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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?

LANGERHANS' CELL HISTIOCYTOSIS (HISTIOCYTOSIS X)

Aetiology of LCH—eliminating the X

It is a true challenge to eliminate the 'X' in the title of the disease, which still represents our ignorance in understanding the aetiology of this disease. The observation by Dr Nezelof that, in all forms of histiocytosis X, the accumulating cell had histological similarities with the normal Langerhans' cell was an important step in understanding the disease [2]. Another important step was the recent finding that the Langerhans' cells from LCH lesions are clonal, i.e. derived from a common precursor [3, 4]. However, despite these achievements, we do not yet have a clear view on the aetiology of LCH. We do not know the reason for the accumulation of the Langerhans' cells and we do not know at all the significance of clonality in LCH. As Professor Arceci mentions, there are several examples of inflammatory processes which are clonal but are not considered cancerous.

Today, we do not even know whether there is a genetic cause for LCH or whether it is merely a reactive disorder, maybe secondary to a microbe, or something else. Eliminating the 'X', as a representative of our ignorance on the cause of LCH, is a true challenge for the next decade.

Treatment of LCH—looking for more specific weapons

Another challenge is to find or develop better weapons in the continuous fight against the disease. The mortality in multisystem LCH is still around 20% i.e. in the same range as acute lymphoblastic leukaemia in children, and the morbidity is also unacceptably high. The morbidity is commonly associated with complications secondary to inflammatory destructive activity in various organs, such as diabetes insipidus and other hormone insufficiencies secondary to involvement of the pituitary/hypothalamic axis, skeletal damage (fractures, kyphosis, face abnormalities) secondary to bone involvement and pulmonary fibrosis secondary to lung involvement. A personal view is that it would be valuable to investigate prolonged but moderate maintenance therapy, which may include methotrexate and 6-mercaptopurine, in a randomised trial aimed at reducing reactivation of the disease and thereby reducing morbidity caused by the inflammatory activity.

It is noteworthy that we still mainly use the same therapeutic weapons that were used 20 years ago, i.e. corticosteroids, vinblastine, etoposide, 6-mercaptopurine and methotrexate (cf. the DAL-HX 83 study) [5]. This may very well mirror our lack of knowledge on the pathophysiological mechanisms, as we have learnt little during the last 20 years. Newer agents, including interferon-alpha, cyclosporin-A, and antithymocyte globulin, have not fulfilled their initial expectations and, as long as the underlying mechanisms of the disease are not revealed, a certain amount of caution may be appropriate with regard to the therapeutic value of new drugs. Another field of interest would be to develop markers of disease activity, in order to monitor the disease activity better, in particular since LCH has a tendency to wax and wane. Recent studies have indicated that easily available tools such as elevated sedimentation rate and thrombocytosis may be useful in this respect but additional markers would be valuable [6].

Another challenge is a field of growing concern; CNS involvement in LCH. Although only a minority of the LCH patients are affected, the consequences for those who are affected are often tragic [7]. A common feature is progressive ataxia, dysarthria, and dysphagia, but alterations in judgment and changes in mental status may also occur. Here again the pathophysiology is totally unknown but, even worse, there is no treatment known to help affected individuals.

HAEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Aetiology of HLH—what is the underlying biology?

In many ways the development in the field of HLH has been more rapid during the last 2 decades compared with LCH. A pronounced hypercytokinaemia has been shown to play a central role in the clinicolaboratory features. The therapeutic results in primary—i.e. inherited HLH (FHL) has increased remarkably from a median survival after diagnosis of only 2 months (without long-term survivors) to a situation where many are cured.

Another major breakthrough was recently achieved when genes for FHL recently and independently were localised at chromosome 9q21.3-22 and 10q21.-22 [8, 9]. However, although we know that lymphocytes and macrophages are profoundly activated and that many symptoms and signs are caused by the remarkable hypercytokinaemia, the underlying biological defect(s) is still unknown, which is another challenge for the next decade. This is a fascinating task, since the explanation may also elucidate important parts of normal immunomodulation. A personal reflection is that the possibility of a defect in the regulation of apoptosis in lymphocytes has to be considered as a mechanism responsible for their non-clonal accumulation.

Another long desired goal may now be within reach, since further genetic studies may provide a basis for appropriate genetic counselling of affected families.

Treatment of HLH—many still die undiagnosed

We have been lucky in achieving a remarkable improvement in survival during the last decade, as mentioned by Professor Arceci. The wide international collaboration in the first international treatment study (HLH-94), with participating colleagues in all six continents, is another success and the accumulating data are a basis for further improvement of survival [10]. One important task will be to reduce the neurological sequelae in these patients, a result of the inflammatory activity in the CNS [11, 12]. The improved BMT (bone marrow transplantation) results using HLA non-identical donors is another important contribution for improved survival [13].

However, the knowledge about the disease itself is still limited even among paediatricians and it is reasonable to believe that many children die without the correct diagnosis, or are diagnosed very late when neurological sequelae are already at hand. Therefore, spreading the knowledge about HLH is an important mission.

Another highly desirable goal would be the development of better diagnostic tools in differentiating primary and secondary HLH. Since a family history rarely is present even among presumably inherited cases and since a virus infection may trigger primary as well as secondary HLH, it may be difficult to discriminate these two conditions. This difficulty has important therapeutic implications, such as whether to proceed directly to BMT after achieving a remission or merely stop therapy, which may be detrimental in primary HLH in the same way as the risk of BMT is unacceptable in patients merely suffering a short lasting secondary HLH. Hopefully,

the genetic breakthrough mentioned above may initiate the development of these diagnostic tools.

In summary, Professor Arceci has provided an extensive review of the intriguing field of the histiocytoses. We have begun to have some insight into these mysterious disorders, but there are still many labyrinths to discover, where we may yet get lost. With international collaboration, improvements will most probably be more rapid. The International Histiocyte Society has an important role in co-ordinating international efforts, in collaboration with the Nikolas Symposium mentioned by Professor Arceci and parents organisations. Great improvements have been made but many more are still awaited.

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