

Historical Review

THE LANGERHANS CELL HISTIOCYTOSIS X FILES REVEALED

In this day and age, when E-mail, Internet searches, conferences and Medline instantly connect one with the latest discoveries in medicine and science, it may be hard to realize that it took years for many diseases to be fully described. Researchers in the late 1800s from different countries would often be working on the same disease and would not realize that until much later. Langerhans cell histiocytosis (LCH) or histiocytosis X is a good example of this. Its history dates back to 1865 when Dr Thomas Smith published the case of a child four-and-a-half years of age with impetigo and three large holes in the calvarium. These defects were thought to be congenital, but review of the provided drawing now suggests LCH (before the invention of the X-ray in 1895, illustration of the abnormality described in a manuscript was provided in the form of a drawing). The impetigo was cured, but the child died from whooping cough a couple of months later. Dr Smith remarked that the only other specimen he had been able to find showing a similar 'congenital deficiency' was that of an older woman in the Museum of Guy's Hospital (Smith, 1865).

In the same period, Paul Langerhans published his landmark manuscript entitled: 'Über die Nerven der menschlichen Haut' when he was a 21-year-old medical student at the Institute of Pathology of the University of Berlin under the mentorship of Professor Virchow (Langerhans, 1868). He used Cohnheim's gold chloride staining technique and described a novel non-pigmentary dendritic cell in the epidermis. He initially regarded these cells as intraepidermal receptors for extracutaneous signals of the nervous system, but corrected this interpretation in 1882. 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 bone marrow-derived and represent the most peripheral outpost of our immune system. These unique histiocytes are now eponymously referred to as Langerhans cells and the proliferation of these cells is known as Langerhans cell histiocytosis.

Paul Langerhans (1847–1888) (Fig 1) was born in Germany. His father as well as both his half-brothers were all physicians. He studied medicine under Haeckel and Virchow and in 1869 he defended his thesis 'Beitrage zur Mikroskopischen Anatomie der Bauchspeicheldruse' (Contributions to the Microscopic Anatomy of the Pancreas), which were found in the

rabbit. Twenty-five years later, Edouard Laguesse found similar cells in the human pancreas and proposed to call them Langerhans islets. After his thesis defence, Langerhans subsequently demonstrated that cinnabar was taken up by white blood corpuscles and never by the red corpuscles, opening the door for Aschoff's concept of reticuloendothelial system.

In 1874, he became Professor Extraordinarius (Full Professor) in Freiburg, but unfortunately a week later he was diagnosed with renal tuberculosis. After a leave of absence, he was released from his duties at the University altogether and left for Madeira. Despite deterioration of his condition, he continued to do research on the fauna of the Atlantic Islands, Madeira in particular. His contributions were numerous and of such quality that in 1909 a polychaete worm was named after him, 'Verriliopsis Langerhansi', by Pierre Louis Andre Favel. He practiced medicine whenever his health allowed. The majority of his patients were German and British people who lived on the island often for health reasons, most notably tuberculosis. Among the Germans were Mr Ebart and his wife. Two years after Mr Ebart's death, Langerhans married Margaretha Ebart in 1885 in Berlin. Paul Langerhans died on July 20 1888 in Madeira, where he is buried in the Anglican cemetery.

Langerhans himself published two papers on tuberculosis, undoubtedly influenced by his own condition as well as the fact that his mother had died of tuberculosis when he was 6 years of age and his half-brother Robert had also contracted the disease (Hausen, 1987; Egeler et al, 1994).

HAND-SCHÜLLER-CHRISTIAN DISEASE

Alfred Hand, a resident-physician at Philadelphia's Children's Hospital, presented a case in 1893 in the Transactions of the Pathological Society of Philadelphia. He described a 3-year-old boy with exophthalmos who was admitted with great thirst and polyuria. Two months later the boy died and the autopsy showed a yellow spot near the right parietal eminence. This was thought to be tuberculosis (Hand, 1893). In 1905 he attended Dr Thomas W. Kay's presentation to the Medical Society of the State of Pennsylvania of a 7-year-old boy with a triad exophthalmos, diabetes insipidus and bone defects (Kay, 1905). Hand noted the similarity between Kay's case and his own, as well as those published by Drs Christian and Schüller (see below). In combination with his years of experience at the autopsy table, this led him to acknowledge that it must have been a different diagnosis (Hand, 1921).

Artur Schüller was a Professor in Vienna when he described a 16-year-old boy with vision complaints and a 4-year-old girl with exophthalmos, great thirst and polyuria (Schüller, 1915). He was an outstanding physician and is

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Fig 1. Paul Langerhans (1847–1888) (permission for reproducing has been provided by Johns Hopkins University Press, as this picture has been published in *Bulletin of the history of Medicine* Vol. 51933).

considered the father of neuroradiology. His interest was broad, as evidenced by the publication of over 300 papers, monographs and books. With the rise of the Third Reich, he left Vienna in 1938, emigrating to Australia.

Dr Henry Christian from Virginia received his MD from Johns Hopkins in 1900. He published a paper in 1920 while he was Physician-in-Chief at the Peter Bent Brigham Hospital in Boston drawing attention to very extensive defects in the skull bones, exophthalmos and diabetes insipidus in a 5-year-old girl (Christian, 1920). Dr Christian was an outstanding teacher and was among the early leaders in stimulating medical research. He stated that 'a careful search of the literature revealed but one report of a similar condition'. This was the report of the two cases described by Schüller. Unfortunately Dr Christian had overlooked Kay's publication. (Kay, 1905).

Eventually, the eponym Hand-Schüller-Christian disease was used to describe a disease occurring in children over 2 years of age, characterized by exophthalmos, lesions in the bones of the skull and diabetes insipidus.

LETTERER-SIWE DISEASE

Karl Aschoff, a German pathologist, considered the body's mononuclear phagocytes as a unified system of cells and introduced the term 'reticulo-endothelial system'. This included the reticulum cells of lymph nodes and spleen; the sinusoidal lining cells of lymph nodes, spleen, liver, bone marrow, adrenal cortex and pituitary; and the free macro-

phages (histiocytes) of extravascular connective tissue (Aschoff, 1924).

His countryman Erich Letterer described an acute fulminant non-leukaemic disorder of the reticulo-endothelial system in a 6-month-old child (Letterer, 1924), while working as an assistant at the Pathologischen Institut of the University of Würzburg. Nine years later his manuscript was followed by a report from Sture Siwe from the University of Lund Sweden. He described a similar disorder in a 1½-year-old girl. In his article, he grouped the previously reported cases, including the one by Letterer, with his own into a well-defined clinical, pathological entity (Siwe, 1933). He characterized the condition by marked splenomegaly, hepatomegaly, lymphadenopathy, localized tumours in the bones, a haemorrhagic tendency, secondary anaemia, and generalized hyperplasia of non-lipoid-storing macrophages in various organs. In his introduction he mentioned for the first time the word 'histiocyten' in connection with reticulo-endotheliose. He suggested that these rare 'Stoffwechselstörungen' (storage diseases) were also known under the names of Gaucher, Niemann-Pick and, interestingly enough, Christian-Schüller.

The first reference to Letterer-Siwe's disease was in a paper by Drs Arthur Abt and Edward Denenholz from Chicago. They acknowledged Letterer's publication and reviewed nine cases using Siwe's criteria, including one of their own (Abt & Denenholz, 1936).

EOSINOPHILIC GRANULOMA OF BONE

In 1930 Dr Mignon from Innsbruck described a granulomatous bone lesion in a 12-year-old boy (Mignon, 1930). This was followed by a detailed and illustrated histological report of several cases of 'Skeletal Lipoid Granulomatosis; Hand-Schüller-Christian Disease' by Dr John Fraser in Edinburgh (Fraser, 1935). These were the first descriptions of otostic histiocytosis.

In 1940 two articles dealing with this same disease were published. The first was written by Drs Sadao Otani and Joseph Ehrlich from Mount Sinai and Lebanon Hospitals in New York City (Otani & Ehrlich, 1940). This was followed a few months later by the second report, by Drs Louis Lichtenstein and Henry Jaffe from the Hospital for Joint Diseases also in New York City (Lichtenstein & Jaffe, 1940). The disease was named 'solitary granuloma of bone' and 'eosinophilic granuloma of bone' respectively. Otani and Ehrlich stated that they had seen seven specimens of solitary granuloma. The lesions were found to have identical histological features, including cellular tissue mainly composed of histiocytes and eosinophils (Otani & Ehrlich, 1940). Lichtenstein and Jaffe described an eosinophilic granuloma of the bone and quoted several similar cases in the literature, including the ones by Otani and Ehrlich. They suggested that these lesions could conceivably represent a virus granuloma and that other osseous lesions, including Hand-Schüller-Christian disease, needed to be differentiated from the one under discussion. It was thought to be a benign disease in spite of the bone destruction and the microscopic appearance.

This was characterized by the presence of compacted tumour-like aggregates of large phagocytic cells, with conspicuous collections of eosinophilic leucocytes interspersed which, in some cases, resembled a neoplasm (Lichtenstein & Jaffe, 1940).

A year later Dr Sidney Farber noted that 'all three conditions (Letterer–Siwe, Schüller–Christian and study of the evolution of bone lesions in Schüller–Christian) represent variations in degree, stage of involvement and localization of the same basic disease process' (Farber, 1941). In a more extensive manuscript, Green & Farber (1942) stated that this notion was confirmed based on histological studies. They concluded: 'Since the aetiology of the process is unknown, there's no rational name to apply to this disease, which process is described as "destructive granuloma of bone"'. Jaffe & Lichtenstein (1944) supported the direction this discussion was taking. They proposed that there was an interrelation: 'Altogether, it would now seem that eosinophilic granuloma of bone, Letterer–Siwe disease as well as Schüller–Christian disease constitute different clinical expressions of the same basic disorder, which seems to predilect the haemopoietic system' (Jaffe & Lichtenstein, 1944).

HISTIOCYTOSIS X

The formulation of this unified concept sparked publication of related cases, whereas previously the different nomenclature proved to be confusing. Pinkus *et al* (1949), as well as Dennis & Rosahn (1951), urged a general designation of the whole malady so as to provide clarity. The recognized types of clinical involvement could then be grouped under one heading while at the same time facilitating distinctions having a bearing on treatment and prognosis.

It was Lichtenstein who introduced in his classic paper in 1953 the unifying concept which allowed all the disease to be included under the name of 'histiocytosis X' (Lichtenstein, 1953). He intended the unification to be primarily pathological, and referred to acute/subacute disseminated, chronic disseminated and localized histiocytosis X. The recognized types of clinical involvement could still be differentiated from one another, so that useful distinctions having a bearing on treatment and prognosis were maintained. He decided to call the entity 'histiocytosis' as this term denotes inflammatory proliferative reaction and is the one feature common to the various pathological expressions of the disease. He continues 'I can devise no better name at present than "histiocytosis X" for specific reference to the disease complex under discussion. It has the advantage of brevity and, by implication, emphasizes the necessity for an intensive search for the aetiological agent, which clearly constitutes the next major assignment now that the pathologic anatomy of the malady is beginning to be somewhat better understood. At all events histiocytosis X will be the general name employed in the ensuing discussion, and this may be appropriately qualified to emphasize the significant peculiarities of any individual case.' Some 10 years later, Louis Lichtenstein considered papers published since 1953 in a



Fig 2. Louis Lichtenstein (1906–77) (permission for reproducing has been provided by the C.V. Mosby Company, as this picture has been published in *Bone Tumors* 5th edition 1977).

new report as well as discussing some of his own recent observations. In this publication he argued that the evidence that emerged from publications after 1953 supported the concept of histiocytosis X as a nosological entity (Lichtenstein, 1964).

Louis Lichtenstein (1906–77) (Fig 2) was born and raised in New York City. He studied medicine at the Yale University School of Medicine, where he received his degree in 1929. After his Pathology Fellowship at Mt. Sinai, New York, his appointment of Instructor of Pathology at the Louisiana State University Medical Centre was the beginning of a productive career in academic medicine. His interest was more diverse in the beginning, ranging from distribution of lipids in Niemann–Pick disease, nephrosis, and metabolism of phosphorus to lymphogranuloma inguinale. He then focused his considerable efforts on bones, culminating in the publication of two definitive textbooks: 'Bone Tumours' and 'Diseases of Bone and Joints'. Dr Lichtenstein was a consultant in Bone Tumours and in Pathology. He was Professor of Pathology at the University of California School of Medicine. He was married and had one son (Miller, 1978).

LANGERHANS CELL HISTIOCYTOSIS

No significant progress in understanding the nature of Langerhans cells was made until 1961, when the ultrastructural features of these cells were first described by Birbeck *et al* (1961). Their description of the electron microscopic study made it possible to reliably identify individual Langerhans cells on the basis of the presence of characteristic organelles, originally referred to as Langerhans bodies, and now better known as 'Birbeck granulae'. These cytoplasmic inclusions were observed by Birbeck *et al* (1961) in the context of vitiligo and seemed to resemble structures in the Langerhans cells of the epidermis. A significant increase in understanding

histiocytosis X took place when Nézelof *et al* (1973) reported that histiocytosis X was the result of the proliferation and dissemination of pathological histiocytic cells, identified as Langerhans cells. In their classic manuscript, the similarity of histiocytosis X-cells and Langerhans cells was postulated on the recognition of Birbeck granules (X-bodies) by electron microscopy (Nezelof *et al*, 1973). Although this research group noticed the similarity at the end of the 1960s, this notion was considered very controversial and it took several years to get the above mentioned manuscript accepted (C. Nezelof, personal communication). After a general acceptance, members of the University of Minnesota suggested a name change from histiocytosis X to Langerhans cell histiocytosis, as the Langerhans cell proved the key-player in all forms of the disease spectrum (Risdall *et al*, 1983). An excellent overview, including a chronological table outlining the early microscopic studies, has recently been provided by Nézelof & Basset (1998).

Dr Christian Nezelof (Fig 3) studied medicine in Paris during the second World War. He specialized in Paediatrics in 1948 at the Hospital des Enfants Malades. He continued his studies under Professor Bodian, a famous British pathologist, in London. He returned to France to complete his training as paediatric pathologist. In 1960 he was full-time pathologist at Necker-Enfants Malades and in 1968 he became chairman of the Department of Pathology. At the same time, from 1970 to 1985 he was Head of INSERM Research Unit. During this period he published an article on the successful growth in nude mice of a tumour after injection of cells from the pleural effusion of a child with malignant histiocytosis. Subsequently his team established the Malignant Histiocytosis DEL cell line. His key role in



Fig 3. Christian Nezelof (1925–).

describing a clinical condition of immune deficiency in childhood, in which the existence of a 'split' in the human lymphoid system towards the T and B cells was recognized, resulted in Nezelof's syndrome. Dr Nezelof continued to contribute to the development of Paediatric Pathology by creating the Groups of Paediatric Pathology located at the Necker-Enfants Malades Hospital, as well as a network of various specialties, and he trained many paediatric pathologists. Dr Christian Nezelof is married and has two children; one of them is a paediatric psychiatrist. Recently, together with Henry Azar, he founded the History of Pathology Society and turned his interest to the contributions of our ancient precursors and the medical changes linked with technical innovation (Abstracted from the yearly announcement of the Christian Nezelof Award of the Histiocyte Society; originally produced by one of the authors).

Whereas the first half of the history of LCH was dedicated to the clinicopathological descriptions, the second part has been filled with clinical trials (Komp, 1987). The approaches to the treatment of LCH have been as varied as the clinical presentation of the disease (Egeler & Nesbit, 1995). Studies have demonstrated the efficacy of a variety of agents. The validity of some of the older reports has been questioned as most if not all these studies reported only initial responses and did not give the follow-up information necessary to evaluate the impact of therapy on survival. There are also considerable doubts inherent in the review of clinical trials that were conducted for more than half a century in a variety of clinical settings and that were based on less than strict clinical and pathological diagnostic criteria. Furthermore, comparisons of results obtained by drugs not assessed by the randomized trial mechanism are open to many uncertainties (Egeler & D'Angio, 1995). For these reasons, international randomized clinical studies, organized through the auspices of the Histiocyte Society, have been initiated since the beginning of the 1990s. These are designed to examine the risks and benefits of specific agents within the different risk groups. These studies compare rates of disease response and recurrence, morbidity, and early and late toxic effects in a prospective randomized fashion (Ladisch *et al*, 1994). Recently the results of the first international randomized LCH study for multisystem disease (LCH-I) were published (Gadner *et al*, 2001). Two of the most commonly used drugs in LCH, vinblastine and etoposide for 24 weeks, were shown to be equally effective. Lack of rapid response within 6 weeks in either treatment arm was shown to be an indication for treatment failure, as two-thirds of these patients succumbed to the disease.

THE HISTIOCYTOSIS NETWORK

In 1985 Dr Giulio D'Angio, Professor of Radiation Oncology of the University of Pennsylvania, convened the first workshop on histiocytosis in Philadelphia, which led to the founding of the Histiocyte Society with Dr Christian Nezelof as first President. This Society is actively involved in international research to develop improved treatment approaches for patients with LCH and the other histiocytoses. Ultimately, the Society's goal is a better understanding of the cause and pathogenesis of the histiocytoses and

dissemination of that information to physicians caring for patients with these diseases. The Histiocyte Society has established standardized nomenclature, clinical and pathological criteria (Chu *et al*, 1987) and treatment approaches (see above). Prospective controlled clinical trials with quality assurance and proper statistical analyses have made it possible to fine-tune treatment options and focus on follow-up (Broadbent *et al*, 1989). Membership has grown to over 200 physicians, nurses and scientists from over 35 different countries (Histiocyte Society, 2001).

At approximately the same time, Jeff and Sally Toughill, whose child had LCH, developed a family network, which resulted in the founding of the Histiocytosis Association of America. Since 1986 this organization's membership has grown to almost 10 000 parents, patients and friends from around the world. Families from several other countries followed the example set by the Histiocytosis Association of America and formed similar organizations. The combined histiocytosis associations have since developed into an international partnership of patients, families, physicians and friends. Although the Histiocytosis Association of America is the primary funder of research (80 international projects), other organizations are now joining the research funding effort. Together these organizations provide mutual support to patients and families, educate physicians and the public through sponsoring of international research symposia and distribute educational literature to physicians around the world.

The Nikolas Symposium, established in 1987 by Paul & Elizabeth Kontoyannis whose son, Nikolas, has suffered from Langerhans cell histiocytosis since 1981, followed these developments. Under the leadership of Dr Jon Pritchard, the Kontoyannis family has pledged its support for the annual Symposia until the time they reach their goal 'of identifying the underlying pathological abnormality causing LCH so that rational and curative treatment can ultimately be developed'. The programme of the yearly think-tank and other activities of the Nikolas Symposium are determined by a Scientific Steering Committee consisting of doctors and scientists from all around the world. This reflects the geographical and disciplinary diversity of those interested in the histiocyte and its disorders, an interest that the Symposia are meant to foster and encourage.

The cross-fertilization between these three organizations has been extremely productive in the advances of LCH. Many of the fundamental questions and ideas for clinical and laboratory research executed by physicians and researchers, funded through grants of the parent groups, have been discussed and developed in the Greece think-tank.

CONTEMPORARY DEVELOPMENTS

The endeavours of physicians and other investigators over the last 10–15 years to work together, to participate in international studies and to share clinical and research-related information have clearly developed the understanding of LCH into an exciting and fast moving field. The

major developments in the clinical arena of LCH have been complemented by productive research concerning the basic nature of the LCH cell and its disorder. The diagnostic lesional cell, the 'LCH cell', is most akin to the normal Langerhans cell, and has an immature phenotype and function. This cell is very sensitive to local factors such as cytokines and growth factors for replication, maturation and differentiation. High expression of cytokines and the co-stimulatory molecules in LCH lesions have been demonstrated. The pattern of cytokine expression favours recruitment of Langerhans cell progenitors, as well as their maturation and rescue from apoptosis, thereby explaining the pathological accumulation of LCH cells (Egeler *et al*, 1999, 2000; Tazi *et al*, 1999; Geissman *et al*, 2001). The fact that clonality has been found in all LCH lesions reported to date (Willman *et al*, 1994) argues that LCH is a neoplastic disorder with varied biological behaviour, which could result from a genetic predisposition (Egeler, 1993).

On the basis of the identification of familial LCH cases (Arico *et al*, 1999) and clonality findings (Willman *et al*, 1994), in combination with studies showing chromosomal instability (Betts *et al*, 1998; Scappaticci *et al*, 2000), the search for potential candidate genes in LCH has begun. Any cytogenetic observation of an abnormal clonal karyotype made in LCH should clearly be extended at the molecular level. Further cytogenetic studies of LCH patients should be encouraged as more extensive work is needed.

CONCLUSION

The 20th century taught us a great deal about understanding LCH. Ultrastructural studies identifying the proliferating cells as part of the Langerhans (dendritic) cell system, followed by establishing internationally accepted definitions of the morphological, immunohistochemical and clinical criteria needed for the diagnosis, and, subsequently, the development of internationally run prospectively, randomized clinical trials, have had a major impact on the clinical management of LCH. These agreements have led to exploring new ventures regarding aetiology and pathophysiology in the last decade, especially in respect to topics such as Langerhans cell biology, the possible role of the immune system, cytokine and co-stimulatory molecule involvement, clonality and cytogenetic research. This will ultimately lead to a better understanding and, subsequently, to a better treatment and improved outcome of patients with Langerhans cell histiocytosis.

ACKNOWLEDGMENT

This manuscript is dedicated to Dr Giulio D'Angio, Professor Emeritus of Radiation Oncology of the University of Pennsylvania, who has been part of the history of Langerhans cell histiocytosis for at least half a century. We would like to thank him for his guidance and for reviewing so many of our manuscripts, including this one. He has been a mentor and a friend for many, many years.

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REFERENCES

- Abt, A. & Denenholz, E. (1936) Letterer-Siwe's disease; splenohepatomegaly, associated with widespread hyperplasia of non lipid-storing macrophages; discussion of the so-called reticulo-endotheliosis. *American Journal of Diseases of Children*, **51**, 499–522.
- Arico, M., Nichols, K., Whitlock, J.A., Arceci, R., Haupt, R., Mittler, U., Kuhne, T., Lombardi, A., Ishii, E., Egeler, R.M. & Danesino, C. (1999) Familial clustering of Langerhans cell histiocytosis. *British Journal of Haematology*, **107**, 883–888.
- Aschoff, L. (1924) Das Reticulo-Endotheliale System. *Ergebnisse Inner Medizin und Kinderheilkunde*, **26**, 1–118.
- Betts, D., Leibundgut, K., Feldges, A., Pluss, H. & Niggli, F. (1998) Cytogenetic abnormalities in Langerhans cell histiocytosis. *British Journal of Cancer*, **77**, 552–555.
- Birbeck, M., Breathnach, A. & Everall, J. (1961) An electron microscope study of basal melanocytes and high-level clear cells (Langerhans cells) in vitiligo. *Journal of Investigative Dermatology*, **37**, 51–63.
- Broadbent, V., Gadner, H., Komp, D. & Ladisch, S. for the Clinical Writing Group of the Histiocyte Society (1989) Histiocytosis syndromes in children: II. Approach to the clinical and laboratory evaluation of children with Langerhans cell histiocytosis. *Medical and Pediatric Oncology*, **17**, 492–495.
- Christian, H. (1920) Defects in membranous bones, exophthalmos and diabetes insipidus; an unusual syndrome of dyspituitarism. *Medical Clinics of North America*, **3**, 849–871.
- Chu, T., D'Angio, G.J., Favara, B., Ladisch, S., Nesbit, M. & Pritchard, J. for the Writing Group of the Histiocyte Society (1987) Histiocytosis syndromes in children. *Lancet*, **1**, 208–209.
- Dennis, J. & Rosahn, P. (1951) The primary reticulo-endothelial granulomas with report of an atypical case of Letterer-Siwe's disease. *American Journal of Pathology*, **27**, 627.
- Egeler, R.M. (1993) Genetic predisposition in Langerhans cell histiocytosis? An hypothesis. Langerhans cell histiocytosis and other histiocytic disorders. PhD Thesis, University of Amsterdam, Haveka BV Alblasserdam, The Netherlands, 181–197.
- Egeler, R.M. & D'Angio, G.J. (1995) Medical Progress: Langerhans cell histiocytosis. *Journal of Pediatrics*, **127**, 1–11.
- Egeler, R.M. & Nesbit, Jr, M.E. (1995) Langerhans cell histiocytosis and other disorders of monocyte-histiocyte lineage. *Critical Reviews of Oncology and Hematology*, **18**, 9–35.
- Egeler, R.M., Zantinga, A.R. & Coppes, M.J. (1994) Paul Langerhans Jr (1847–1888); a short life, yet two eponymic legacies. *Medical and Pediatric Oncology*, **22**, 129–132.
- Egeler, R.M., Favara, B.E., van Meurs, M., Laman, J.D. & Claassen, E. (1999) Differential in situ cytokine profiles of Langerhans-like cells and T-cells in Langerhans cell histiocytosis: abundant expression of cytokines relevant to disease and treatment. *Blood*, **94**, 4195–4201.
- Egeler, R.M., Favara, B.E., Laman, J.D. & Claassen, E. (2000) Abundant expression of CD40 and CD40-ligand (CD154) in paediatric Langerhans cell histiocytosis lesions. *European Journal of Cancer*, **36**, 2105–2110.
- Farber, S. (1941) The nature of "Solitary or Eosinophilic Granuloma" of bone. *American Journal of Pathology*, **17**, 625–629.
- Fraser, J. (1935) Skeletal lipid granulomatosis (Hand-Schüller-Christian's disease). *British Journal of Surgery*, **22**, 800–824.
- Gadner, H., Grois, N., Arico, M., Broadbent, V., Ceci, A., Jacobson, A., Komp, D., Michaelis, J., Nicholson, H.S. & Ladisch, S. for the Histiocyte Society (2001) A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. *Journal of Pediatrics*, **138**, 728–734.
- Geissmann, F., Lepelletier, Y., Fraitag, S., Valladeau, J., Bodemer, C., Debre, M., Leborgne, M., Saeland, S. & Brousse, N. (2001) Differentiation of Langerhans cells in Langerhans cell histiocytosis. *Blood*, **97**, 1241–12484.
- Green, W. & Farber, S. (1942) 'Eosinophilic or Solitary Granuloma' of bone. *Journal of Bone and Joint Surgery*, **24**, 499–526.
- Hand, A. (1893) Polyuria and tuberculosis. *Archives of Pediatrics*, **10**, 673–675.
- Hand, A. (1921) Defects of membranous bones, exophthalmos and polyuria in childhood: is it dyspituitarism? *American Journal of Medical Science*, **162**, 509–515.
- Hausen, B. (1987) Paul Langerhans, Life and Work Part I,II,III. *American Journal of Dermatopathology*, **9**, 151–156.
- Histiocyte Society (2001) www.document. URL: <http://www.histio.org/society>.
- Jaffe, H. & Lichtenstein, L. (1944) Eosinophilic granuloma of bone. A condition affecting one, several or many bones, but apparently limited to the skeleton, and representing the mildest clinical expression of the peculiar inflammatory histiocytosis also underlying Letterer-Siwe disease and Schuller-Christian disease. *Archives of Pathology*, **37**, 99–118.
- Kay, T. (1905) Acquired hydrocephalus with atrophic bone changes, exophthalmos, and polyuria (with presentation of the patient). *Pennsylvania Medical Journal*, **9**, 520–521.
- Komp, D.M. (1987) Historical perspectives of Langerhans cell histiocytosis. *Hematology/Oncology Clinics of North America*, **1**, 9–21.
- Ladisch, S., Gadner, H., Arico, M., Broadbent, V., Grois, N., Jacobson, A., Komp, D. & Nicholson, H.S. for the Histiocyte Society (1994) A randomized trial of etoposide vs. vinblastine in disseminated Langerhans cell histiocytosis. *Medical and Pediatric Oncology*, **23**, 107–110.
- Langerhans, P. (1868) Über die Nerven der menschlichen Haut. *Archiv der Pathologischen Anatomie*, **44**, 325–337.
- Langerhans, P. (1882) Berichtigungen (u.a. zu den Nervenenden der Haut, und Nervenfasern im Rete). *Archiv der Mikroskopischen Anatomie*, **20**, 641–643.
- Letterer, E. (1924) Aleukamische retikulose (ein Beitrag zu den proliferativen Erkrankungen des Reticuloendothelialapparates). *Frankfurter Zeitschrift der Pathology*, **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. *American Medical Association Archives of Pathology*, **56**, 84–102.
- Lichtenstein, L. (1964) Histiocytosis X (eosinophilic granuloma of bone, Letterer-Siwe Disease, and Schuller-Christian Disease. *Journal of Bone and Joint Surgery*, **46**, 76–90.
- Lichtenstein, L. & Jaffe, H. (1940) Eosinophilic granuloma of bone. *American Journal of Pathology*, **16**, 595–604.

- Mignon, F. (1930) Ein granulationstumor des stirnbeins. *Fortschritte Röntgenstrahlen*, **42**, 749–751.
- Miller, W. (1978) Lichtenstein L. *American Journal of Clinical Pathology*, **69**, 656.
- Nézelof, C. & Basset, F. (1998) Langerhans cell histiocytosis research. Past, present, and future. *Hematology and Oncology Clinics of North America*, **12**, 385–406.
- Nézelof, C., Basset, F. & Rousseau, M. (1973) Histiocytosis X: Histogenic arguments for a Langerhans' cell origin. *Biomedicine*, **18**, 365–371.
- Otani, S. & Ehrlich, J. (1940) Solitary granuloma of bone, simulating primary neoplasm. *American Journal of Pathology*, **16**, 479–490.
- Pinkus, H., Copps, L., Custar, S. & Epstein, S. (1949) Reticulo-granuloma: report of a case of eosinophilic granuloma of bone associated with nonlipid reticulosis of skin and oral mucosa under the clinical picture of Hand-Schuller-Christian Disease. *American Journal of Diseases of Children*, **77**, 503.
- Risdall, R.J., Dehner, L.P., Duray, P., Kobinsky, N., Robison, L. & Nesbit, M.E. (1983) Histiocytosis X (Langerhans' cell histiocytosis). Prognostic role of histopathology. *Archives of Pathology and Laboratory Medicine*, **107**, 59–63.
- Scappaticci, S., Danesino, C., Rossi, E., Klersy, C., Fiori, G.M., Clementi, R., Russotto, V.S., Bossi, G. & Arico, M. (2000) Cytogenetic abnormalities in PHA-stimulated lymphocytes from patients with Langerhans cell histiocytosis. *British Journal of Haematology*, **111**, 258–262.
- Schüller, A. (1915) Über eigenartige schadeldefekte im jugendalter. *Fortschritte Auf der Gebiete Rontgenstrahlen*, **23**, 12–18.
- Siwe, S. (1933) Die reticuloendotheliose – ein neues krankheitsbild unter den hepatosplenomegalien. *Zeitschrift Fur Kinderheilkunde*, **55**, 212–247.
- Smith, T. (1865) Skull cap showing congenital deficiency of bone. *Transactions of the Pathological Society of London*, **16**, 224–225.
- Tazi, A., Moreau, J., Bergeron, A., Dominique, S., Hance, A.J. & Soler, P. (1999) Evidence that Langerhans cells in adult pulmonary Langerhans cell histiocytosis are mature dendritic cells: importance of the cytokine microenvironment. *Journal of Immunology*, **163**, 3511–3515.
- Willman, C.L., Busque, L., Grith, B.B., Favara, B.E., McClain, K.L., Duncan, M.H. & Gilliland, D.G. (1994) Langerhans' cell histiocytosis (histiocytosis X) – a clonal proliferative disease. *The New England Journal of Medicine*, **331**, 154–160.

Keywords: history, histiocytosis X, Langerhans cell histiocytosis.