Br. J. Cancer (1994), **70**, (Suppl. XXIII) S11-S16

Langerhans Cell Histiocytosis – Clinical and Epidemiological Aspects

Valerie Broadbent FRCP[1], R. Maarten Egeler MD, PhD[2], & Mark E. Nesbit Jr., MD[3]

[1]*Consultant Paediatric Oncologist, Paediatric Oncology Unit, Box No 181, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 2QQ, England;* [2]*Sophia Kinderziekenhuis, Molewaterplein 60, 3015 GJ Rotterdam, PO Box 70029, 3000 LL Rotterdam, The Netherlands;* [3]*Department of Pediatrics and Therapeutic Radiology, Box No 484, UMHC, University Hospital and Clinic Harvard and East River Road, Minneapolis, MN 55455, USA.*

Summary Langerhans cell histiocytosis is a disease which frustrates both clinician and scientist. Its aetiology is unknown, its pathogenesis is ill understood and the clinical course is unpredictable. Historically, the different nomenclatures reflecting the first clinical descriptions by Hand (1893, 1921), Schuller (1915) and Christian (1920), and subsequently by Letterer (1924) and Siwe (1933), led to confusion only partially resolved by Lichtenstein (1953) who recognised that the disease in each of these clinical syndromes were components of a spectrum of disease involving the histiocyte. He proposed his unifying concept of Histiocytosis X – 'X' being the unknown aetiological factor. In 1973, Nezelof recognised the lesional cell as a 'Langerhans-like' cell but it took another decade for the disease to be recognised as a single entity and the term Langerhans cell histiocytosis to be internationally accepted. The publication, by the Histiocyte Society (1987), of their classification of the histiocyte disorders together with criteria for pathological diagnosis and clinical evaluation of Langerhans cell histiocytosis have consolidated the position. This article details the wide variety of clinical manifestations of the disease and its sequelae and discusses possible epidemiological factors. Finally it looks at the potential implications of recent scientific research on the management of the disease.

Historical background

In 1865 Paul Langerhans Jr. first studied medicine in Jena, Germany, and subsequently at the University of Berlin, where he became a pupil of Cohnheim and Virchow. It was here, at the age of 20, that Dr Paul Langerhans Jr. made his first contribution to medicine when, using Cohnheim's gold chloride staining technique, he described a novel non-pigmented dendritic cell in the epidermis. This work resulted in a paper entitled: "Ueber die Nerven der menschlichen Haut" (On the Nerves of the Human Skin) (Langerhans, 1868). He initially regarded these cells as intra-epidermal receptors for extracutaneous signals of the nervous system, but corrected this interpretation in 1882[1]. In a short communication, he acknowledged his erroneous assumption: "However I am now convinced ... that my cells are in no way essential for nerve endings" (Langerhans, 1882). Today we know that these cells are derived from precursors of the monocyte/macrophage lineage in the bone marrow. They represent the most peripheral 'outpost' of our immune system, playing a role in delayed hypersensitivity (Silberg, 1973). These unique histiocytes are now eponymously referred to as Langerhans cells (Nézelof *et al.*, 1973) and the disease characterised by proliferation of these cells is known as Langerhans[2] cell histiocytosis (LCH).

At the same time as Dr Langerhans' discovery, in 1865, Thomas Smith (Smith, 1865) published a case of a boy four and half years of age with 3 large holes in the skull. These deficiencies were thought to be congenital, but the published appearances of the skull lesions suggest LCH. The definitive history of LCH started exactly 101 years ago. In 1893 Alfred Hand (Hand, 1893) published a case of a 3 year old boy with thirst, polyuria, exophthalmos and hepatosplenomegaly. Despite therapy the patient died and at autopsy a soft and mobile spot, thought to be tuberculosis, was noted near the right parietal eminence, on the inside of the skull. After publications of similar cases by Arthur Schüller (Schüller, 1915) and Henry Christian (Christian, 1920), Hand (Hand, 1921) began to doubt the diagnosis of tuberculosis in his patient. In his publication "Defects of membranous bones, exophthalmos and polyuria in childhood: is it dyspituitarism?" he reviewed the cases and suggested that the primary process might be either benign or neoplastic, producing exophthalmos and polyuria by pressure. For a long time patients with (a) defects of membranous bones, (b) exophthalmos, and (c) polyuria were diagnosed as having 'Hand-Schüller-Christian disease'.

Subsequently a similar but generalised disease entity was described by Letterer (Letterer, 1924) and, 9 years later, reviewed by Siwe (Siwe, 1933). Subsequently, the name 'Letterer-Siwe disease' was used to identify this acute fulminant non-leukaemic disorder of the reticuloendothelial system with prominent splenomegaly, hepatomegaly, lymphadenopathy, localised tumours in the bones, haemorrhagic tendency with purpuric skin eruptions and secondary anaemia. In 1940, 2 articles dealing with a similar eosinophilic lesion, as first described in the 19th century by Thomas Smith (Smith, 1865), were published in the American Journal of Pathology (Otani & Ehrlich, 1940; Lichtenstein & Jaffe, 1940). In spite of the bone destruction and the microscopic appearance characterised by the presence of compacted tumour-like aggregates of large phagocytic cells, with conspicuous collections of eosinophilic leucocytes interspersed, they thought that the process was benign and named it 'solitary granuloma' or 'eosinophilic granuloma'. Subsequently, it became clear that some patients with the same histopathological pattern had multiple bone lesions (Green & Farber, 1942). In 1953 Lichtenstein, in a classic paper, (Lichtenstein, 1953) introduced the unifying concept of "Histiocytosis X". He intended the 'unification' to be primarily pathological and referred to acute/disseminated, chronic disseminated, and localised Histiocytosis X. The recognised types of clinical involvement could still be differentiated from one another so that useful distinctions, with a bearing on treatment and progress, were maintained. The year 1973 saw another milestone in the understanding of 'Histiocytosis X'. Nezelof *et al.* (Nezelof *et al.*, 1973) suggested that these processes were the result of the proliferation and dissemination of pathological histiocytic cells, identified as Langerhans- like cells. Subsequently, the term 'Langerhans cell histiocytosis' was suggested as an alternative to 'Histiocytosis X'.

As well as their firmly established classification of the

[1]It is interesting to note that Hosoi *et al.* (Nature, 1993) recently demonstrated nerve endings abutting epidermal dentritic cells! (Eds)

[2]and/or accumulation (Eds).

Correspondence: Dr V.A. Broadbent, Consultant Paediatric Oncologist, Paediatric Oncology Unit, Box No 181, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 2QQ, England.

'Histiocytosis Syndromes' in children, (Pritchard and Broadbent, this volume), the Histiocyte Society have also established 'confidence levels' for the diagnosis of LCH (Writing Group of the Histiocyte Society, 1987). "Presumptive diagnosis" is permitted when examination of conventionally- processed tissue reveals lesions consistent with those defined in the literature. A higher level of diagnostic confidence, referred to as "diagnosis", is justified when these findings are supplemented by the presence of at least two of the following positive stains: S-100 protein, ATP-ase, α-D-mannosidase or peanut lectin binding. "Definitive diagnosis" requires the demonstration either of Birbeck granules in lesional cells by electron microscopy, or of CD1a (T6) antigenetic determinants on the surface of lesional cells. In 1989, the Clinical Writing Group of the Histiocyte Society suggested a standardized approach to the initial evaluation of children with LCH (Clinical Writing Group of the Histiocyte Society, 1989). Aside from the self-evident benefits of accurate communication between physicians and comparison of results obtained by different treatment centres, the main purpose was to facilitate large- scale cooperative international studies of the natural evolution of LCH and its response to treatment. Details of the first co-operative study, known as 'LCH1', are provided by Ladisch and Gadner (this volume).

Incidence and epidemiology

LCH can present at any period ranging from birth to old age with a peak between 1–3 years. The incidence in the paediatric range has been estimated at 3–4 per million with males affected twice as commonly as females. The disease incidence in the adult population is harder to define since the wide clinical spectrum leads it to present to a variety of different organ specialists and notification is not obligatory. The disease is most probably underdiagnosed because bone lesions are often symptomless, while painful swellings (on the head, in children, for example) can be mistaken for trauma while mild skin and scalp disease may be misdiagnosed as seborrhoeic eczema. There is no evidence for a racial difference in incidence, but the pattern of the disease may vary. For instance, lung disease seems to be relatively common in China (Hu, personal communication Nikolas Symposium, 1991). Forty of the 50 deaths in 277 patients diagnosed at the Beijing Children's Hospital between 1955 and 1990 were from respiratory failure. The disease has been reported in twins but is essentially sporadic.

Very limited data are available regarding the epidemiology of LCH, largely because of its relatively low incidence. In order to examine the incidence, time trends, geographical distribution, risk factors and outcome in Denmark from 1975 to 1989, Carstensen and Ornvold performed an extensive epidemiologic study (Carstensen and Ornvold, 1993). Of a total population of 5.1 million people, 1 million children under the age of 15 years old were at risk. Ninety children (62 M, 28 F) with a median age of 2.4 years had a confirmed diagnosis of LCH, giving an incidence rate of 1.08 per 200,000 children a year. Thirty-three patients (37%) had multisystem disease and 14 (36%) of these had 'organ dysfunction'. Of the 9 children (10% of the total) who died of the disease, 8 had 'organ dysfunction'. None of the remaining 57 patients with single-system LCH died of disease but permanent 'sequelae' were common. Some pre-natal and post-natal risk factors – delivery route, birth complications, low birth weight, ABO and Rh blood type – were considered, but generating a hypothesis on aetiology in this large population-based study was not possible.

Despite the difficulties inherent in such studies, especially the lack of a specific hypothesis, prospective epidemiologic investigations of LCH seem worthwhile. Members of the University of Minnesota Pediatric Oncology and Epidemiology Division recently initiated such an investigation. Parent members of the Histiocytosis Association of America and Canada have been sent a questionnaire designed to collect information relating to sociodemographics, family medical history, exposures and other events during pregnancy, birth details, health and development of the patient and their home environment. This information will be compared to the responses of 4500 parents of children with cancer and 850 parents of children who have neither LCH nor cancer. It is anticipated that the survey will provide sufficient information to form the basis of a testable hypothesis relating to the aetiology of LCH in children and possibly provide a lead to genetic and environmental risk factors.

Clinical manifestations

General features

LCH has a wide clinical spectrum and prognosis varies accordingly. In older children 'single system' disease, usually affecting bone, is a common presentation and may spontaneously regress or require minimal treatment. In the current international LCH trial, 122 of 225 registered patients have single system disease and in all of these the disease is confined to bone (Gadner H, personal communication, 1993). LCH confined to skin or to lymph nodes has, however, also been reported. In very young babies, the commonest presentation is with multisystem disease, sometimes with 'organ failure' and profound constitutional upset including fever and failure to thrive. Mortality in this sub-group of patients is still relatively high (Starling, 1987). Between these extremes there is a large group of patients with multisystem disease without 'organ failure' who require systemic treatment whilst their disease runs a fluctuating course and eventually 'burns itself out', with or without sequelae. In adults, liver and spleen involvement is less common but there is a higher incidence of lung involvement, possibly associated with smoking (Friedman *et al.*, 1981).

Organ involvement

Almost every organ in the body can be involved though as yet there are no reports of renal, bladder, gonad or adrenal involvement. The following list of organs is in descending order of frequency of detection.

Bone

Painful swelling is the most common presenting feature. The skull is most commonly affected (Figure 1) followed by the long bones, flat bones and vertebrae. The bones of the hands

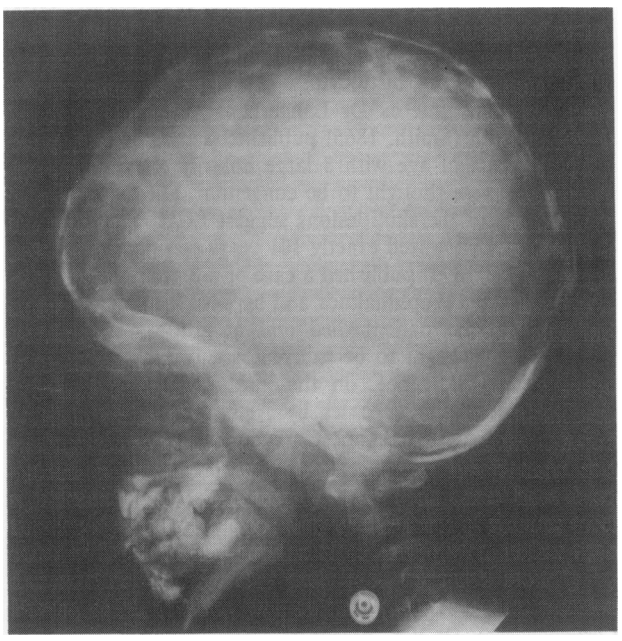

Figure 1 Osteolytic skull lesions in a child with LCH presenting with chronically discharging ears.

and feet are rarely involved. There may be adjacent soft tissue swelling and ulceration of the overlying skin or mucous membrane. Periorbital disease usually presents as proptosis but optic nerve compression is rare. Spinal cord compression is also a rare complication of vertebral involvement. Pathological fracture through a lesion may occur in the weight-bearing long bones and, paradoxically, may accelerate healing of the lesion. Skeletal x-rays are superior to radioisotope bone scan for the detection of lesions (Chrone-Munzebrock & Brassow, 1983) which usually appear as well defined osteolytic areas with a surrounding 'halo' of sclerosis if the defect has started to heal. Periosteal reaction may be excessive and mimic malignancy (Figure 2).

Skin

Skin rash is particularly common in infants and can be difficult to distinguish from seborrhoeic eczema. It affects the inguinal region (Figure 3 (*see colour section*)) and the perineum, the axillary folds and the necklace and lumbo-sacral areas. Lesions may be more discrete in the form of raised pinkish brown papules scattered over the trunk and may heal with depigmentation. Often the scalp rash resembles cradle cap. A particular form of the disease (Hashimoto & Pritzker, 1973) may be seen in neonates and only affects the skin. Clinically, it resembles healing chickenpox with raised purplish lesions scattered over the trunk, face, palms and soles which heal spontaneously within 6 months.

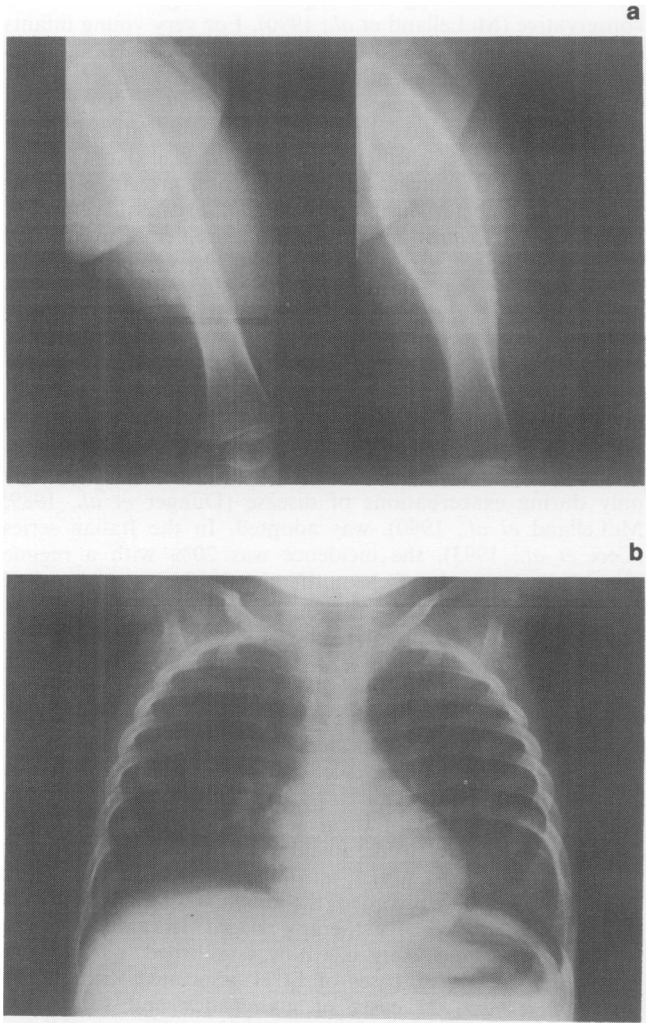

Figure 2 X-ray appearance of an LCH lesion in the femur in a baby who presented with a painful swollen thigh (**a**) aged 6 months and (**b**) aged 7 months. The extensive periosteal reaction mimics malignancy, especially Ewings sarcoma/PNET. Chest X-ray 2 years later (**c**) shows an osteolytic lesion in the L 9th rib.

Lymph nodes and thymus

Cervical lymph nodes are most commonly affected and may reach a massive size but other node groups, including mediastinal and abdominal glands can be affected. Involvement of Waldeyer's ring can cause upper airways obstruction. Superior vena cava obstruction from mediastinal glands has been reported (Mogul *et al.*, 1993). In older children and adults a particularly intractable problem may arise when a lymph node discharges through the skin with chronic sinus formation (Sacks *et al.*, 1986). Thymic enlargement may be obvious on chest x-ray and was the only site of disease in 2 of 4 cases described by Siegal *et al.* (Siegal *et al.*, 1985). However, even when the thymus is not radiologically enlarged morphological changes may be seen on biopsy, as in 5/7 cases reported by Osband *et al.* (Osband *et al.*, 1981).

Ears

Aural discharge, either from extension of skin rash into the aural canal causing otitis externa, or from polyps of histiocytic tissue extending into the canal from a bony lesion is a common presenting feature as in 31/131 patients reviewed by Irving *et al.* (Irving *et al.*, 1993). It is of utmost importance to distinguish between the two, but often impossible without examination under anaesthesia and careful aural toilet. Obstinate otitis externa may require topical treatment with mustine (Sheehan *et al.*, 1991), whereas polyps can be removed by curettage followed by intralesional steroid injected into the underlying bony lesion (Egeler *et al.*, 1992). The mastoid bones may be involved, mimicking mastoiditis, and persistent middle ear disease can cause deafness from ossicle damage.

Bone marrow and peripheral blood

Mild 'anaemia of chronic disease' is a common finding. It may have a dietary component as poor appetite is a common symptom. Occult gut disease may also contribute. Reversal of the CD4-CD8 ratio is present in 70% of patients (Osband *et al.*, 1981) and may mirror the disease process, reverting to normal as disease regresses (Davies *et al.*, 1983).

Pancytopenia due to bone marrow 'dysfunction'[3] may occur, particularly in young infants, and is usually associated with gross hepatosplenomegaly and a poor prognosis (McClain *et al.*, 1983). Bone marrow aspirate shows infiltration with either hemophagocytic macrophages or 'LCH cells', or both.

Liver and spleen

Hepatosplenomegaly is common. Ascites and oedema due to hypoalbuminaemia and bleeding due to coagulopathy (prolonged prothrombin time and/or partial thromboplastin time) may indicate 'liver failure'. Histologically there is periportal infiltration with 'LCH cells' which are CD1 positive but rarely contain Birbeck granules (see Favara and Jaffe this issue). Obstructive jaundice is rare and is associated with a histological picture resembling sclerosing cholangitis (Leblanc *et al.*, 1981). Very rarely is it caused by infiltration of the gall bladder. A solitary nodule of LCH within the liver parenchyma or porta hepatica may mimic a tumour or abscess.

Gross splenomegaly is usually part of multisystem disease in very young children and is often associated with pancytopenia (see above).

[3]The term 'Bone marrow dysfunction', though widely used, may be a misnomer. Many chidren with LCH and pancytopenia have a cellular bone marrow, suggesting active peripheral 'consumption' of blood cells, rather than failure of production. Late in the disease, however, the bone marrow may become severely hypoplastic; (Eds)

Lung

Pulmonary LCH can occur in isolation, especially in adults, but is usually part of multisystem disease. In children, tachypnoea with subcostal recession is often the only clinical sign but the disease may be detected incidentally when a chest x-ray shows fine interstitial shadowing due to micronodular granulations. On CT scanning, the nodules may appear cystic. Respiratory function tests may show small stiff lungs with decreased total lung volume and compliance (Marcy & Reynolds, 1985; Ha *et al.*, 1992).

Confirmation of diagnosis rests with finding 'LCH cells' on biopsy or in bronchial washings. In adults and older children pneumothorax, resulting from rupture of an underlying bulla, is quite common. Bullae are the result of cavitation within the fibrotic micronodules, with coalescence to form larger cavities which appear as 'honeycombing' on chest x-ray. 'Pulmonary failure' is generally regarded as an unfavourable prognostic feature and severe lung disease may certainly be life-threatening. However Ha *et al.* (1992), studying a series of 45 consecutively diagnosed children with multisystem LCH, from a single institution, found no excess of deaths in the group of 18 children with radiological and/or laboratory evidence of lung involvement, compared to the 27 with no evidence of lung involvement. Prospective studies are needed but lung involvement *per se* does not necessarily indicate an unfavourable prognosis.

Endocrine system

Diabetes insipidus is the commonest endocrinopathy and may pre-date the diagnosis of LCH. Confirmation by appropriate water deprivation testing and, if available, measurement of urinary arginine vasopressin (AVP) levels is essential as partial defects occur and may spontaneously remit (Dunger *et al.*, 1989). Gadolinium-enhanced magnetic resonance imaging (MRI) is the imaging investigation of choice. Thickening of the pituitary stalk and loss of the posterior pituitary "bright" signal in T2-weighted images are seen[4].

Anterior pituitary function may be compromised in up to 50% of patients with diabetes insipidus, with growth hormone most commonly affected (Broadbent *et al.*, 1993). However, growth failure in children with LCH may be multifactorial (Braunstein & Kohler, 1981; Dean *et al.*, 1986). Persistent cytokine production due to chronic disease, occult gut involvement causing malabsorption, vertebral collapse, growth hormone deficiency and cortico-steroid treatment may each contribute. Panhypopituitarism may occur. In these cases, MRI usually shows a hypothalamic mass.

Involvement of the thyroid (Lahey *et al.*, 1986) and pancreas (Yu *et al.*, 1993) have been reported but have not caused endocrine dysfunction. Gonadal and adrenal involvement have not yet been reported.

Gastrointestinal tract

Oral involvement with ulceration of palatal or gingival mucoae, usually without an adjacent bony lesion in the maxilla or mandible, is common. The palatal ridges, especially those adjacent to the upper molars, are often broadened and the overlying mucosa has a granular appearance when there is infiltration with disease. Premature eruption of 'floating' milk teeth is characteristic of LCH.

Failure to thrive may be caused by malabsorption due to involvement of the gastrointestinal tract which is difficult to prove unless jejunal biopsy includes the muscle coat. Of the patients with biopsy-proven LCH reported by Keeling and Harries (Keeling & Harries, 1973), around half had a history of loose frequent stools, and in most patients there was infiltration of the mucosa or submucosa by Langerhans cells. In those who presented without diarrhoea, the serosa or muscle coat was involved. Recent data (Kelly K., Malone M. & Pritchard J, unpublished observations) suggest that colonic involvement may be commoner than previously suspected.

[4]The loss of "bright signal" is not 'disease-specific'. The same appearance can be observed in patients with idiopathic diabetes insipidus. Eds.

Differential diagnosis

Difficulty in diagnosing LCH is more often a result of a failure to consider the diagnosis, rather than a failure in distinguishing it from other diseases. Radiologically, bony lesions – particularly if solitary – may mimic a malignant tumour. Cervical lymphadenopathy, particularly when massive, must be differentiated histologically from 'sinus histiocytosis with massive lymphadenopathy' (Rosai Dorfman disease). Distinction from familial or sporadic hemophagocytic lymphohistiocytosis (HLH) is usually quite easy. The clinical picture is usually very different. For instance, skin rash and bony disease are hardly ever seen in HLH, but CNS involvement is relatively common. Laboratory confirmation of HLH is via raised serum triglycerides, decreased plasma fibrinogen, cerebrospinal fluid pleocytosis and abundant hemophagocytosis in the bone marrow. Malignant histiocytosis is extremely rare in children, and can be distinguished from LCH both histologically and immunohistochemically.

Sequelae

The outlook for patients with single system disease is excellent with minimal long term sequelae so long as treatment is conservative (McLelland *et al.*, 1990). For very young infants with 'bone marrow failure' and/or liver dysfunction, mortality is 30–50%, regardless of treatment (Gadner *et al.*, 1987; McLelland *et al.*, 1990; Ceci *et al.*, 1993). Most patients, however, have multisystem disease without organ dysfunction and 50% suffer long term sequelae (Komp *et al.*, 1980; Sims, 1977) including small stature, growth hormone deficiency, diabetes insipidus, partial deafness, cerebellar ataxia, loss of dentition, orthopaedic problems, pulmonary fibrosis and biliary cirrhosis with portal hypertension. There is no evidence that prolonged treatment prevents sequelae, with the possible exception of diabetes insipidus. Diabetes insipidus affected only 4% of children in the DAL-HX series (Gadner *et al.*, 1987) of trials, in which 'maintenance' chemotherapy was continued for 2 years. By contrast, diabetes insipidus occurred in 36% of children attending a single UK institution at which a conservative treatment approach, using intermittent short courses of steroid therapy only during exacerbations of disease (Dunger *et al.*, 1989; McLelland *et al.*, 1990), was adopted. In the Italian series (Ceci *et al.*, 1993), the incidence was 20% with a regime using a 28 day cycle of chemotherapy for 9 courses (total of 36 weeks).

A 5% incidence of malignancy in long term survivors was reported by Greenberger *et al.* (Greenberger *et al.*, 1981). However, the association between LCH and a variety of malignancies is now recognised (Egeler *et al.*, 1993) at a frequency higher than expected by chance alone. Currently there are 91 reported cases of LCH and a malignant neoplasm in the same individual. In 22 cases the malignancy was leukaemia, 16 (73%) of them acute non-lymphoblastic leukaemia (ANLL). In children with 'sporadic' acute leukaemia, the ratio of ALL to ANLL is 3–4%. In 64% (14 cases) the diagnosis of LCH preceded the diagnosis of leukaemia, a sequence suggestive of a therapy-related process.

The Histiocyte Society has now established a registry to collect, prospectively, cases of LCH associated with cancer. In its first year, 27 cases of malignancy and LCH were reported in the same individual (Egeler *et al.*, unpublished data). In 13, the associated malignancy was either acute lymphoblastic leukaemia (ALL) (5 cases) or ANLL (8 cases). Two distinct patterns of association are already evident -ALL preceding LCH, and LCH preceding ANLL. The sequence

ALL→LCH (4/5 cases) suggests that LCH may be a 'secondary' process, as all of these children were undergoing ALL therapy at the time of the diagnosis of LCH. It is plausible that the immunosuppression associated with the ALL therapy in some way played a role in the development of these cases of LCH. Conversely, in 7 of 8 cases with an LCH→ANLL sequence, the LCH had been treated with chemotherapy alone (4 cases), radiation alone (1 case) or both modalities (2 cases). In these 7 cases the temporal sequence and the time interval between the 2 diagnoses suggested that the ANLL might have arisen as a consequence ('secondary' leukaemia) of the LCH treatment.

Patients with disseminated LCH, especially those with organ 'dysfunction' at the time of diagnosis, have only a 45–50% probability of 5 year survival (Komp, 1987), Although complications of some of the more hazardous types of therapies are now well known, the safest and most effective treatment for LCH has not yet been established. The risk:benefit ratio of using chemotherapy and/or radiotherapy, and the manner of their use, need to be weighed carefully. Patients should not be denied chemotherapy for fear of therapy-related second malignancies when the LCH itself, without effective treatment, poses a greater risk.

Future considerations

The "de-cancerisation" of LCH in the 1980's led to a loss of interest in the disease by several national groups involved in the study of paediatric cancer. As a result, registration of patients and funding of treatment trials became difficult. The Histiocyte Society, the Histiocytosis Association of America and other parent groups and the Nikolas Symposia emerged to fill this need. The Histiocyte Society's classification of the Histiocytoses set standards for clinical and laboratory evaluation of patients and in 1991 the first international randomised treatment trial (LCH-1) was launched (Ladisch and Gadner, this volume). All the patients in LCH-1 are diagnosed and evaluated according to the Histiocyte Society's published criteria (Clinical Writing Group of the Histiocyte Society, 1989).

A continuing dialogue between physicians who treat patients with LCH, worldwide, is essential for further treatment advances but imaginative investigative research is also essential to progress. The 'LCH cell' seems to be the 'key-player' in LCH. The normal Langerhans cell constitutes only approximately 2% of all epidermal cells, but its antigen-presenting properties mean that it plays a critical role in cutaneous immunological reactions (Stingl *et al.*, 1980). Langerhans cells interact with neighbouring keratinocytes, recirculating T lymphocytes and peripheral lymph nodes, to form an integrated system of skin-associated lymphoid tissue (SALT), which acts as the most peripheral outpost of the immune system and mediates cutaneous immunosurveillance (Streilein, 1983). Whilst some of the enigmas surrounding the Langerhans cells have been clarified, many other questions relating to the biology of the cell are unanswered. Further studies on the basic biology of the Langerhans cell are of the utmost importance.

The role of cytokines in regulating action of lymphocytes, histiocytes and Langerhans cells is now better understood (Luger, 1989). Many of the systemic and local signs and symptoms of LCH may be the result of the effect of one or more of the cytokines (Arenzana-Seisdedos *et al.*, 1986; Barbey *et al.*, 1987; Favara, 1991). Combining the known immunologic aberrations found in LCH (Nesbit *et al.*, 1981; Osband *et al.*, 1981), the disease may be the result of an exaggerated action or loss of control of action of cytokines. Recent reports by Caux *et al.* (Caux *et al.*, 1992) indicate that various growth factors co-operate in the generation of Langerhans cells. Granulocyte-macrophage colony stimulating factor (GM-CSF) and Tumour Necrosis Factor-α (TNFα) appear to increase production of Langerhans cells from CD34+ haematopoietic precursor cells. In addition, *in situ* analysis of cytokine mRNA expression can be studied in lesions from patients with LCH using newly-developed techniques, such as the polymerase chain reaction (PCR) combined with cell surface immunohistochemistry. With these methods it may be possible to start unravelling the complexities of faulty 'inter-cellular communication' occurring in LCH.

Recent evidence suggests that, in some cases at least, LCH is a clonal disorder, rather than a reactive disease (Willman *et al.*, 1993 and this volume). Assessment of clonality in non-lymphoid lineages is now possible with the recent development of molecular technologies. Restriction fragment length polymorphisms in X-linked DNA probes in lesional biopsies from female patients can nowadays be assessed in all cell lineages. Experiments with specific combinations of restriction enzymes on LCH- tissue of female patients have revealed evidence of clonality (see Willman this issue). These findings must be verified in larger series of patients. Subsequently, appropriate trials must be designed to determine whether "clonality" is an important prognostic factor, with therapeutic implications.

A continued dialogue between clinicians and scientists is essential to solve remaining questions as to the basic pathophysiology of LCH. The Nikolas Symposia provide a unique setting whereby scientists are exposed to the clinical facets of the disease and clinicians are exposed to the 'cutting edge' of science.

References

ARENZANA-SEISDEDOS, F., BARBEY, S., VIRELIZIER, J.L., KORN-PROBST, M. & NEZELOF, C. (1986). Histiocytosis X purified (T6–) cells from bone granuloma produce interleukin 1 and prostaglandin E2 in culture. *J. Clin. Invest.*, **77**, 326–329.

BARBEY, S., GANE, P., LE PELLETIER, O. & NEZELOF, C. (1987). Histiocytosis X Langerhans cells react with antiinterleukin-2 receptor monoclonal antibody. *Pediatr. Pathol.*, **7**, 569–574.

BRAUNSTEIN, G.D. & KOHLER, P.O. (1981). Endocrine manifestations of histiocytosis. *Am. J .Pediatr. Hematol. Oncol.*, **3**, 67–75.

BROADBENT, V.A. & PRITCHARD, J. (1985). Histiocytosis X: current controversies. *Arch. Dis. Child*, **60**, 605–607.

BROADBENT, V., DUNGER, D.B., YEOMANS, E. & KENDALL, B. (1993). Anterior pituitary function and CT/MR imaging in patients with Langerhans cell histiocytosis and diabetes insipidus. *Med. Pediatr. Oncol.*, **21**, 31–35.

CARSTENSEN, H. & ORNVOLD, K. (1993). The epidemiology of Langerhans cell histiocytosis in children in Denmark, 1975-1989. *Med. Pediatr. Oncol.*, **21**, 387–388.

CAUX, C., DEZUTTER-DAMBUYANT, C., SCHMITT, D. & BANCHEREAU, J. (1992). GM- CSF and TNF-α co-operate in the generation of dendritic Langerhans cells. *Nature*, **360**, 258–261.

CECI, A., DE TERLIZZI, M., COLELLA, R., LOIACONO, G., BALDUCCI, D., SURICO, G., CASTELLO, M., MARIA TESTI, M., DE BERNARDI, B., INDOLFI, P., MACCHIA, P., MADON, E., MANCINI, A. & ROSATI, D. (1993). Langerhans cell histiocytosis in childhood: results from the Italian Co-operative AIEOP-CNR-H.X '83 Study. *Med. Pediatr. Oncol.*, **21**, 259–264.

CHRISTIAN, H.A. (1920). Defects in membranous bones, exophthalmos and diabetes insipidus; an unusual syndrome of dyspituitarism: a clinical study. *Med. Clin. N. Amer.*, **3**, 849–871.

CLINICAL WRITING GROUP OF THE HISTIOCYTE SOCIETY (BROADBENT, V., GADNER, H., KOMP, D.M. & LADISCH, S.). (1989). Histiocytosis syndromes in children: II. Approach to the clinical and laboratory evaluation of children with Langerhans cell histiocytosis. *Med. Pediatr. Oncol.*, **17**, 492–495.

CRONE-MUNZEBROCK, W. & BRASSOW, F. (1983). A comparison of radiographic and bone scan findings in histiocytosis X. *Skeletal Radiol.*, **9(3)**, 170–173.

DAVIES, E.G., LEVINSKY, R.J., BUTLER, M., BROADBENT, V.A., PRITCHARD, J. & CHESSELLS, J.M. (1983). Thymic hormonal therapy in histiocytosis X (letter). *N. Engl. J. Med.*, **309**, 493–494.

DEAN, H.J., BISHOP, A. & WINTER, J.S.D. (1986). Growth hormone deficiency in patients with histiocytosis X. *J. Pediatr.*, **109**, 615–618.

DUNGER, D.B., BROADBENT, V., YEOMAN, E., SECKL, J.R., LIGHTMAN, S.L., GRANT, D.B. & PRITCHARD, J. (1989). The frequency and natural history of diabetes insipidus in children with Langerhans-cell histiocytosis. *N. Eng. J. Med.*, **321**, 1157–1162.

EGELER, R.M., NEGLIA, J.P., ARIC, M., FAVARA, B.E., HEITGER, A. & NESBIT, M.E. (1994). Acute leukemia in association with Langerhans cell histiocytosis. A Report of the Langerhans Cell Histiocytosis-Malignancy Study Group. *Med. Pediatr. Oncol.*, In press.

EGELER, R.M., NEGLIA, J., PUCCETTI, D.M., BRENNAN, C. & NESBIT, M.E. (1993). The association of Langerhans cell histiocytosis with malignant neoplasms. *Cancer*, **71**, 865–873.

EGELER, R.M., THOMPSON, R.C. Jr., VOTE, P.A. & NESBIT, M.E. Jr. (1992). Intralesional infiltration of corticosteroids in localized Langerhans cell histiocytosis. *J. Pediatr. Orthop.*, **12**, 811–814.

FAVARA, B.E. (1991). Langerhans' cell histiocytosis; pathobiology and pathogenesis. *Semin. Oncol.*, **18**, 3–7.

FRIEDMAN, P.J., LIEBOW, A.A. & SOKOLOF, J. (1981). Eosinophilic granuloma of lung. *Medicine*, **60**, 385–396.

GADNER, H., HEITGER, A., RITTER, J., GÖBEL, U., JANKA, G.E., KUHL, J., BODE, U., & SPAAR, H.J. (für die Mitglieder der DAL-HX-Studie). (1987). Langerhanszell-Histiozytose im Kindersalter -Ergebnisse der DAL-HX 83 Studie. *Klin. Pädiat.*, **199**, 173–182.

GADNER, H. (1993). Personal Communication.

GREEN, W.T. & FARBER, S. (1942) "Eosinophilic or Solitary Granuloma" of bone. *J. Bone. Joint. Surg.*, **24**, 499–526.

GREENBERGER, J.S., CROCKER, A.C., VAWTER, G., JAFFE, N, & CASSADY, J.R. (1981). Results of treatment of 127 patients with systemic histiocytosis (Letterer-Siwe syndrome, Schüller-Christian syndrome and multifocal Eosinophilic Granuloma). *Medicine*, **60**, 311–338.

HA, S.Y., HELMS, P., FLETCHER, M., BROADBENT, V. & PRITCHARD, J. (1992). Lung involvement in Langerhans' cell histiocytosis. Prevalance, clinical features, and outcome. *Pediatr.*, **89**, 466–469.

HAND, A. (1893). Polyuria and tuberculosis. *Arch. Pediatr.*, **10**, 673–675.

HAND, A. (1921). Defects of membranous bones, exophthalmos and polyuria in childhood: is it dyspituitarism? *Am. J. Med. Science*, **162**, 509–515.

HASHIMOTO, K. & PRITZKER, M.S. (1973). Electron microscopic study of reticulohistiocytoma – an unusual case of congenital, self-healing reticulohistiocytosis. *Arch. Dermatol.*, **107**, 283–289.

HOSOI, J., MURPHY, G.F., EGAN, C.L., LERNER, E.A., GRABBE, S., ASAMINA, A. & GRANSTEIN, R.D. (1993). Regulation of Langerhans cell function by nerves containing calcitonin gene-related peptide. *Nature*, **363**, 159–163.

HU, Y.M. (1991). Personal Communication.

IRVING, R.M., BROADBENT, V. & JONES, N.S. (1994). Langerhans cell histiocytosis in childhood: management of head and neck manifestations. *Laryngoscope*, **104**, 64–70.

KEELING, J.W. & HARRIES, J.T. (1973). Intestinal malabsorption in infants with histiocytosis X. *Arch. Dis. Child.*, **48**, 350–354.

KOMP, D.M. (1987). Langerhans cell histiocytosis [Editorial]. *New. Eng. J. Med.*, **316**, 747–748.

KOMP, D.M., EL MAHDI, A., STARLING, K.A., EASLEY, J., VIETTI, T.J., BERRY, D.H. & GEORGE, S.L. (1980). Quality of survival in Histiocytosis X. A Southwest Oncology Group Study. *Med. Pediatr. Oncol.*, **8**, 35–40.

LAHEY, M.E., RALLISON, M.L., HILDING, D.A. & ATER, J. (1986). Involvement of the thyroid in histiocytosis X. *Am. J. Pediatr. Hematol. Oncol.*, **8**, 257–259.

LANGERHANS, P. (1868). Über die Nerven der menschlichen Haut. *Arch. Pathol. Anat.*, **44**, 325–337.

LANGERHANS, P. (1882). Berichtingungen (u.a. zu den Nerveneden der Haut, und Nervenfasern im Rete). *Arch. Mikrosk Anat.*, **20**, 641–643.

LEBLANC, A., HADCHOUEL, M., JEHAN, P., ODIEVRE, M. & ALAGILLE, D. (1981). Obstructive jaundice in children with histiocytosis X. *Gastroenterol.*, **80**, 134–139.

LETTERER, E. (1924). Aleukamische retikulose (ein Beitrag zu den proliferativen Erkrankungen des Retikuloendothelisalapparates). *Frankf. Zeit. Pathol.*, **30**, 377–394.

LICHTENSTEIN, L. (1953). Histiocytosis X. Integration of Eosinophilic Granuloma of bone, "Letterer-Siwe Disease", and "Schuller-Christian Disease" as related manifestations of a single nosologic entity. *A. M. A. Arch. Pathol.*, **56**, 84–102.

LICHTENSTEIN, L. & JAFFE, H.L. (1940). Eosinophilic Granuloma of Bone. *Am. J. Pathol.*, **16**, 595–604.

LUGER, T.A. (1989). Epidermal cytokines. *Acta. Derm. Venereol (Stoch)*, **69**, 61–76.

MARCY, T.W. & REYNOLDS, H.Y. (1985). Pulmonary histiocytosis. *Lung*, **163**, 129–131.

MCCLAIN, K., RAMSAY, N.K.C., ROBISON, L., SUNDBERG, R.D. & NESBIT, M.E. (1983). Bone marrow involvement in Histiocytosis X. *Med. Pediatr. Oncol.*, **11**, 167–171.

MCCLELLAND, J., BROADBENT V., YEOMANS, E., MALONE, M. & PRITCHARD, J. (1990). Langerhans cell histiocytosis: the case for conservative treatment. *Arch. Dis. Child.*, **65**, 301–303.

MCCLELLAND, J., PRITCHARD, J. & CHU, A. (1987). Histiocytosis X -current controversies. In: *Hematology/Oncology Clinics of North America*, Osband, M.E., Pochedly, C. (eds) pp. 147-162. W.B. Saunders.

MOGUL, M., HARTMAN, G., DONALDSON, S., GELB, A., LINK, M., AMYLON, M. & GLADER, B. (1993). Langerhans' cell histiocytosis presenting with the superior vena cava syndrome: a case report. *Med. Pediatr. Oncol.*, **21**, 456–459.

NEZELOF, C., BASSET, F. & ROUSSEAU, M.F. (1973). Histiocytosis X: Histogenic arguments for a Langerhans' cell origin. *Biomedicine*, **18**, 365–371.

NESBIT, M., O'LEARY, M., DEHNER, L.P. & RAMSEY, N.K.C. (1981). Histiocytosis. The immune system and the histiocytosis syndromes. *Am. J. Pediatr. Hemat. Oncol.*, **3**, 141–149.

OSBAND, M.E., LIPTON, J.M., LAVIN, P., LEVEY, R., VAWTER, G., GREENBERGER, J.S., MCCAFFREY, R.P. & PARKMAN, R. (1981). Histiocytosis X -Demonstration of abnormal immunity, T-cell histamine H2-receptor deficiency, and successful treatment with thymic extract. *N. Engl. J. Med.*, **304**, 146–153.

OTANI, S. & EHRLICH, J.C. (1940). Solitary granuloma of bone, simulating primary neoplasm. *Am. J. Pathol.*, **16**, 479–490.

RISDALL, R.J., DEHNER, L.P., DURAY, P., KOBINSKY, N., ROBISON, L. & NESBIT, M.E. (1983). Histiocytosis X (Langerhans' cell histiocytosis). *Arch. Pathol. Lab. Med.*, **107**, 59–63.

ROSENFIELD, N.S., ABRAHAMS, J. & KOMP, D. (1990). Brain MR in patients with Langerhans cell histiocytosis: findings and enhancement with Gd-DTPA. *Pediatr. Radiol.*, **20**, 433–436.

SACKS, S.H., HALL, I., RAGGE, N. & PRITCHARD, J. (1986). Chronic dermal sinuses as a manifestation of histiocytosis X. *Br. Med. J.*, **292**, 1097–1098.

SCHÜLLER, A. (1915). Uber eigenartige Schadeldefekte im Jugendalter. *Fortschr. Rongenstr.*, **23**, 12–18.

SHEEHAN, M.P., ATHERTON, D.J., BROADBENT, V. & PRITCHARD, J. (1991). Topical nitrogen mustard: an effective treatment for cutaneous Langerhans cell histiocytosis. *J. Pediatr.*, **119**, 317–321.

SIEGAL, G.P., DEHNER, L.P. & ROSAI, J. (1985). Histiocytosis X (Langerhans cell granulomatosis) of the thymus. A clinicopathologic study of 4 childhood cases. *Am. J. Surg. Pathol.*, **9**, 117–124.

SILBERBERG, I. (1973). Apposition of mononuclear cells to Langerhans cells in contact allergic reactions. *Acta. Derm. Venerol.*, **53**, 1–12.

SIMS, D.G. (1977). Histiocytosis X: follow up of 43 cases. *Arch. Dis. Child.*, **52**, 433–440.

SIWE, S. (1933). Die Reticuloendothliose -ein neues Krankheitsbild unter den Hepatosplenomegalien. *Z. Kinderheilk*, **55**, 212–247.

SMITH, T. (1865). Skull cap showing congenital deficiency of bone. *Trans. Pathol. Soc. Lond.*, **16**, 224–225.

STARLING, K.A. (1987). Chemotherapy of histiocytosis X. *Haemat. Oncol. Clin. N. Am.*, **1**, 119–122.

STINGL, G., TAMAKI, K. & KATZ, S.I. (1980). Origin and function of epidermal Langerhans cells. *Immunol. Rev.*, **53**, 149–182.

STREILEIN, J.W. (1983). Skin-associated lymphoid tissues (SALT): orgins and functions. *J. Invest. Dermatol.*, **80**, 12s–16s.

WILLMAN, C.L., MCCLAIN, K.L., DUNCAN, M.H., KANAPILLY-CHAVEZ, L., GRIFFITH, B.B., ISSACSON, P.G., SCHNELL, B., GRESWICK, M.V. & FAVARA, B.E. (1993). Molecular studies of clonality indicate that Langerhans cell histiocytosis (LCH) is a clonal histiocytic neoplasm. *Lab. Invest.*, **68**, 128A.

WRITING GROUP OF THE HISTIOCYTE SOCIETY (CHU, T., D'ANGIO, G.J., FAVARA, B., LADISCH, S., NESBIT, M. & PRITCHARD, J. (1987). Histiocytosis syndromes in children. *Lancet*, **1**, 208–209.

YU, R.C.H., ATRA, A., QUINN, C.M., KRAUSZ, T. & CHU, A.C. (1993). Multisystem Langerhans cell histiocytosis with pancreatic involvement. *Gut*, **34**, 570–572.