 affected persons per 100 000 children per year [47, 101]. While this incidence has been confirmed in other parts of the world as well, it is likely to represent an underestimation because of previous uncertainty concerning defined diagnostic criteria, as well as some 'nonfamilial' cases not necessarily being reported [47]. There is an equal distribution between males and females. An increased incidence is observed, however, in ethnic groups where consanguinity is more prevalent, as well as in any families in which parents are related [46, 101–104].

These observations are consistent with an autosomal recessive inheritance pattern for primary cases of HLH. The age of onset for the majority of familial cases is less than 1 year of age, although cases have been observed during prenatal development up to the age of 8 years [47, 103]. In contrast, infection or malignancy-associated HLH tends to have a later onset [48, 103]. In children, while about half of the cases occur under 3 years of age, less than 20% occur in patients less than 1 year of age [47, 48, 103]. Of interest, in a review of published cases, only 13 of the 219 reported cases were clearly associated with an underlying immunodeficiency or immunosuppressive treatment [47]. These data suggest that the same primary genetic defect or a defect along the same functional pathway may be present in familial and non-familial cases. The earlier onset of the familial cases and the later onset of the non-familial cases would also suggest a 'two

Table 6. *Cytokine profiles in Langerhans cell histiocytosis (LCH) and haemophagocytic lymphohistiocytosis (HLH)*

Cytokine	LCH (lesional)	LCH (serum or plasma levels)	HLH—familial§	HLH—non-familial§
IL-1	++++	+/–		
IL-2†	++++	+/–	+++	+++
IL-3*	++++	+/–		
IL-4	++++	+/–	+/–	+/–
IL-5	–			
IL-6	++++		++++	++++
IL-7				
IL-8	++++	+/–		
IL-9				
IL-10			++++	++++
IL-11				
IL-12			+++	+++
IFN-α				
IFN-γ‡	++++		++++	++++
TNF-α†	++++		++++	++++
GM-CSF*†	++++			
LIF†	++++			
MIP α			++++	++
Neopterin			++++	++++
CD40 Ligand*,‖	++++			
CD40 Receptor†,‖	++++			
sIL2R (CD25)		+/–	++++	++
sCD8			++++	++
IL1 RA			++++	++++

*Expressed by lymphocytes; †expressed by histiocytes; ‡presence in lesions disputed; §all levels are systemic and determined for serum or plasma; ‖these and other expression data were kindly provided by Drs Maarten Egeler, B.E. Favara, M. van Meurs, J.D. Laman and E. Claasen. The symbols –, +/– and different numbers of plus marks refer to no expression, equivavocal expression and increasing levels of expression respectively. IL-1–IL-12, interleukins 1–12; IFN-α, alpha-interferon; IFN-γ, gamma-interferon; TNF-α, tumour necrosis factor-α; GM-CSF, granulocyte macrophage-colony stimulatory factor; LIF, leukemia inhibitory factor; MIPα, macrophage inflammatory protein α.

hit' model, with the former group inheriting a damaged allele and the latter group subsequently developing the abnormal allele. Such a model would account for the earlier onset of familial cases and the observed common clinical phenotype. Furthermore, any significant degree of immunosuppression plus a triggering agent (e.g. certain viruses) could also affect the pathways leading to HLH in the inherited forms of the disorder.

HLH—potential pathophysiological pathways

There is no definitive evidence that the macrophages or lymphocytes in patients with HLH are clonal in origin [47, 76]. A possible exception is the reporting of clonal T lymphocytes based on viral integration sites in Epstein–Barr virus (EBV)-associated HLH and which may reflect a clonal expansion of reactive T lymphocytes to the virus, such as specific viral peptides [105–108].

The histological features of HLH are quite distinct from LCH. HLH is characterised by cytologically non-malignant infiltrates of lymphocytes and macrophages [47]. Other inflammatory cell types are not a significant part of this infiltration. Macrophages appear activated and haemophagocytosis (i.e. all haematopoietic elements, not just red blood cells) is often observed [109]. The infiltrative lesions and macrophage activation can disrupt normal tissue architecture and function, such as can be observed in the liver as well as in the central nervous system. Pancytopenia may result from the haemophagocytosis, blood cell trapping in liver and spleen, as well as by bone marrow replacement with activated histiocytes. Coagulopathy, hypofibrinogenaemia and lipid abnormalities may result from liver dysfunction, as well as macrophage activation and turnover associated with increased secretion of proinflammatory cytokines and consumption of blood and serum constituents. Skin rashes may also develop due to infiltration and local release of proinflammatory cytokines. This picture of lymphohistiocytic infiltration associated with RES and immune dysregulation is observed in both the familial HLH, as well as in HLH associated with infections, malignancy or immunosuppression.

In contrast to LCH, a much more consistent, albeit not yet completely clear, picture of immune abnormalities has emerged for HLH (Table 7) [47, 48]. A central finding in familial HLH has been the low to absent natural killer (NK) cell activity, as well as decreased cell-mediated cytotoxicity due to cytolytic T cells (CTL) [47, 48, 110, 111]. This has been observed in patients prior to any therapy. In addition, the function of NK and CTL activity has been shown to improve following bone marrow transplantation of patients with familial HLH [47, 110, 111]. Of particular note is that decreased NK activity has also been demonstrated in apparently healthy parents and siblings of patients with familial HLH [112]. This finding suggests that additional genetic changes or modifying genes influence the development or course of even inherited HLH. There are many examples of this in medicine, including the recent description of varied phenotypes in families with FAS receptor defects [113–116]. It is also of immense interest that patients with Chediak–Higashi syndrome, which is characterised by abnormal granules in white blood cells and defective NK function, develop HLH during the later, accelerated phases of the disorder of in response to viral infections including EBV [117–119].

Table 7. *Immune function in Langerhans cell histiocytosis (LCH) and haemophagocytic lymphohistiocytosis (HLH)*

Immune function	LCH	HLH—familial	HLH—non-familial
No. Lymphocyte	Normal	Decreased	Decreased
No. B cell (CD19+)	Variable	Decreased	Decreased
No. T cell (CD4+)		Decreased	
No. T cell (CD8+)		Decreased	
CD4/CD8 ratio		Normal	
No. NK cell	Variable	Normal to decreased	Normal to decreased
NK function		Decreased	
CTL function		Decreased	
Serum Ig	Variable	Variable	Variable
ADCC	Variable	Decreased	Decreased
Mitogen response	Variable	Decreased	Decreased
No. B cell (CD19+)	Variable	Normal %	Normal to increased

ADCC, Antibody-dependent cell-mediated cytotoxicity; NK, natural killer cell, CTL, cytotoxic or cytolytic T lymphocyte.

An important question is whether the observed decreased NK (and CTL) function is the primary defect or a result of another abnormality of the immune system modulating the function of effector lymphocytes. The presence of low to absent NK function in apparently healthy family members argues that the NK abnormality is not sufficient for the disease to develop. In addition, studies documenting improved NK and CTL function with disease remission following non-ablative (and non-curative) treatments would suggest that the NK defect is not primary. Such data have, however, not been entirely without controversy [110, 120]. Further, the *in vitro* circumvention of defective NK function through exogenous cytokines or stimuli would provide evidence that another component of the immune system which downregulated NK function was the culprit. Thus far, such data have not been reported to establish this possibility definitively.

Nevertheless, the likely result of this dysregulation is the elaboration of a cytokine profile quite distinct from either localised or systemic LCH. HLH is characterised by enormously increased levels of systemic cytokines, in contrast to the local production of cytokines observed in LCH (Table 6) [97, 98, 121–124]. And while some subtle differences in profiles between familial and non-familial HLH have been reported, a relatively consistent pattern has emerged. It is from this profile of cytokine production that several hypotheses of both aetiology and pathophysiology have been generated (Figure 2) [47, 97, 98, 122, 123]. Of particular interest are the very high levels of IL-2, IL-10, IL-12 and γ-interferon. Macrophages and B cells are potent sources of IL-12 which, in turn, can activate T lymphocytes of the TH1 type [98, 125]. TH1 lymphocytes play important roles in the generation of cytotoxic responses, whereas TH2 lymphocytes primarily function in the induction of antibody-mediated immune responses [126]. Stimulated TH1 lymphocytes produce IL-2 and interferon-γ which, in turn, upregulate both T cells and macrophages. Ironically, IL-2 should also augment NK numbers and activity. This raises the question as to whether NK cells are unresponsive to such stimulatory cytokines or whether suppressive cytokines are present.

In this regard, it is of interest that high levels of IL-10 are observed in patients with HLH. IL-10 is also produced by histiocytes and TH2 lymphocytes; one of its functions is to downregulate TH1 responses and NK activity [98]. However, if IL-10 is an immunological 'off-switch', then why is

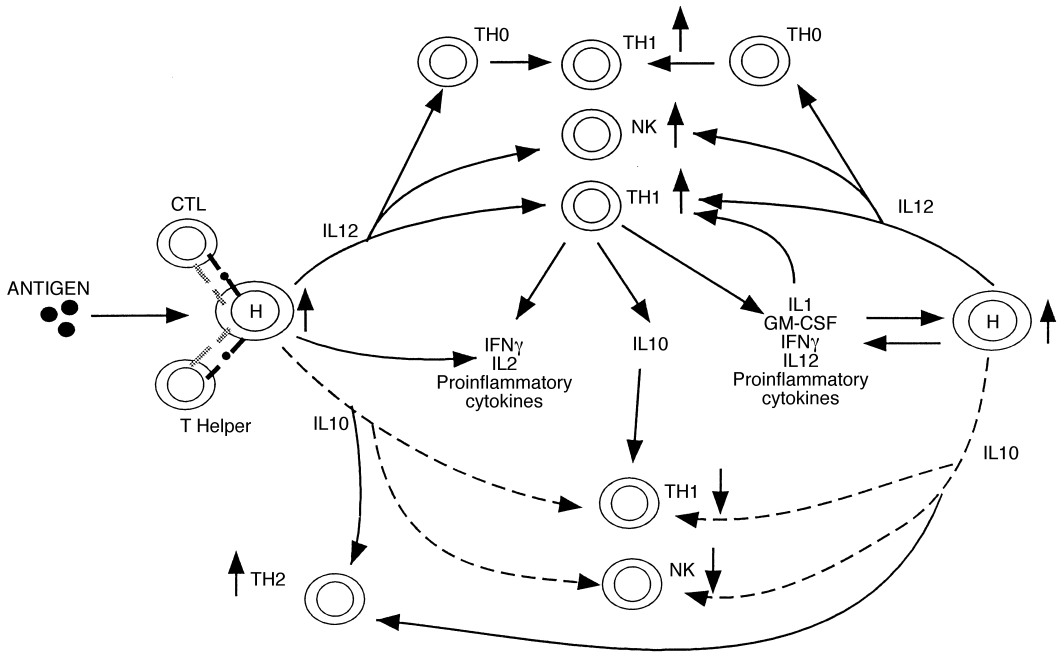

Figure 2. Cytokine pathways and haemophagocytic lymphohistiocytoses (HLH). This schematic represents possible relationships involved or defective in HLH. The solid lines indicate positive regulatory pathways, while the dashed lines indicate inhibitory or negative effects. The large solid circles represent antigen sources such as bacterial, viruses or even endogenous proteins. The small solid circles represent the processed antigen now shown expressed in association with a MHC Class I or II molecule which are, in turn, represented by the short solid lines. The shaded short lines represent costimulatory receptors providing the second signal of T cell activation. CTL, cytolytic T lymphocyte; TH1, Type I lymphocyte involved in cell mediated immunity; TH2, Type II lymphocyte involved primarily in regulation antibody-mediated immunity; TH0, a precursor lymphocyte; H, histiocyte. Please see the text for a detailed discussion.

there continued immune activation in HLH? The possibility of a defective suppressor cell response would be one explanation. In addition, IL-4 is able to suppress IL-10 production, but IL-4 has not been shown to be elevated in HLH [47, 48]. This raises the possibility that the upregulation of IL-10 is due to a block in responsiveness or production of IL-4, thus allowing IL-10 to be constitutively overproduced. Further, IL-4 can function to inhibit macrophage activation; thus, the relative low levels of IL-4 may also contribute to the macrophage activation observed in HLH. It is also possible that although IL-12 is produced at high levels, a defective IL-12 response alters cytotoxic T cell functions, but still allows for IL-2 expansion. At this time there does not appear to be a completely consistent explanation for the profound activation of macrophages and lymphocytes, along with production of cytokines and their currently known functions. However, available data would point to a defect primarily or secondarily involving the normally balanced production and responses of IL-4, IL-10, IL-12 and γ-interferon (Figure 2).

These data do strongly support the concept that HLH (familial or non-familial) is due to a fundamental immune abnormality (i.e. an immunodeficiency syndrome) and not a primary proliferative disorder like LCH. LCH is therefore most likely to be the result of a dendritic cell abnormality and any abnormal immune system changes representing a result of the interactions (direct or indirect) of the LCH cell with lymphocytes. In contrast, HLH is more likely a primary (or acquired) immune deficiency which has profound consequences for macrophage activation. The acquired form of HLH is also associated with immunosuppressive or dysregulation as a result of a patient's underlying disease or by the treatment for that disease (Figure 3). Thus, the classification

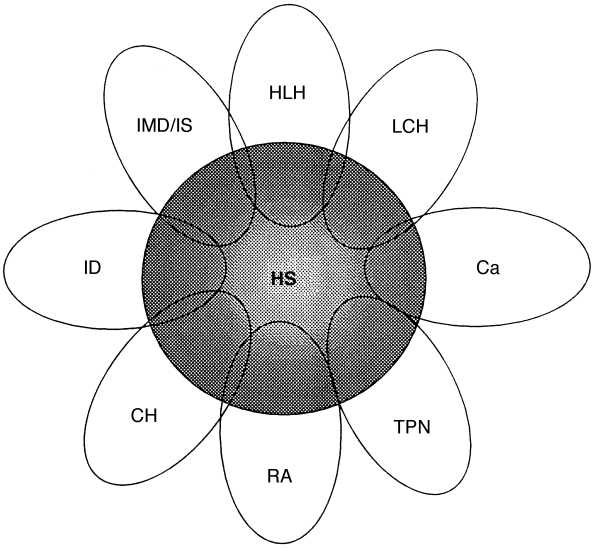

Figure 3. Interrelationships among disorders with the potential for developing a haemophagocytic syndrome. The development of a haemophagocytic syndrome (HS) can occur due to primary or inherited immunodeficiency, as well as secondary to a variety of disorders which result in the abnormal stimulation or suppression of the immune system. In addition, the treatment of a number of disorders can result in immunosuppression which may lead to uncontrolled activation of both lymphocytes and macrophages due to lack of inhibitory controls. Some of these disorders are themselves closely related as shown by the overlapping areas of the oval and circular shapes. HS, haemophagocytic syndrome; HLH, haemophagocytic lymphohistiocytosis; LCH, Langerhans cell histiocytosis; Ca, cancer; TPN, total parenteral nutrition; RA, rheumatoid arthritis; CH, Chediak–Higashi Disease; ID, infectious diseases; IMD/IS, immunodeficiency/immunosuppression.

of HLH as one of the histiocytoses may be done only through 'guilt by association'. HLH could more accurately be classified among the primary immunodeficiency syndromes. In fact, HLH would best be classified as one of the genetic disorders of T lymphocyte/macrophage activation in which the defective gene has not yet been identified (Table 8). This would suggest some modification of the current classification schema as shown in Table 9.

SEPARATE TREATMENT APPROACHES FOR SEPARATE DISEASES

The initial historical lack of distinction of severe LCH and HLH also resulted in these different disorders being treated similarly. However, with the improved understanding of these two disorders in terms of their underlying biology and distinct clinical courses, therapeutic approaches have diverged.

LCH

The treatment of patients with LCH has varied over the past century according to what was believed to be the cause of the disorder, as well as what potentially therapeutic options were available. For example, when LCH was believed to be secondary to infectious agents, antibiotics were used. While this approach did not prove to be very effective, it has not gone completely out of favour as demonstrated by more recent reports using trimethoprim-sulphamethoxazole [127]. The belief that LCH was primarily an immune dysregulatory disorder led to the use of immunosuppressive treatments such as steroids, ATG (antithymocyte globulin) and cyclosporin [128]. These approaches have proven to be at least partially effective in ameliorating the signs and symptoms of the disease, possibly by interrupting the local activation of T lymphocytes and decreasing cytokine production. A third approach has been based on the evidence that LCH is a primarily proliferative disorder of dendritic cells and should be treated more like cancer with antineoplastic drugs and radiation therapy [129–131]. The formation of the International Histiocyte Society in the late 1980s provided the opportunity to accrue sufficient numbers of patients with LCH to begin to establish uniform diagnostic and response criteria to therapy.

Localised LCH

Based on several non-randomised studies and clinical experience, there is now a fairly strong consensus that patients with isolated bone lesions usually require minimal treatment usually involving only biopsy and curettage [130, 131]. Recurrence at the site of the initial lesion or the development of another lesion elsewhere does not usually require additional surgery. If such lesions are asymptomatic, it is possible that they may need no intervention and can spontaneously resolve. Alternatively, if a lesion is causing pain or discomfort but is not likely to result in a cosmetic or functional abnormality, the use of oral non-steroidal anti-inflammatory agents such as naprosyn, indomethacin or ibuprofen may result in prompt relief of symptoms and subsequent resolution of the lesion with eventual healing of the bone [132]. This may occur through the inhibition of lesional IL-1 and prostaglandin E_2 secretion [96]. Three to four weeks of treatment may be required. Alternatively, intralesional injection of steroids has been shown to offer prompt relief of symptoms secondary to localised bone lesions and their subsequent resolution [133, 134]. These injections are relatively easy to perform but, for safety reasons, should preferably be done under radiographic guidance. Peripheral sites are usually most effectively and safely treated with this approach. For lesions which threaten to compromise function (e.g., vision) or cause cosmetic disfigurement, then more immediate intervention should be employed such as with low dose (400–800 cGy) radiation therapy [135–137]. Even though this dose of radiation therapy is low, there remains concern over the development of secondary malignancies following exposure to ionising radiation.

Localised disease of the skin can usually be effectively treated topically with cleansing, antibiotics and steroid creams [4, 138]. Refractory, localised skin disease may

Table 8. T cell/macrophage activation syndromes

Disorder	Inheritance	Gene defect
Chediak–Higashi syndrome	AR	LYST [226, 227]
Griscelli syndrome	AR	Myonin Va [228]
XLP	X	SAP [229, 230]
HLH	AR	?

XLP, X-linked lymphoproliferative disease; AR, autosomal recessive; X, X-linked; HLH, haemophagocytic lymphohistocytosis.

Table 9. Alternative classification of histiocytic disorders

- Histologically non-malignant proliferative disorders
  - Dendritic cell-related
    - Langerhans cell histiocytosis
    - Juvenile xanthogranuloma
    - Dendritic cell histiocytomas
- T lymphocyte/macrophage activation disorders
  - Haemophagocytic syndromes associated with immune deficiency/dysregulation
    - Primary or familial haemophagocytic lymphohistiocytosis
    - Chediak–Higashi syndrome
    - Griscelli disease
    - XLP
  - Haemophagocytic syndromes associated with infection
    - Secondary or non-familial haemophagocytic lymphohistiocytosis
      - Infection associated haemophagocytic syndrome (IAHS)
        - Viral, bacterial, ricketsial, amoebic, protozoal
  - Haemophagocytic syndromes associated with malignancy
    - Malignancy associated haemophagocytic syndrome (MAHS)
  - Sinus histiocytosis with massive lymphadenopathy (Rosai–Dorfman disease)
  - Solitary histiocytoma (macrophage phenotype)
  - Multicentric reticulohistiocytosis (frequently associated with arthritis)
  - Generalised eruptive histiocytoma
- Malignant disorders
  - Monocytic leukaemia (FAB classification M5)
  - Malignant monocytic cell neoplasm
  - Malignant dendritic cell neoplasm
  - Malignant macrophage cell neoplasm
- Storage disorders
  - Inherited
    - Sphingolipidoses
    - Mucopolysaccharidoses
    - Mucolipodoses
  - Acquired
    - Associated with high turnover states of haematopoietic cells (e.g. CML)

CML, chronic myeloid leukaemia.

require topical nitrogen mustard, usually prepared as a 20% solution and applied directly on to lesions [139]. In addition, phototherapy with methoxypsolaren plus PUVA (psorlaren ultraviolet activated light) exposure can be effective [140, 141]. However, these latter two approaches carry a higher risk of being carcinogenic. For extensive skin disease which is causing significant problems, such as chronic superinfection, cosmetic disfigurement or pruritis, then systemic therapy may be required. In this situation, pulse steroids or vinblastine are usually effective; etoposide has also been used in this setting [142]. Systemic therapy may also be required for localised disease of lymph nodes, especially when they develop fistulae.

Multifocal and multisystem LCH

Patients with multifocal and/or multisystem disease defined according to several different staging systems will usually benefit from systemic therapy. Both morbidity and mortality are reduced [129, 130]. However, significant disagreement has arisen over how much, what type and how intense such treatment should be.

Two cooperative trials in the 1980s attempted to 'risk group stratify' the intensity of therapy building on Lahey's work in defining prognostic groups [143, 144]. The AIEOP-CNR-HX 83 study from Italy staged or grouped patients according to whether they had organ dysfunction [145]. Those patients that did not have organ dysfunction were considered to be a 'good risk' group; they were further subdivided into those with single system or multisystem disease. Patients with organ dysfunction were considered to be a poor risk group. The therapy for the good risk group initially consisted of immunotherapy (with thymic extract) followed by an escalation schema using monochemotherapy starting with vinblastine (12 weeks of therapy), then moving to doxorubicin (4 cycles) and etoposide (4 cycles) depending upon clinical response. The poor risk group was treated with multiagent chemotherapy including prednisone, doxorubicin, vincristine and cyclophosphamide.

Several important conclusions came out of this study. Immunotherapy with thymic extract was only used in 10 patients and showed one complete response; this therapy was subsequently abandoned. Complete response rates were determined for vinblastine (63%), doxorubicin (43%) and etoposide (88%) in the sequential schema used. This is, therefore, not a measurement of response of the different agents in completely chemotherapy-naïve patients, but does demonstrate significant activity of the three drugs. The relapse rate following vinblastine (24%) and etoposide (7%) were lower than that found for doxorubicin (67%), although these values were not statistically significant. This information plus the somewhat lower response rate of doxorubicin in combination with its potential for cardiac toxicity has significantly decreased enthusiasm for it in patients with at least good prognostic criteria. For poor-risk patients, the complete response rate to the multi-agent regimen was only 18%, and 55% of these patients died. The overall survival was 100% for good risk patients and approximately 46% for poor-risk patients.

A second cooperative group trial from the Austrian/German group (DAL-HX 83/90) also attempted to stratify by risk group: Group A included patients with multifocal bone disease; Group B included patients with soft tissue involvement but no organ dysfunction; Group C included patients with organ dysfunction [146, 147]. After an initial 6 week induction with vinblastine, etoposide and prednisolone, each group was given a year of 'risk adapted' maintenance therapy. This consisted of mercaptopurine, vinblastine and prednisolone for all patients but with etoposide being added for Group B and etoposide plus methotrexate used for Group C. Complete disease resolution was achieved in 91% of patients in Groups A or B and 67% of Group C. Recurrence frequency occurred in 12, 23 and 42% in Groups A, B and C, respectively. While overall mortality was only 9%, it was 38% in the poorest risk group.

Several other reports have questioned the need for intensive treatment (or any treatment) in patients with good prognostic characteristics [148]. In these studies patients were only treated if there were significant signs and/or symptoms associated with the disease. In the study by McLelland and colleagues, the overall mortality was 18% but was 36% in the poorest risk group [148]. A similar 'sequential' approach to treatment was reported from the Dana-Farber Cancer Institute (DFCI) by Filocoma and colleagues in 66 paediatric patients [149]. The results showed an overall mortality of 15.6% with 43% mortality in the worst prognostic group. These studies suggest that the outcome for patients using this 'minimalist' approach to therapy is not essentially different from the more intensive approaches. However, comparing different studies with relatively small numbers of patients carries much risk and can lead to false conclusions. For example, comparison of the incidence of diabetes insipidus has shown the following: 36% in the McLelland report [148]; 15% in a report by Rosenzweig and colleagues from the DFCI [150]; 20% in the AIEOP-CNR-HX 83 study [145] and 15% in the DAL-HX study [147]. In fact, the percentage of patients with LCH who develop diabetes insipidus has been reported to range from 4% to 42% in a number of different studies employing different levels of treatment intensity [150].

The first trial sponsored by the International Histiocyte Society (LCH I) randomised patients to receive either vinblastine or etoposide as induction therapy [151]. High-dose methylprednisolone (30 mg/kg daily for 3 days) was given to both groups. This randomisation was for all children with multisystem disease. No significant difference was found in the initial response for vinblastine compared with etoposide with complete resolution being achieved in approximately 50% of patients for both regimens [151]. Of note is that while many non-randomised studies have shown etoposide to have a higher response rate than vinblastine, the randomised LCH I International trial showed no difference. The absence of a difference for vinblastine and etoposide in newly diagnosed patients versus the relatively high response rates noted for etoposide in patients with disease resistant to vinblastine could have several explanations. One might conclude that the patients treated with etoposide after failing vinblastine were not truly resistant to vinblastine. Another likely explanation involves the relatively small numbers of patients included in the single arm trials of etoposide. Indeed, the relatively poor response rate for patients on the LCH I trial who were crossed over to the alternative induction agent because of lack of response to the initial drug supports these explanations.

Overall mortality was 18% with 47% of deaths occurring in the group of patients who did not show an initial response to 6 weeks of therapy [151]. The trial allowed for a crossover to the other induction treatment for initial non-responders, but only 34% of these ultimately had a favourable outcome

demonstrating that a poor initial response to vinblastine plus steroids or etoposide plus steroids portends a poor outcome. However, a particularly excellent prognostic group of patients with multisystem disease was defined as those patients over 2 years of age at diagnosis with no significant involvement of the haematopoietic system, liver, lungs or spleen. In this group, there was a 100% survival and a 90% response to therapy. This observation was also made in the DAL-HX 83/90 study [130, 146, 147].

When one compares LCH I with DAL-HX 83/90, overall survival was not different. However, the risk of recurrent or reactivated disease in patients who initially showed a good response to therapy was 68% on LCH I and 43% for DAL-HX 83/90 [130]. There was also a difference in the risk of developing diabetes insipidus between the two studies with 42% for LCH I and 15% for DAL-HX 83/90 [130]. While such comparisons might suggest that the more intense regimen predicts an improved outcome with a lower risk of disease reactivation and diabetes insipidus, such a conclusion would be premature, knowing the wide variability of outcomes from different studies and the problems encountered when comparing chronologically disparate trials. However, the LCH II trial will try to address this question in high-risk children with multisystem LCH in a prospective, randomised manner by comparing induction with continuous oral prednisolone and vinblastine with or without etoposide. Continuation therapy includes 6 months of oral mercaptopurine with vinblastine along with 5 days of oral prednisolone every three weeks. The alternative, more intense continuation arm will add etoposide. Pending the results of this trial, scepticism over more aggressive treatment regimens may be on firm ground.

Thus, during this period of nearly 100 years, several important features of LCH and therapeutic issues have become evident regardless of the underlying cause of the disease: (1) definitive risk groups can be identified and the extent of disease has important implications for treatment and outcome; (2) patients with minimal involvement usually require minimal or no treatment; (3) patients with more extensive disease involvement clearly benefit in terms of morbidity and survival by treatment with regimens including systemic cytotoxic agents; (4) the initial response to therapy for patients with severe disease predicts outcome; i.e. poor initial responders have poor outcomes; and (5) treatment intensification for higher risk patients has not yet been proven to be beneficial.

Treatment strategies for refractory and/or recurrent LCH:

The LCH I trial showed that an initial poor response to therapy for patients with multisystem disease predicted a poor overall outcome for both morbidity and mortality. A major area for improvement is in the treatment of those patients who do not respond to conventional therapies. To this end a variety of cytotoxic and immunomodulatory approaches have been attempted [130]. Anecdotal responses have been reported for a variety of agents used alone or in combination [131].

The nucleoside inhibitor, 2-chlorodeoxyadenosine (2CdA) has been utilised in quite a number of children and adult patients over the past several years based on the excellent responses which were observed in patients with hairy cell leukaemia, chronic lymphocytic leukaemia and Waldenstrom macroglobulinaemia [82, 152–155]. Although 2CdA was initially developed as an antilymphocytic agent, cells of the monocytic lineage are particularly sensitive to this agent, which kills cells at all stages of the cell cycle by inducing apoptosis [156]. Finally, because 2CdA is also immunosuppressive, it provides yet another mechanism by which the pathophysiology of LCH could be interrupted [157]. The responses reported with 2CdA at a variety of dosing and delivery schedules have been sufficient for the International Histiocyte Society to test this agent in a phase II trial of patients stratified according to whether they have a poor prognosis (with organ dysfunction), intermediate prognosis (multisystem disease without organ dysfunction) or are low risk (chronic, indolent, recurring disease). In addition, patients will be evaluated by standard response criteria established in the LCH I study. Another intriguing feature of 2CdA is its synergistic interaction with cytosine arabinoside, a characteristic which has been exploited in the treatment of patients with AML [158]. Thus, for those patients who fail 2CdA as a single agent, the combination of 2CdA and cytosine arabinoside will be examined in this phase II trial.

A variety of immunomodulatory therapies have been used to treat patients with LCH. Based on the findings that patients with LCH demonstrated an increase in circulating lymphocytes spontaneously cytotoxic to human fibroblasts and the conclusion that this might be related to a T lymphocyte suppressor defect, the use of thymic extract to augment immune function was used [159]. A benefit was reported for patients with multisystem disease but not for the most severely affected patients. The fact that subsequent studies have not confirmed this finding may relate to the difficulty of truly determining whether responses are due to the therapeutic intervention in patients who often have a variable clinical course [160, 161]. This again emphasises the importance of the response criteria set up by the LCH I study for evaluating new therapies. A more recent report has used IL-2 in order to augment natural killer cell activity and produce an 'anti-tumour' response in a patient with LCH [162]. While the patient was reported to have had a significant clinical response, one must be wary of concluding too much from single patient experiences in a disease whose clinical course varies considerably over time.

Other immunomodulatory approaches have attempted to interrupt the localised level of immune activation and cytokine secretion in LCH lesions by using immunosuppressive agents. Clearly steroids (and possibly other cytotoxic agents) may in part be effective through this mechanism. In addition, antithymocyte sera and cyclosporin may provide some benefit to patients with refractory disease by decreasing the level of cytokine production, although this has never been definitively shown [163, 164]. Based on its antiviral (although there is no compelling evidence that LCH has a viral aetiology) and antiproliferative characteristics, α-interferon has been used in a few patients, but the results have been disappointing [165–167]. The use of thalidomide, a moderately immunosuppressive drug, has only been used in a few patients with mixed results [168–170].

The current extreme of cytotoxicity and immunosuppression is allogeneic haematopoietic stem cell transplantation (SCT). While sustained responses have been obtained using this treatment modality, the results thus far reported in the literature have very likely not reflected a true representation of all patients undergoing this treatment modality [171–176].

Another issue is that very few patients have undergone SCT. This may be in part due to the fact that more effective therapies at diagnosis and for relapsed/refractory disease have circumvented the need for even using SCT. Preliminary results from the IBMTR database would suggest that approximately half the patients may survive with control of their disease following SCT from related donors, whereas survival is extremely low for transplantation with unrelated donors (Egeler, Arceci, Coppes and Filipovich, Children's Hospital Medical Center, Cincinnati, Ohio, U.S.A. and Alberta Children's Hospital, Calgary, Canada).

The use of autologous SCT (ASCT) in patients with LCH has also not been adequately tested. ASCT reduces the need to search for a donor and eliminates the problems associated with graft-versus-host disease. However, several problems with this type of approach include whether or not the cell responsible for LCH would or would not contaminate autologous bone marrow or peripheral stem cells, as has been observed for leukaemia and neuroblastoma [177–179]. The use of CD34-positive progenitors with or without depletion of Langerhans cells might reduce the risk of this happening; whether mobilised stem cells collected from the peripheral blood would have advantages is also unknown, although dendritic cells certainly are known to circulate [180]. Careful scientific and clinical studies are needed to evaluate these possibilities fully.

Clearly, much more work needs to be done with standardised approaches in experienced centres to determine what clinical criteria should be used for SCT in patients with refractory LCH. A standardised preparative regimen and a priority list of acceptable donors should also be explored.

Unique sites of refractory LCH and/or consequences of LCH

The development of progressive sclerosing cholangitis in patients with a history of LCH remains a rare but potentially devastating complication [131, 181–186]. It has been estimated that 15–20% of all cases of sclerosing cholangitis may be due to patients with LCH [187]. The cause is unclear, but on biopsy one does not usually find LCH cells and the sclerosing cholangitis does not respond to the approaches used to treat LCH. It is interesting to note that sclerosing cholangitis has also been described in patients with CD40 ligand deficiency, a disease characterised by immune dysfunction [188]. While treatment with anti-inflammatory agents, such as steroids, cholchicine, methotrexate, cyclosporin or FK506, may offer some benefit, these patients may often require liver transplantation [189–191]. Having a history of LCH is not a contraindication for liver transplantation in that the transplanted liver has not been shown to be at significant risk of developing sclerosing cholangitis [192–196].

The development of progressive pulmonary insufficiency, usually due to fibrosis, also represents a major therapeutic challenge. For patients with active LCH involving the lung, therapy should be aggressively pursued according to standardised protocols, as described above. However, for patients with progressive fibrosis, few therapeutic options are available [131]. It is therefore imperative to know whether active LCH is present; this will usually require a lung biopsy. For the situation of progressive fibrosis, anti-inflammatory agents such as inhaled or systemic steroids in conjunction with bronchodialators may provide some relief [131, 197, 198]. The identification of agents which can inhibit and even reverse lung fibrosis are clearly needed; some promising agents are currently being tested in animal models of pulmonary fibrosis [199].

Involvement of the CNS in patients with LCH can take on several different forms [200–202]. Pituitary involvement classically presents with signs and symptoms of diabetes insipidus. MRI of the brain will often reveal a thickened pituitary stalk and absence (also sometimes seen in normal individuals) of a posterior pituitary 'bright spot'. The first and most important course to take for patients with a history of diabetes insipidus is to document chemically whether they really have diabetes insipidus. Once the diagnosis of diabetes insipidus is established, the decision as to whether (and with what) to treat a patient must be made. While reversal of diabetes insipidus has been reported in several studies utilising low-dose radiation therapy to the hypothalamus and pituitary, the documentation of diabetes insipidus has not always accompanied such reports [135, 203]. Other studies have further questioned the potential for long-term endocrine dysfunction or the development of secondary malignancies following even low-doses of radiation therapy [135, 150, 203, 204]. More recent data would suggest that, in some circumstances diabetes insipidus may be reversible with radiation therapy but that treatment needs to be delivered within a few days of the onset of symptoms [135, 150, 203, 204]. Other systemic cytotoxic agents such as high-dose steroids have not been shown to provide benefit [135, 150, 203, 204].

Parenchymal brain involvement with LCH can occur with (1) local proliferation expansion of active LCH; or (2) focal and often symmetric development of gliosis [202]. Patients may present with ataxia, dysarthria, dysphagia, hyperreflexia and changes in mental status. Hydrocephalus may also develop possibly as a result of LCH involvement of the absorptive lining of the ventricles. Whether or not a biopsy should be taken from such lesions remains controversial. Knowing whether a lesion is due to active LCH would be potentially important in that there would appear to be a higher probability that the disease would respond to radiation therapy and possibly some cytotoxic agents such as 2CdA. However, no effective treatment has yet been identified for lesions more typically associated with gliosis, making the need for a biopsy less compelling. In addition, the gliotic changes that have been observed may remain stable for many years without evidence of progression; alternatively, progressive neurological deterioration may occur. Similar radiographical changes can also be observed in completely asymptomatic patients. The aetiology of this syndrome remains unknown. The proposal that it may represent a type of 'paraneoplastic' syndrome has been made [131, 181, 202]. This would also account for the often symmetric distribution of the lesions possibly secondary to a lymphocyte or antibody recognised epitope shared by similar parts of the brain. Alternatively, such lesions might result after an initial cellular insult followed by an abnormal repair process. Unfortunately, one can only currently offer supportive care to patients who develop the progressive form of this complication.

HLH

Without treatment, familial HLH is a progressive disease which results in death by infection and/or bleeding within a few months. Initial therapeutic attempts using cytotoxic agents met with only moderate success [205–207]. Plasma or blood exchange was attempted based on observations that the serum of patients with familial HLH was immunosuppressive

due to hyperlipidaemia [45]. While improvement was observed in some patients following plasma exchange, responses were transient. The treatment of patients with HLH like those with LCH, led to the observation that the combination of vinblastine plus steroids was quite effective in controlling the disease for a period of time. However, the introduction of epipodophyllotoxins, particularly etoposide, along with high-dose steroids, led to the development of the most effective therapy for inducing disease remission [206, 208, 209]. The recognition of a high prevalence of diffuse CNS involvement by HLH led to the addition of cranial radiation and intrathecal methotrexate (MTX) [207]. While cranial radiation was initially used, this treatment modality is not recommended for upfront therapy. Immunosuppressive approaches to the treatment of HLH have also been shown to have activity. These have included ATG as well as cyclosporin A [210, 211].

Unfortunately, while chemotherapy can induce remissions lasting several years in some patients with familial HLH, there is no precedent for the disease being cured. The introduction of allogeneic SCT by Fischer and associates demonstrated that familial HLH could indeed be cured with this approach [212]. Current therapeutic recommendations include remission induction with dexamethasone, etoposide and intrathecal MTX followed by maintenance dosing with steroids plus etoposide and cyclosporin A [48, 213]. For familial cases, allogeneic SCT with a matched related donor continues to be the treatment of choice. The recommended preparative regimen includes busulfan, cyclophosphamide and etoposide [214, 215]. Nearly equivalent results have also been reported using unrelated donors with up to a one antigen mismatch and employing T cell depletion to reduce the risk of graft-versus-host disease [216–218]. The observation of patients staying in remission for long periods of time following SCT, even though they have become haematopoietic chimera, suggests that even partial reconstitution of immune function may be sufficient to control the disease in some circumstances [219]. The importance of having the disease under control or in remission prior to SCT has been well documented. The prognosis is particularly poor in patients with active CNS disease who undergo SCT [214–218].

Distinguishing familial from non-familial HLH (e.g. IAHS) is often not possible based strictly on clinical grounds. Even the discovery of an infectious agent does not prove that a patient does not have a familial or primary form of HLH because such patients often have co-existing evidence for infection with viruses and/or bacteria [48]. In addition, a positive family history may not be present to confirm that a patient has primary HLH. And while a persistent lack of NK cell function may suggest the inherited form of HLH, this has not been unequivocally proven to be the case. Nevertheless, it is quite evident that patients with either known familial HLH or a non-familial form usually benefit by the same initial treatment with cytotoxic and immunosuppressive therapy [48].

The International Histiocyte Society has recently developed a protocol using induction therapy with dexamethasone and etoposide along with intrathecal methotrexate followed by continuation therapy with the same drugs, but including cyclosporin A for patients with either form of HLH [47, 220]. Approximately 60% of children with IAHS treated with this approach show a significant response with the best response rates in children over 3 years of age [48].

For patients with HLH believed to be IAHS and who enter a remission in their initial 8 weeks of therapy, it has been recommended that they should be observed off-therapy before proceeding with further continuation therapy and SCT [48]. If the disease reactivates, then further therapy can be reinitiated along with plans for SCT. However, with an overall survival of approximately 50%, one might reasonably argue that if a haematopoietic stem cell donor is available, then SCT should be considered following the initial therapy. For some subgroups of patients the prognosis is possibly even worse, such as those patients with EBV-related haemophagocytic syndrome [48, 213]. This group of patients has been reported to have greater than a 60% mortality, but this figure may not be entirely accurate because nearly 20% of the patients did not have clinical outcome data reported [48].

Some patients may develop HLH secondary to immunosuppressive therapy for another disorder. These patients may benefit by an initial attempt to reduce their immunosuppressive therapy. When it is suspected that the haemophagocytic syndrome is a result of a complicating infection, then antiviral or antimicrobial therapy should be tried. The initial treatment for patients with malignancy-associated haemophagocytic syndrome should always be directed at the primary cancer if possible. If the primary cancer is in remission and a patient develops haemophagocytic syndrome secondary to the immunosuppressive consequences of antineoplastic therapy, then treatment with etoposide and steroids as per the HLH protocol may be beneficial. Of particular interest is the development of an HLH syndrome in patients heavily treated for LCH. While it is most probable that these patients have developed secondary HLH, the transition that RES cell types can make between the dendritic and macrophage lineages makes this phenomenon most intriguing. Because these patients may have already been treated with steroids and etoposide, alternative treatments have been used. For example, several children who have developed this complication have been observed to respond to 2CdA or 2CdA in combination with cytosine arabinoside (Arceci, Children's Hospital Medical Center, Cincinnati, Ohio, U.S.A.).

SOME THOUGHTS FOR THE PRESENT AND FUTURE

While significant progress has been made in the treatment of histiocytic disorders over the past 100 years, advances have come about through relatively empirical approaches based on successes in what were considered different manifestations of the same disease. For example, when LCH was considered to be due to a type of infection, antimicrobial agents were used. When it was considered to be a disorder of immune dysregulation, then immunosuppressive or immunostimulatory approaches were used. And when LCH was considered to be a primarily proliferative disorder, antineoplastic agents have been used. The treatment for patients with HLH has also seen forays into a variety of approaches from supportive care and plasmapheresis to cytotoxic plus immunosuppressive regimens. Ironically the treatment of patients with HLH arose in part out of the initial confusion of this disorder with disseminated forms of LCH. With the growing evidence that HLH (familial or non-familial) is primarily a disorder of immune dysfunction, treatments have evolved in that direction with immunosuppression and replacement of as yet unknown cellular components of the immune system with allogeneic SCT. Throughout these therapeutic adventures, a

quilt of treatment approaches has been stitched together that has truly improved the outcome of patients with LCH and HLH.

As can be seen from the previous discussion there are very few truly effective therapeutic agents for advanced stage LCH or relapsed/progressive HLH. Furthermore, the more aggressive approaches have significant short and possibly long-term toxicity. With increased survival of patients with LCH, the late sequelae of therapy, the disease or a combination of the two take on a more significant concern. Clearly, secondary malignancy is one that also needs to be further understood. Alternatives to therapies associated with a high tumorigenic potential need to be developed. In addition, it is unclear whether patients with LCH (or subsets of these patients) will have increased susceptibility to certain cytotoxic regimens. The neuropsychiatric and neuroendocrine characteristics of active LCH, as well as the long-term signs and symptoms are clearly greater than had been initially expected. This remains an incredibly challenging area for further investigation [202, 221]. In this same regard, issues of long-term outcome and function are now just being able to be answered for patients with HLH who have been successfully treated with stem cell transplantation [222].

There are still too many patients who still do not adequately respond to these regimens and very few treatment options exist for them. The development of more effective and less toxic therapies are, therefore, much needed. From where will these new treatments come?

Over the past 50 years there has been a growing belief that the improved understanding of the molecular basis of disease would eventually lead to more specific, less toxic and more effective therapies. There has also been an increasing impatience for results which have precipitated premature hope followed by disappointment. However, throughout this period, important steps forward have been made through careful laboratory experimentation, clinical insight and the translation of these into novel therapeutic approaches. This could not be more true than in the histiocytic disorders.

An improved understanding of the lineage relationships and functional capabilities of the cells comprising the RES system has led to more refined definitions and biologically based classification of the histiocytic disorders. This has not been just an academic pursuit, but has had critical implications for current and future therapeutic approaches. For example, the identification of cell-type specific markers has provided potential targets for the development of antibody-directed therapies to the CD1a surface protein on Langerhans cells [223, 224]. Information concerning the cytokine milieu of LCH lesions provides additional opportunities for interrupting the pathophysiological basis of LCH. The discovery that LCH is a clonal, proliferative disorder of Langerhans cells provides the basis for investigating the genetic causes for the disease, as well as the molecular characteristics of LCH cells contributing to a treatment-resistant phenotype. Work on the immune defect responsible for abnormal lymphocyte function, especially the decreased NK and CTL activity, in HLH is just getting started. Clearly, the next step in this direction, as in LCH, is to define the responsible molecular cause(s) and physiological pathways.

Rapid progress being made on the human genome project and in dendritic/macrophage biology needs to be applied to histiocytic disorders. Therefore, more dialogue and real collaboration need to be developed by linking the work of clinicians with these laboratory investigators. For example, it is imperative that a worldwide network be developed for the identification of familial cases of both LCH and HLH with published (possibly through the internet) family trees and accessibility of stored tissue samples. Of course, confidentiality and privacy for patients and families must be maintained. Access to such material should be through solid scientific proposals which are reviewed in a rigorous and timely manner. This type of approach has been conducted for a variety of disorders which has led to the identification of the responsible defective gene(s) involved for diseases such as Huntington's chorea, Duchenne's muscular dystrophy, Fanconi anaemia and a variety of cancer predisposition syndromes. The International Histiocyte Society could provide the forum by which to galvanise and focus work on the aetiology, characterisation and treatment of the histiocytic disorders.

The myth of Pandora tells us that after the evils of the world escaped from her infamous box, she was able to close it just in time to prevent hope from being lost. Although the histiocytic disorders must truly represent one of those evils, there is much hope for continued improvement in our understanding and treatment of patients afflicted by them. That hope is further strengthened by the growing international cooperation of laboratory scientists, clinical investigators, patients and families toward achieving these goals.

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Commentary

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EXPLORING THE LABYRINTHS OF THE HISTIOCYTOSES

With the very comprehensive and well-written review by Professor Arceci as a back-ground (see above), this commentary will focus on some of the challenges we face for the next decade(s) in the understanding of these disorders and in the treatment of patients suffering from them, rather than going into detailed comments on the review itself.

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As mentioned by Dr Arceci, the reticuloendothelial system (RES) was referred to as the 'Tower of Babel' by Gall [1] and our better understanding of this system is reflected in the title of his review, 'The Histiocytoses: the Fall of the Tower of Babel'. However, we must be aware that these disorders still are like labyrinths (a complicated system of paths and blind paths where the core is difficult to find) to the medical society today, and although we may have revealed some of their parts they are still largely undiscovered. What do we hope to find while exploring the mystery of these labyrinths?