DENDRITIC CELLS AND THE BRAIN IN LCH

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Friday, May 7, 1999

The session opened with **Dr. Arceci** welcoming the delegates to the symposium.

Dr. Egeler then discussed the historical and clinical perspectives of Langerhans cell histiocytosis (LCH) that is diagnosed in > 1/200,000 children per year, affecting, 1/10,000 children and is probably underdiagnosed. It occurs at all ages but >50% of cases are in children 0-15years of age. Prognostic factors include the number of organs involved, dysfunction of organs such as liver, lung and hematopoetic system, age <2 years at diagnosis and the response following 6 weeks of treatment. The presentation of LCH in different organ systems was discussed. End stage disease in liver and lung, must be treated by lung or liver transplantation. No satisfactory assessment has been found for CNS disease. Dr. Egeler described the pathologic diagnostic criteria of LCH as well as the differences between activated normal Langerhans cells and LCH cells. **Dr. Jaffe added** that the diagnosis should be made on clinicopathologic rather than purely pathologic criteria. He also emphasized the need for caution in diagnosing lymph node LCH as reactive nodes may contain CD1a positive histiocytes.

Drs. Grois and Prayer then presented their experience with neurologic involvement and consequences in LCH. Between 1991 and 1999, 85 LCH patients with CNS manifestations were reviewed using questionnaires, medical reports, review of pathology and of MRI scans. Based on the review CNS LCH was divided clinically into 3 categories:

a) Hypothalamic - pituitary disease usually presenting as Diabetes Insipidus (DI).

b) Extraaxial space-occupying lesions in subdural space, epidural space, arachnoid, choroid plex.us Yid pineal gland. The comment was made that normal blood-brain barrier penetrability may explain LCH of these yeas.

c) Neurodegenerative disease. It was speculated that this resembled Multiple System Atrophy like pattern, occurring mainly in the cerebellum, basal ganglia and pons, and occasionally seen in supratentorial white and grey matter. Most often present with cerebellar and pontine dysfunction. Psychomotor retardation and behavioral disturbances were relatively frequent. Pathology was available in 12 patients and primarily shows gliosis, loss of Purkinje cells, perivascular histiocytic infiltration and demyelination. Based on MRI findings, CNS LCH was classified into 6 categories - abnormalities of white matter, grey matter, extraparenchymal, hypothalamic-pituitary, atrophy and therapy related. Dr. Prayer discussed the differential diagnoses of MRI findings. They concluded that there was overlap of clinical groups and the types of lesions within individual patients. Risk factors for development of CNS LCH are multisystem LCH and skull involvement, in particular skull base lesions. However, there were no factors that predict for development of neurodegenerative disease. Many questions remain to be answered including the true incidence and the pathogenesis of CNS LCH, the reason for the predeliction for the hypothalamic pituitary region, the significance of pineal changes or the possible etiologic events (viral infection, auto-antibodies, altered melatonin metabolism?). An additional area of contention was the use of the term neuro-degeneration and whether there was evidence on the MRI scans of neurodegeneration such as neuronal loss (cortical chinning).

Dr. Favara discussed the neuropathology of LCH and correlated his findings with the MRI - based classification described by Drs. Grois and Prayer. The lesions seen in the grey matter and the hypothalamic pituitary area appear to be due to typical LCH lesions

that occur in areas where the blood brain barrier is known to be incomplete. Some of the extraparenchymal lesions have an appearance similar to juvenile xanthogranuloma with xanthomatosis and occasional Touton giant cells. The cerebellar biopsies showed no pathology in 2 cases while the others showed rarefaction, edema and a small number of histiocytes around blood vessels. Members of the audience commented on the similarity to the appearance of the spinal cord in HIV patients and queried whether these "neurodegenerative changes" are due to cytotoxin release by LCH cells.

Saturday, May 8, 1999

Dr. Austyn provided a review of the dendritic cell (DC) lineages. After the basics of processing DC (immature) and co-stimulating DC (mature), Dr. Austyn discussed the range of DC with their phenotype in lymphoid tissue, in non-lymphoid tissue and in the circulation.

Dr. Caetano Reis e Sousa then presented the in vivo regulation of DC cell function by microbial stimuli. Immunity to foreign antigens is favored by co-immunization with microbial and inflammatory stimuli. His research group has demonstrated that these stimuli activate DC in vivo, leading to accelerated migration to the T-cell areas of lymphoid tissues, increased presentation of antigen, upregulation of co-stimulatory molecules and production of cytokines such as IL-12. Interestingly, the lymphoid DC subset, thought to correspond to the interdigitating cells of lymphoid tissues, showed the most dramatic responses to in vivo microbial challenge. Different DC subsets or different forms of DC activation may regulate the response to antigen challenge and determine the balance between tolerance and immunity.

Dr. Matsuno then focussed on DC recruitment to liver and blood-lymph translocation. The liver is an essential immune organ for a host defense. It is armed not only with a powerful macrophage (Mϕ) system but also is constantly surveyed by a heavy traffic of DC and lymphocytes. In infection and inflammation, DC traffic in the liver is accelerated. DC in the liver capture and process antigens, enter the draining lymph and accumulate in the T-cell area of hepatic lymph nodes. DC in the lymph nodes present antigens to T- and B-cells initiating immune responses. In accelerated states, DC precursors are recruited to the liver, and soon translocate to hepatic lymph. Even mature lymph DC can undergo a blood-lymph translocation from the liver to hepatic lymph nodes after intravenous injection into normal rats. Rat Kupffer cells in the hepatic sinusoids are capable of selectively trapping DC from the blood in vivo and in vitro suggesting involvement of certain adhesion molecules. The accelerated traffic and the presence of blood-lymph translocation would induce rapid and efficient immune responses and thus contribute to the local defense against antigens within tissues as well as systemic defense against blood-borne antigens.

Dr. Thrasher showed disturbances in DC trafficking in the Wiskott - Aldrich syndrome (WAS). WAS is a rare inherited X-linked recessive disease characterized by immune dysregulation and microthrombocytopenia. Recently, the biological mechanisms that are responsible for the pathophysiology of WAS have been shown to be linked to the regulation of the actin cytoskeleton of hematopoietic cells. The WAS protein (WASp) is now known to be a member of a unique family that shares domain structures, and which are responsible for transduction of signals from the cell membrane to the actin cytoskeleton. The interaction between WASp, the Rho family GTPase Cdc42, and the

cytoskeletal organizing complex Arp2/3 are probably critical to many of these functions, which when disturbed result in measurable defects of cell polarization and motility. In particular, defects in DC trafficking may explain some of the immunological features of the disease.

The innate immune response is rapid, restricts potential infection and alarms the acquired immune system response. **Dr. Fraser** discussed the role of the innate immune system in the control of infections. Recent molecular studies suggest that pathogens and their hosts have co-evolved, with the pathogens expressing Pathogen Associated Molecular Patterns (PAMPs) and the host leukocytes expressing Pattern Recognition Receptors (PRRs). Many of the host receptors have broad binding specificity to deal with a spectrum of pathogens. The mannose binding protein (MBP) is a soluble opsonin and a member of the collectin family of molecules. This family of molecules acts as "ante-antibodies" in the clearance of pathogens. It is of considerable interest as to whether genetic defects or polymorphisms in the PRRs or collectin family might predispose individuals to infection from particular pathogens thus driving the acquired immune response atypically in the absence of an innate response.

A well-known feature of LCH is the destructive bone lesions and there has been considerable interest in the mechanisms that regulate osteoclast differentiation and number of multinucleated giant cells in the bone lesions. **Dr. Chambers** reviewed recent advances that have revealed the key cytokine produced by osteoblasts that is both necessary and sufficient for the differentiation, survival and functional activation of osteoclasts. This molecule TRANCE (tumor necrosis factor-related activation-induced cytokine) (also identified as RANKL, OPGL, and ODF), is expressed as a membrane-inserted ligand by osteoblasts or stromal cells and it binds to RANK (also known as TRANCE-R), a member of the TNF receptor family. These studies facilitate the generation of large numbers of osteoclasts *in vitro* which will without doubt lead to rapid advances in our understanding of the regulation and mode of action of these cells in health and disease, and their relationship with other cells of the mononuclear phagocyte lineage.

The theme of the functional molecules of the TNF family continued with a presentation by **Dr. Chaplin**. There is interest in the role of the TNF family and their receptors in the development and differentiation of the lymphoid system, an issue of relevance to LCH. He has examined the role of membrane bound lymphotoxin in the development of secondary lymphoid tissues by studying the development of these structures in mice deficient in membrane bound lymphotoxin or the lymphotoxin receptor. These studies demonstrate that membrane bound lymphotoxin is not necessary for the development of the white pulp of the spleen but is required for the maintenance and maturation of the follicular DC network and the marginal sinus structure. The membrane bound lymphotoxin signal comes from developing B-cells showing that they are essential for the development of the tissue within which they will mature.

Sunday, May 9, 1999

The issues surrounding mechanisms of inflammation within the CNS are clearly of direct relevance to patients with LCH. As discussed by **Dr. Perry**, the parenchyma of the brain appears to be uniquely protected against pro-inflammatory insult although this protection is variable through ontogeny, and can be disturbed in situations such as trauma.

Conventional DC are not present in brain, but in some acute inflammatory states they do appear. An effective inflammatory response is essential for survival but it also has the capacity to cause bystander damage to normal tissue. The microenvironment of the CNS has a profound effect on inflammatory processes within it. The resident tissue Mϕ, are atypical and appear switched off or down regulated by mechanisms that are at present unknown. Following challenge of the brain with an acute inflammatory agent the response in the brain is atypical when compared to peripheral tissues. Vascular reaction and leukocyte recruitment are limited. In contrast following a stroke, or trauma to the brain the resistance of the brain to inflammation is overcome and inflammatory cells exacerbate the lesion. In chronic neurodegeneration disease such as Alzheimer's, Parkinson or prion disease the inflammatory response is dominated by the presence of activated mononuclear phagocytes. The inflammatory molecules secreted from these cells are distinct from those secreted by Mϕ present in acute injuries to the brain. If an inflammatory stimulus persists or escapes the destructive power of the innate inflammatory response then the acquired response will be initiated. In the microenvironment of the brain, however, a pathogen may persist without recognition by the immune system. However, following peripheral sensitization of the immune system, T-cells readily find the pathogen in the brain and initiate a local inflammatory response with the recruitment of T- and B-lymphocytes, Mϕ and DC. The atypical inflammatory response in the brain microenvironment suggests that the brain has evolved mechanisms to tightly regulate the inflammatory response since it has the potential to cause significant bystander tissue damage. Understanding the factors that regulate leukocyte recruitment to the brain may be of value for understanding the neurological consequences of histiocytoses.

Dr. Sedgwick continued the discussion on brain APCs. The CNS is generally considered to be an immunologically compromised site. This is caused by specialized vascular barriers to leukocyte traffic, absence of normal lymphatic drainage and the low incidence of professional APC end associated lack of expression of class I and class II molecules encoded by the major histocompatibility gene complex. However, effective immunological surveillance of the CNS by T-cells is evident and inflammation by a variety of cell types with consequent immunologically mediated tissue destruction can proceed. These events are thought to be due to the presence of perivascular Mϕ as well as resident CNS Mϕ, or microglia, that can act as APC and drive T-cell activation. In contrast to studies in which microglia derived from the immature CNS and cultured for extended times are used as APC, Dr. Sedgwick's studies with fully differentiated, *ex vivo* adult CNS resident microglia show that microglial cells are limited in their APC capacities *in vitro.* Such microglia when used as APC, support T-cell effector function with minimal proliferation. Ultimately T-cell apoptosis occurs. All outcomes are reminiscent of the fate of T-cells within the CNS *in vivo*. Microglia removed from the *in situ* environment, may de-differentiate and exhibit functions not normally seen *in* vivo. This being the case, what is it that represses microglial cell activities *in* vivo? Interactions between neuron and glia via ligand/receptor pairs on the two cell types are likely to be critical in glial cell homeostasis. Gene knockout (KO) mice were prepared lacking an Ig-superfamily molecule widely distributed in the periphery, including on DC, lymphocytes and endothelial cells, but also highly expressed on neurons of the CNS.

This molecule appears to regulate activation of Mϕ, which may therefore be important in the pathophysiology of CNS histiocytosis. Thus, increased Mϕ numbers and activation, both in the steady state and after stimulus *in vivo*, and manifest in a variety of tissues including substantial consequences for CNS microglia was observed in the KO mice, indicating the identification of a novel and broadly-relevant pathway of Mϕ regulation. Defects in such regulatory pathways may underlie dysregulation of cells within the monocyte/Mϕ lineage in a variety of pathological states.

Dr. Nichols, an Artemis Fellow, described another immune regulatory molecule, recently identified as the gene involved in X-linked lymphoproliferative disease (XLP). XLP is a rare immunodeficiency disorder associated with overwhelming lymphocyte proliferation and histiocyte activation after primary exposure to Epstein-Barr virus. XLP might serve as a model with which to elucidate molecular pathways critical to the activation of histiocytes in hemophagocytic disorders. Dr. Nichols and her co-workers are focussing on the immunodeficiency in XLP to determine the function of this gene in regulation of lymphocyte activation.

Dr. Leenen presented the role of DC in the pituitary and other endocrine organs. Three major regulatory systems can are responsible for maintaining body integrity and homeostasis: the nervous system, the endocrine system and the immune system. DC and Mϕ have long been recognized as members and major regulators of the immune system. Extensive immunohistochemical investigations have shown that DC and Mϕ are normal constituents of virtually all endocrine organs: pituitary, ovaries as well as testes, thyroid, pancreas and others. These contain distinct populations of DC and Mϕ. Several lines of evidence underline the functional relevance of DC and Mϕ in these organs. In general, modulation of endocrine activity coincides with significant changes in the immune populations present. It may be concluded that an intricate level of cross-talk exists between the various components of the endocrine system and different DC and Mϕ populations. Two aspects of LCH deserve special attention. First, a recent epidemiological study revealed a relatively high correlation between LCH and thyroid disease in the proband, and to a lesser, yet significant, extent between LCH and a family history of thyroid disease. It is far from clear, however, what the causal relationship is. Second, diabetes insipidus is a frequent complication of LCH. It is thought to be the consequence of abnormalities at the level of the vasopressin-secreting neurohypophysis. The adenohypophysis, however, contains a population of so-called folliculo-stellate cells, which bears strong resemblance to myeloid DC, including expression of MHC class II and CDIa antigens, and the ability to present antigen. Recently, it has been shown that at least a subpopulation of these folliculo-stellate cells is bone marrow-derived and has a relatively high turn-over under steady state conditions. It is therefore tempting to speculate that selective homing of aberrant LCH cells to the pituitary, using the same pathway as regular folliculo-stellate cells, underlies this pathology in LCH.

Dr. Lynn from the Royal College or Pediatrics and Child Health (London) discussed the important role of national and international surveys to study the prevalence and natural history of rare diseases such as LCH. Rare diseases are, paradoxically, an important cause of morbidity and mortality in childhood. Individually uncommon, together they number in the thousands. The difficulty in recognizing a rare disease can result in delayed diagnosis with its attendant likelihood of preventable complications or even

death. Such diseases are difficult to study since little is known about the spectrum of clinical manifestations, pathological changes, sequelae and management; many of them are characterized by chronicity and by high rates of disabling sequelae or death. By definition the study of rare diseases requires the collaboration of a large number of clinicians provide the health care of a large population, in order to generate a sufficient number of cases to derive meaningful, generalisable knowledge. Networks of collaborating clinicians are required to undertake descriptive epidemiological surveys or studies of natural history. To address this the British Paediatric Surveillance Unit was set up in 1986. The success of the BPSU led to its methodology being copied throughout the world, and to the establishment of the International Network of Paediatric Surveillance Units. Methodology was discussed on the basis of epidemiological surveillance of over 60 rare diseases across the world.

Dr. Murphy then discussed the advantages and potential problems of Integrating LCH Studies into Clinical Trial Groups. There are obvious advantages of performing studies of LCH in collaborative clinical trial groups, as considerable synergy can be achieved by pooling of knowledge, expertise, case material and outcomes. The rarity of LCH also precludes any single center from conducting definitive clinical trials. Cancer clinical trials groups are well-established and could potentially provide a platform for studies of LCH. Clinical trials groups are multidisciplinary multi-institutional networks linked by operations/statistical centers with defined performance and quality criteria. In the United States, the clinical cooperative groups are supported by peer-reviewed awards from NCI and are tied to the terms of cooperative agreements governing compliance, data monitoring, protection of human subjects, audits and toxicity/adverse event reporting. Cancer clinical trials groups conceivably could conduct clinical trials for LCH, but, for the last decade, LCH trials have been conducted largely through the Histiocyte Society. Progress in treatment trials will depend on improved fundamental understanding of the underlying pathogenesis of LCH and generation of novel treatment strategies for trial design.

Monday May 10, 1999

Dr. Matthews described new brain imaging techniques. Magnetic Resonance Imaging techniques that allow simultaneous acquisition of information on brain morphology (size, shape), brain pathology, and neurophysiological measures. They can be acquired serially and non-invasively to allow direct correlation's with clinical symptoms and signs. New image analysis techniques promise highly sensitive measures of change that can be used as surrogate markers for assessing therapeutic interventions. Functional imaging techniques are now being integrated with biochemical and morphological measures of pathology to assess directly the substrates of functional impairment and disability. Of particular interest is the potential of magnetic resonance spectroscopy (measuring biochemical changes in brain) and functional magnetic resonance imaging (measuring the hemodynamic response to local brain activation) to identify functional abnormalities in morphologically normal brains. Ongoing research suggests that ultimately imaging of parameters critical to understanding the CNS inflammatory responses, such as lymphocyte trafficking, may be possible.

Dr. Banati presented Mϕ ligands and CNS imaging. Microglia are cells of mononuclear-phagocyte lineage that constitute approximately 20% of non-neuronal cells in the healthy

adult human brain. They are distributed throughout the brain occupying non-overlapping territories. In normal tissue, microglia have highly ramified processes and a richly pleated outer cell membrane. Though their function in this 'resting' condition is not yet understood, microglia respond rapidly to a variety of pathological stimuli. Apart from inflammatory processes w.th recruitment of blood-borne cells, neuronal injury as such -with or without subsequent neuronal cell death - invariably leads to a transient activation of microglia around the injured neuron. Hence, independent of the specific cause of neuronal injury, the detection of activated microglia can be used as a surrogate marker of ongoing acute (e.g. inflammatory) or chronic e.g. neurodegenerative) cerebral pathology. (R)PK11195 is a specific ligand of the peripheral benzodiazepine binding site (PBBS), that in vivo and in the absence of invading blood-borne cells is primarily expressed on activated microglia. Labeled with carbon-11, this ligand can be used to study activated human microglia in vivo by positron emission tomography. First experience using this marker in a variety of inflammatory and non-inflammatory diseases, such as Rasmussen's encephalitis, herpes encephalitis. Parkinson's and Alzheimer's disease shows that microglial activation is found locally (around focal lesions) but also along large neural tract systems. This activation pattern of the brain's intrinsic immune effector cells (i.e. microglia) along functional and anatomical neural networks is the basis of the emerging concept of 'neuroinflammation' in primarily non-inflammatory, neurodegenerative diseases.

Dr. Geissmann, the other Artemis Fellow, presented his work on the physiology of DC and its relationship to the pathophysiology of LCH. A key question about LCH is: Does LCH arise from monocytes or from a distinct CD1a+ bone marrow precursor? The identification of a normal or abnormal precursor cell or one that presents molecular features that may predispose to the disease would help understand LCH. He has demonstrated that, in vitro in the presence of TGFß1, found in muscosal epithelium and skin, the monocyte is a precursor of Langerhans cells. He provided evidence that TGFß1 plays a critical role in the regulation of differentiation and maturation of human Langerhans cells. No molecular defect is known to be associated with LCH, and it is not known whether LCH results from a primary defect in some Langerhans cells, or if precursor cells are affected. Also, it is not known if a multi-step model, as observed in some malignancies, may be relevant to LCH. The clinical heterogeneity of the disease, however, implies that any study has to consider the different clinical groups of patients. Hypothetically, the monocyte could be the precursor of the lesional cells in LCH. Studies are underway searching for: (1) clonality in circulating monocytes in patients with LCH, and (2) to identify a more committed precursor in the blood of patients.

Dr Vargha-Khadem presented results of a study of neuropsychological outcome in patients with LCH. An extensive series of neuropsychological tests known to be sensitive to the functions of different brain regions were administered to approximately 28 patients. Three groups of patients were distinguished: 1) those without CNS involvement, 2) those with hypothalamic/pituitary involvement only and 3) those with CNS involvement other than diabetes insipidus. Comparisons were made among these three groups and with patients with acute lymphoblastic leukaemia (ALL) who were investigated five years after finishing treatment. Some of the patients with ALL had received 18 cGy cranial irradiation, while others had received high dose methotrexate to protect against CNS relapse. Although the number of patients thus far studied is low, the findings strongly suggest that children with

LCH and CNS involvement, particularly those with multisystem disease have significant abnormalities in long term follow-up of cognitive functions. Those patients with only diabetes insipidus were not different from other patient groups, including normal controls. These studies emphasise the need for preventing involvement of the CNS in LCH.

Dr. Gur discussed several novel approaches to quantifying neurocognitive and neurobiological function in normal persons and in patients with a variety of neuropsychiatric disorders. Of particular interest was the demonstration of profound differences observed between males and females and changes observed during aging. Further, patients with CNS disorders, such as schizophrenia, show characteristic abnormalities which are consistent even when compared among different ethnic and racial groups. These studies provide a sophisticated approach to mapping neurocognitive function and abnormalities in patients and point out the critical importance of controlling for sex and age.

Dr. D'Angio affirmed that there were no conclusive data to indicate that radiation therapy played any role in LCH involvement of the CNS with the possible exception of DI when treated very soon after the onset of symptoms. He pointed out that only carefully designed studies would settle this long-standing issue. They would require careful documentation of the time of onset of symptoms, the specific MRI changes present, and definitive chemical documentation that patients indeed have DI. Radiation therapy could possibly play a role in the rare type of active, progressive LCH parenchymal involvement. It is conceivable that radiation therapy could decrease Mϕ/monocyte and lymphocyte infiltration and subsequent tissue damage that could be behind this type disease. This is because Mϕ/monocytes when activated are radio responsive; otherwise they are radio un-responsive. This type of progressive disease is so uncommon that it is almost impossible to conceive of a valid study being mounted. Only anecdotes could be expected. Last, radiation therapy would not be indicated for the type of symmetric changes associated with gliosis that are more commonly seen.

Dr. Grois reviewed the outcome of over 30 patients with a variety of types of CNS involvement with LCH. Of particular interest are patients with CNS involvement without any as yet obvious symptoms as well as those who have stable disease by MRI but continue to show progressive neuromuscular and neurocognitive deterioration. About 50% of patients with multiple system atrophy (MSA)-like disease showed progression and 4 such patients had fatal outcomes three of whom had involvement of the pons. Thus far, CNS involvement in LCH appears to be independent of treatment. DI is not usually influenced by therapeutic intervention, and that the MSA-like disease may be severe and even fatal. A protocol including a thorough diagnostic program was proposed, which includes a therapeutic trial with melatonin for patients with MSA-like disease. The rationale for the use of melatonin is based in on its anti-oxidant potential and that pineal gland involvement that has been observed in some cases of LCH.

Drs. Arceci and Austyn then summarized the symposium. This 10th Nikolas Symposium was devoted to the biology, neurocognitive assessment and clinical spectrum of LCH involvement of the CNS. The conference began with a description of the clinical spectrum of LCH involvement of the CNS, which can include extension of skull lesions into the parenchyma, leptomeningeal involvement, hypothalamic/pituitary involvement,

localized or multifocal parenchymal involvement and more diffuse and often symmetric involvement of such regions as the cerebellum, putamen and pons.

A number of talks on the biology of inflammatory responses in the brain showed that novel mechanisms of regulating CNS immune responses exist that tend to decrease primary inflammation. However, activated lymphocytes, Mϕ and DC are capable of migrating into the brain and causing tissue damage. In addition to DC causing damage to neurons, it was also shown that damaged neurons could profoundly influence the physiology of microglial cells that in turn can present antigen to T lymphocytes and further recruit other mononuclear phagocytes. Although very few brain biopsies of CNS involvement by LCH have been examined, there is little evidence that LCH involvement of the CNS is a primary neurodegenerative disease, but rather one which is more likely to be the result of neuronal damage as a secondary phenomenon of Mϕ and T-cell activation. There is no data to suggest that antineuronal antibodies are the cause of the CNS pathology although this is clearly another area that needs exploration.

A number of extremely sophisticated imaging modalities are being developed which will provide a refined linkage between form and function. The ability to image the presence of mononuclear cellular infiltrates in the brain using modified ligands for cell surface receptors offers the potential opportunity to detect early CNS pathology secondary to Mϕ activation. The further development of more precise neurocognitive methods now provides the means by which to develop more accurate descriptions of pathology.

Several areas for future work to be focussed on arose from this meeting. There remains the need for novel biologic studies to be linked to the procurement of brain biopsies. Work currently being done in neuroimaging and neurocognitive assessment should provide new standards for understanding patients with CNS involvement. They may also help to determine earlier involvement of the CNS and thereby give an opportunity for earlier intervention and even prevention. Understanding the mechanisms of macrophage and T-cell activation in relation to neuronal damage may help to refocus therapeutic interventions on targeting these cellular lineages.

R. Maarten Egeler, M.D., Ph.D., Proceedings Editor 1999.