The classification of the histiocytoses has evolved based on new understanding of the cell of origin as a bone marrow precursor. Although the pathologic features of the histiocytoses have not changed per se, molecular genetic information now needs to be integrated into the diagnosis. The basic lesions of the most common histiocytoses, their patterns in different sites, and ancillary diagnostics are now just one part of the classification. As more is understood about the cell of origin and molecular biology of the histiocytoses, future classifications will be refined.

Langerhans cell histiocytosis (LCH) is a heterogeneous disease characterized by common histology of inflammatory lesions containing Langerin\(^+\) (CD207) histiocytes. Emerging data support a model in which MAPK activation in self-renewing hematopoietic progenitors may drive disseminated high-risk disease, whereas MAPK activation in more differentiated committed myeloid populations may induce low-risk LCH. The heterogeneous clinical manifestations with shared histology may represent the final common pathway of an acquired defect of differentiation, initiated at more than one point. Implications of this model include re-definition of LCH as a myeloid neoplasia and re-focusing therapeutic strategies on the cells and lineages of origin.

The discovery of recurrent somatic genomic alterations in Langerhans cell histiocytosis (LCH) has led to a new understanding of LCH as a clonal neoplastic disorder. Most of the abnormalities described to date affect the RAS/RAF/MEK/extracellular-signal-regulated kinase (ERK) pathway: more than 50% of LCH cases carry activating mutations in \(BRAF\), whereas another 10% to 28% carry activating mutations of \(MAP2K1\), which encodes MEK1. The pathogenetic importance of these mutations has been confirmed by reports of significant clinical responses to RAF inhibitors.
Langerhans cell histiocytosis (LCH) is a disease caused by clonal proliferation of CD1a+/CD207+ cells that is characterized by a spectrum of varying degrees of organ involvement and dysfunction. Treatment of LCH is risk adapted; patients with single lesions may respond well to local treatment, whereas patients with multi-system disease and risk-organ involvement require more intensive therapy. Although survival for patients without organ dysfunction is excellent, mortality rates for patients with organ dysfunction may reach 30% to 40%. For patients with low-risk disease, although cure is almost universal, disease reactivation rates are in excess of 30%.

Diseases of the central nervous system (CNS) are common in patients with Langerhans cell histiocytosis (LCH). Besides active LCH lesions, neurodegenerative (ND) lesions of the cerebellum and/or basal ganglia may occur as late sequelae of LCH. While the etiology of this ND disease remains unclear, biomarkers in cerebrospinal fluid (CSF) may reflect the activity of CNS disease in these patients. However, no well-planned CSF studies have yet been performed in patients at high risk for ND-CNS-LCH. Potential parallels with other neuroinflammatory/neurodegenerative diseases suggest the utility of examining these other disorders in establishing strategies for the prevention and/or treatment of ND-CNS-LCH.

Hemophagocytic Lymphohistiocytosis (HLH), an inherited life-threatening inflammatory disorder, has gained growing recognition not only in children but also increasingly in adults over the past 2 decades. HLH involves inborn defects in lymphocytes, which normally mediate control of infectious and inflammatory conditions within the immune system and in other tissues. In the context of inherited defects in cytotoxic cells and other immune cells, the disorder is classified as familial or primary HLH. Secondary HLH occurs in the settings of infections or underlying rheumatologic disorders. Secondary HLH also accompanies some lymphoid malignancies.

Familial hemophagocytic lymphohistiocytosis (FHL) is a rare heritable disorder of immune regulation that is typically characterized by sudden onset of severe systemic illness. Functional impairment or absence of 1 or more of several proteins that participate in lymphocyte cytotoxicity underlies the disease. Although FHL usually presents in infancy, age of onset is variable and dependent on genetic and environmental factors. Initial treatment
consists of immune suppression, whereas definitive treatment requires hematopoietic cell transplantation.

Hemophagocytic Lymphohistiocytosis in Adults
Meghan Campo and Nancy Berliner

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal syndrome of pathologic immune dysregulation characterized by clinical signs and symptoms of extreme inflammation. HLH can occur as a genetic or sporadic disorder and, though seen as an inherited condition affecting primarily a pediatric population, can occur at any age and can be encountered in association with a variety of underlying diseases. Clinically, the syndrome, whether genetic or acquired, is characterized by fever, hepatosplenomegaly, cytopenias, and activated macrophages in hematopoietic organs. Therapy centers on suppression of this hyperinflammatory state with cytotoxic, immunosuppressive therapy and treatment of any existing HLH triggers.

Macrophage Activation Syndrome
Angelo Ravelli, Sergio Davì, Francesca Minoia, Alberto Martini, and Randy Q. Cron

Macrophage activation syndrome (MAS) is a potentially life-threatening complication of rheumatic disorders that occurs most commonly in systemic juvenile idiopathic arthritis. In recent years, there have been several advances in the understanding of the pathophysiology of MAS. Furthermore, new classification criteria have been developed. Although the place of cytokine blockers in the management of MAS is still unclear, interleukin-1 inhibitors represent a promising adjunctive therapy, particularly in refractory cases.

The Role of Hematopoietic Stem Cell Transplantation in Treatment of Hemophagocytic Lymphohistiocytosis
Sarah Nikiforow

The role of reduced-intensity allogeneic hematopoietic stem cell transplantation (HSCT) from a variety of donor sources in improving survival for children with familial hemophagocytic lymphohistiocytosis (HLH) is well-documented. The heterogeneity of adult-onset HLH has complicated evaluation of initial therapy and of HSCT as definitive treatment. Therapy for adults with HLH is often individualized, but institutions are now generating algorithms that include HSCT based on growing experience. Consolidation of these data is needed to optimize management of the growing number of adults recognized to have HLH and to achieve dramatic improvements in survival.