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Acknowledgements

P.J.S. and D.A.W. are supported by the Nottingham Children's Brain Tumour Research Centre. Thanks to J. Hewitt, B. Coyle, V. Sottile and R. Grundy for their constructive criticism of the manuscript. Thanks also to M. Hyatt for help with the production of figure 1 and J. Davies for figure 3.

Competing interests statement

The authors declare no competing financial interests.

Online links

DATABASES

The following terms in this article are linked online to:

Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene
α-fetoprotein | IGF2 | p107 | p53 | *PTCH* | *RB* | SHH | TIMP1 | WT1 | WT2

National Cancer Institute: http://cancer.gov/
medulloblastoma | neuroblastoma | retinoblastoma | Wilms' tumour

OMIM: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM
Gorlin's syndrome | Turcot's syndrome

SUPPLEMENTARY INFORMATION

See online article: S1 (table)

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SCIENCE AND SOCIETY

The Nikolas Symposia and histiocytosis

Peter C. L. Beverley, R. Maarten Egeler, Robert J. Arceci and Jon Pritchard

Abstract | Histiocytoses are a group of rare diseases that involve histiocytes (literally tissue cells (Greek), but in reality tissue-resident macrophages and dendritic cells), which are derived from bone-marrow stem cells. Histiocytoses pose problems similar to those of other rare diseases of childhood. Individual physicians see few cases, disease material is hard to collect and families suffer from lack of information and understanding. In this article, we describe how a series of 'think tank' meetings, the Nikolas Symposia, which have concentrated on Langerhans cell histiocytosis, have furthered our understanding of this enigmatic disease.

As a result of the rarity of diseases like the histiocytoses, the initial descriptions are usually reports of small numbers of cases in specialist medical journals. Therefore, recruitment of scientists with diverse research skills to work on the disease might not occur. The formation of medical societies with interests in particular rare diseases may alleviate the problem, but these organizations could have a narrow interest focussed on diagnosis and treatment. Similarly, patients and parents' groups are understandably often preoccupied with matters to do with treatment, outcome and family support. Drug companies are not interested in developing specific therapies because it is impossible to recover their development costs.

Box 1 | **Classification of histiocytoses**

Work carried out by the Histiocyte Society[16] and the World Health Organization led to the following classification of histiocytic diseases. For further information, see the WHO International Classification of Diseases in the Online links box.

Disorders of varied biological behaviour

- **Dendritic-cell-related disorders. For example, Langerhans cell.**
- **Secondary dendritic-cell processes. For example, juvenile xanthogranuloma and related disorders; and solitary histiocytomas of various dendritic-cell phenotypes.**
- **Macrophage-related disorders. For example, primary haemophagocytic lymphohistiocytosis (familial and sporadic); secondary haemophagocytic syndromes (infection or malignancy related); Rosai–Dorfman disease (sinus histiocytosis with massive lymphadenopathy); and solitary histiocytoma with macrophage phenotype.**

Malignant disorders

- **Dendritic-cell-related histiocytic sarcomas. These involve specific dendritic cell types such as Langerhans cells, interdigitating cells and follicular dendritic cells.**
- **Monocyte-related disorders. For example, monocytic leukaemia; acute myelomonocytic leukaemia; chronic myelomonocytic leukaemia; extramedullary monocytic tumour or sarcoma; macrophage-related histiocytic sarcoma.**

Funding bodies often prefer to devote their scarce resources to more common conditions with perceived greater societal impact. These features of rare conditions, with an incidence of between 1 and 7 cases per million of the population, have caused them to be named 'orphan' diseases.

Histiocytoses: the diseases

Histiocytoses derive from two main lineages: phagocytic monocytes and macrophages found in blood and tissues; and dendritic cells, the principal function of which is to act as professional antigen-presenting cells. The two forms of histiocytosis most often encountered in children are Langerhans cell histiocytosis (LCH) and haemophagocytic lymphohistiocytosis (HLH), the first a disease of epidermal antigen-presenting dendritic cells called Langerhans cells (LCs), and the second of mononuclear phagocytes (BOX 1). In both conditions there may be accumulation of histiocytic cells in organs and tissues throughout the body. Both are rare, with an incidence for LCH of around 1:200,000 children per year[1], peaking at 1–3 years. In HLH, which has an incidence of about 1:1,000,000 per year, genetic factors have been identified in approximately half of cases[2,3], whereas in LCH the role of specific genes is less clear cut. HLH still has a relatively poor prognosis, although bone-marrow transplantation has improved the outlook such that approximately 50% of patients now survive. By contrast, the overall mortality in LCH is lower (10–20%), but many survivors suffer severe long-term consequences of the disease and subsets of patients continue to have progressive disease that is refractory to current therapies.

LCH in children is very diverse. Approximately two-thirds of patients present with single-system disease, commonly in bone. Many of these patients require minimal treatment or the lesions resolve spontaneously, but even in these patients there may be permanent, mainly orthopaedic consequences[4]. At the other extreme and most often in young infants, the presentation is multisystem with organ failure, and among patients who do not respond to treatment within the first few weeks, mortality may be as high as 20% irrespective of treatment[5]. Between these extremes lie patients with multisystem disease without organ failure in whom the disease runs a fluctuating course and may eventually 'burn out', often leaving serious residual disabilities. Sequelae are common in patients with multisystem disease and include small stature because of growth-hormone deficiency, diabetes insipidus, cerebellar ataxia, deafness, orthodontic problems, lung fibrosis, liver cirrhosis and malabsorption due to gastrointestinal involvement[6]. As well as these late physical effects, neuropsychological problems can be a major problem. Central nervous system (CNS) damage is an especially distressing feature of LCH and the pathogenesis of this damage is obscure, but modern methods of imaging, in particular magnetic resonance imaging, and psychological assessment are important new tools for determining the extent of CNS disease[7,8] (FIG. 1). Second malignancies, particularly T-cell acute lymphoblastic leukaemia (T-ALL), occur in LCH patients with a much higher than expected

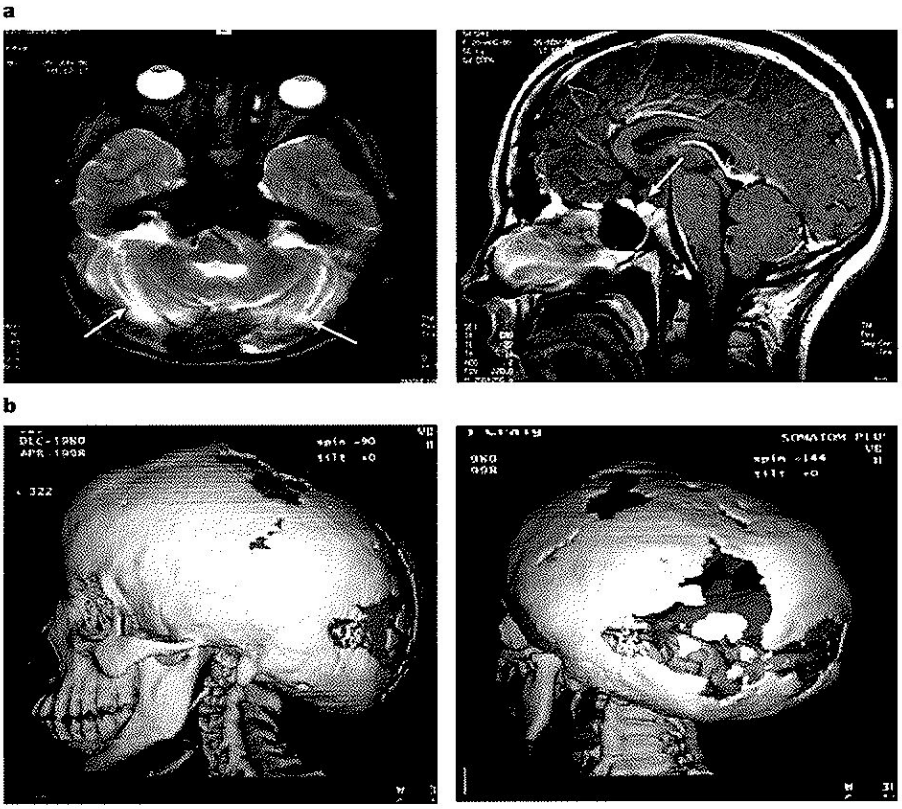

Figure 1 | **Magnetic resonance imaging scans showing permanent damage to areas of the brain and bones of the skull. a** | Horizontal and vertical sections through the brain. Arrows indicate areas of increased density in the cerebellum and pituitary. **b** | Several Langerhans cell histiocytosis bone lesions in the skull.

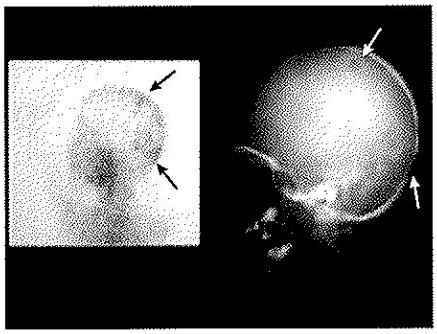

Figure 2 | **Radiolabelled monoclonal antibody to CD1a localizing to active Langerhans cell histiocytosis lesions in the bones of the skull.** Right panel shows a conventional skull X-ray of a child with Langerhans cell histiocytosis. The arrows indicate osteolytic bone lesions. Left panel shows a scan of the same child's skull following infusion of radiolabelled CD1a antibody. Arrows indicate the same bone lesions, which have concentrated the radiolabel.

frequency[9]. The association with clonal malignant diseases of early haematopoietic precursor cells indicates that there might be underlying genetic abnormalities in these cells in LCH, a finding that is in accord with the finding of a common immunoglobulin gene rearrangement in B cells and LCH cells of one patient[10]. However, later development of acute non-lymphocytic leukaemia might be a treatment-related effect.

It is now clear that LCH occurs in adults as well as children. In fact, recent, preliminary figures from a national incidence survey in the United Kingdom indicate that there are just as many cases presenting in adult life as in childhood and that a similar spectrum of disease can be found in adults. Whether 'adult' cases are *de novo* in that age group or represent cases arising in childhood, but manifesting only in adult life, is intriguing but unknown, although a few patients who had LCH as children later developed pulmonary LCH. What is clear is that both active and (probably) passive smoking greatly increase the risk of pulmonary LCH in adult patients[11,12].

The features of LCH, suggestive on the one hand of malignancy or on the other of an inflammatory process, have provided a rationale for therapy either with anticancer drugs or anti-inflammatory and immunosuppressive agents. The outcome of international trials of anticancer agents, sponsored by the Histiocyte Society, demonstrates that for multisystem disease this approach represents the most effective current therapy[4,5]. However, whether and when to institute aggressive therapy, such as bone-marrow transplantation, remains a difficult question.

Box 2 | **Who is Nikolas?**

Nikolas is the first child of Paul and Elizabeth Kontoyannis. At birth, his parents noticed that his mouth looked 'different' to normal babies and that he had a nappy rash, which was difficult to treat. A dermatologist biopsied the rash and diagnosed Letterer–Siwe disease, confirmed as histiocytosis X by Jon Pritchard. Nikolas was treated with surgery to his mouth and a short course of low-dose corticosteroids. The skin and lung Langerhans cell histiocytosis (LCH) regressed and Nikolas became a happy, healthy baby, passing his developmental milestones normally[50].

Aged 2 years, Nikolas developed LCH scalp disease and lytic bone lesions. He was treated with topical nitrogen mustard and prednisone for 6 months. He improved but, aged 6–7 years, showed signs of cerebellar dysfunction, which was confirmed by a magnetic resonance imaging (MRI) scan (FIG. 1). He was treated with six courses of oral etoposide for 6 months, without improvement. At age 10 years, he developed raised intracranial pressure, due to stenosis of the aqueduct of Sylvius, which was relieved by creating a fistula between the third and fourth ventricles. The intracranial pressure normalized and cerebellar function stabilized.

Nikolas underwent early puberty and suffered psychological difficulties, eventually stemmed by intensive counselling and support. His growth rate decreased and he was shown to be growth-hormone deficient. Growth-hormone therapy was given from 11 to 16 years when growth was completed. His remaining hypothalamic–pituitary axis (HPA) function was normal, but he has 'compensated' diabetes insipidus. After a fall and femoral fracture, osteoporosis was demonstrated. Nikolas also developed epilepsy, which is successfully managed by anticonvulsant drugs, without signs of cerebral cortical LCH or scarring.

Now, Mr Kontoyannis — aged 23 years — is a semi-independent adult with cerebellar ataxia, well-controlled HPA dysfunction and epilepsy, and who is on therapy for osteoporosis. He has a part-time office job, spending a much of his spare time working with computers. A lasting impression from everyone who meets 'Nik' is one of admiration and affection for this young man, with his outgoing and engaging personality. He is a worthy ambassador for the growing constituency of LCH survivors who are handicapped by this cunning and enigmatic disease.

Recent developments have also resulted in more innovative forms of therapy, including the experimental testing of an antibody against CD1a for diagnostic immunolocalization and therapy of LCH[13,14] (FIG. 2). These clinical investigations provide encouraging evidence that it might be possible to target LCH cells in patients, and development of a human CD1a antibody is continuing (G. Bechan, D. Lee and R.J.A., unpublished observations). The Nikolas Symposia have facilitated much of the progress outlined above. Specifically, the symposia have directly initiated or stimulated the investigative work and subsequent findings demonstrating the current lack of evidence for a viral aetiology; the clonality of the pathogenic Langerhans cell and the search for somatic mutations; the types and cellular origins of the cytokines in LCH lesions and how these cytokines can lead to the pathophysiology of the disease; the study of familial clustering and concordance in twins; the potential for targeted immunotherapy; and the link with and importance of chronic neurodegenerative CNS disease.

The Nikolas Symposia

A first step to progress with many disease groups is an accepted classification system, as this provides a firm foundation for physicians around the world to identify disease entities and compare the outcome of different treatments in homogenous groups of patients, however rare. In 1987, the Writing Group of the Histiocyte Society published the first widely accepted classification of histiocytic disorders, and firm diagnostic criteria based on clinical and histological features were established for these disorders[15,16] (BOX 1). At the same time, Paul and Elizabeth Kontoyannis, whose son Nikolas had been diagnosed with histiocytosis X (BOX 2), wished to promote understanding of these enigmatic diseases and so came together with research-minded physicians to organize the first Nikolas Symposium. From the outset, the meetings deliberately set out to harness the motivation of parents to help the patients, the expertise of doctors who treat these diseases and share their experience through the Histiocyte Society, and the willingness of research scientists to attack novel problems.

The annual symposia — 15 so far — are funded by the parents of LCH patients and always involve parents support groups (TABLE 1). Practical aspects of disease management are regularly discussed at the symposia and illustrated by discussion of 'difficult cases' with the families' and/or

Table 1 | **The Nikolas Symposia**

Meeting	Year	Topic (outcome)
1st Nikolas Symposium	1989	LCH – an immunological disease? (Identified avenues for future research and the importance of determining clonality[25,26,27,48].)
2nd Nikolas Symposium	1990	Viruses as a possible trigger in LCH – developing a strategy. (No evidence for viral aetiology[17,18].)
3rd Nikolas Symposium	1991	The role of cytokines in LCH. (Stimulated much work on cytokines[34,36].)
4th Nikolas Symposium	1992	The neuropathology and pharmacology of LCH. (Led to long-term studies of neurological and psychosocial aspects of the disease[7,8].)
5th Nikolas Symposium	1993	Langerhans cell histiocytosis therapeutics present and future. (Stimulated use of antibodies for localization and treatment of disease[13,14].)
6th Nikolas Symposium	1995	Cell biology and molecular biology in LCH. (Discussed dendritic-cell differentiation and cell survival and death.)
7th Nikolas Symposium	1996	Apoptosis in LCH. (Stimulated work on the cell cycle and survival[32,33].)
8th Nikolas Symposium	1997	Migration and *in vivo* interactions of immune cells. (Led to work on chemokines[37].)
9th Nikolas Symposium	1998	Genetics and animal models of Langerhans Cell Histiocytosis (LCH). (Identified the need for animal models.)
10th Nikolas Symposium	1999	Dendritic cells and the brain in LCH.
Joint meeting of the Histiocyte Society and the Nikolas Symposium	2000	The molecular basis of LCH and the meaning of clonality.
11th Nikolas Symposium	2001	Acute and chronic cytokine networks leading to tissue damage.
12th Nikolas Symposium	2002	Dendritic cell differentiation: Signals, signalling and functional consequences: Clues to possible therapy. (Analysis of the functional consequences of aberrant antigen expression [38,43,49]).
13th Nikolas Symposium	2003	Langerhans cell histiocytosis: neoplasia or immune dysregulation?
14th Nikolas Symposium	2004	Langerhans cell histiocytosis: Bystander cells, interactions, pathophysiology.
15th Nikolas Symposium	2005	Dendritic cell plasticity.

patients' consent, often in their presence. Although physicians are accustomed to wrestling with the problems of complex, distressing and chronic diseases, scientific participants are often much affected by this contact with parents and patients and might begin to pursue LCH-related projects. Conversely, clinicians are often inspired by their contact with diverse scientific experts to embark on new lines of research. Over the years, the symposia have continued to provide a forum to bring together these groups to discuss the problems of histiocytoses, to pinpoint research questions and stimulate clinicians and scientists to carry out the research, and they are now widely recognized to be a catalyst for research on LCH. Symposium organizers and participants interact, in turn, with parents, patients and other scientists around the world, and with the Histiocyte Society, which is a separate and much larger international collaboration between clinicians, scientists, pathologists and others (BOX 3).

The Nikolas Symposia and LCH

From the outset, the symposia entered into the major debates surrounding LCH, principal among these being the issue of what LCH is and what causes it. Two key areas were proposed for investigation at the outset. The first was the role of infectious agents either in transformation or as an initiating trigger. Although no viral agent has been identified so far[17,18], the remarkable finding that *Helicobacter pylori* is involved in mucosa-associated lymphoid tissue lymphoma[19] and the discovery of several new human herpes viruses over the past few years, one of which is clearly involved in the aetiology of Kaposi's sarcoma[20,21], indicate that the involvement of pathogens should not be discounted. Furthermore, it has become clear that pathogens can influence the phenotype of cells of the immune system[22,23], a finding of particular relevance to the view that LCH could be a disorder in which normal differentiation of Langerhans cells is blocked[24].

A second key debate to which the symposia have contributed is the question of whether LCH is a neoplasm. Discussion of the features of LCH, its variants and associated conditions (such as juvenile xanthogranuloma and the macrophage-activation syndromes) regularly takes place at the symposia to emphasize how varied the disorder can be and help to form a consensus as to the hallmarks that identify LCH itself. LCH lesions often consist of a mixed cellular infiltrate containing the diagnostic LCH cells, macrophages, eosinophils, T-cells and, frequently, multinucleate giant cells (FIG. 3). During the first few symposia, it was regarded as vital to determine whether any or all of the cellular components of the typical LCH 'granuloma' migrated into the tumour or actually proliferated there. Within a year, investigators in London had identified LCH as a 'proliferative' disorder of LCH cells by detecting nuclear antigens characteristic of dividing cells. The same publication showed that although LCH cells share many features with skin Langerhans cells, they also show abnormal features such as the expression of placental alkaline phosphatase[25]. However, most LCH lesions do not show the aberrant nuclear morphology that is characteristic of most malignant neoplasms. At the same time, prompted by this debate, two groups investigated the issue of the clonality of LCH cells by using the Humara assay to analyse polymorphisms in the human androgen-receptor gene. They found that most lesions in children are indeed clonal[26,27], demonstrating that LCH is a clonal proliferative disorder of an immature Langerhans cell with variable clinical behaviour. Although clonal proliferations of lymphocytes are sometimes observed in infectious diseases and in elderly normal individuals, these commonly consist of normal T lymphocytes clonally expanded by specific antigens[28,29]. Clonality does not prove that LCH is a 'cancer,' but the results challenge laboratory-based scientists to try to identify relevant somatic mutations.

More recently, the arguments in favour of a non-neoplastic origin for LCH have been set out by Nezelof and Basset[24] and can be summarized as follows. Histologically, LCH

Box 3 | **Interactions of the Nikolas Symposia**

Various groups exist throughout the world to promote an understanding of the histiocytosis-related diseases. These groups function either to promote basic and clinical research into the disease, such as the Histiocyte Society (http://www.histio.org/society/), or have been established as patient support and family support groups (http://greece.histiocytosis.info/, http://www.histiocytose.org/, http://www.histiozytose.org/, http://www.istiocitosi.org/html/, http://www.histio.nl/, http://www.lch.be/, http://www.histiocytos.se/). Other groups, such as the Histiocytosis Association of America (http://www.histio.org/association), the Histiocytosis Research Trust (http://www.hrtrust.org) and the Nikolas Symposium (http://www.niksym.org/) function to serve all three communities — patients and families, clinical researchers and basic researchers — in a combined effort to find a cure.

lesions are granulomatous and (even in 'late' disease) retain this granulomatous character rather than the cellular homogeneity of a malignant neoplasm. LCH cells characteristically resemble normal LCs rather than showing maturation arrest. The uniform distribution of LCH lesions, indicating orderly recruitment of the cells to tissues, is unlike the haphazard spread of malignant neoplasms. Regression of LCH lesions is frequent but rare in true malignancies. Finally, no cell line has been established from LCH cells either *in vitro* or by transfer into immunocompromised hosts.

Nevertheless, the symposia have continued to explore the view that LCH is a neoplasm with a spectrum of clinical manifestations varying from benign and spontaneously resolving to highly malignant and fatal. Several lines of evidence have contributed to this view. The first, already mentioned above, is the incidence of related second neoplasms, which is greater than would be expected by chance[9]. Moreover, there is evidence that up to 1% of probands have another first- or second-degree relative with the disease, and consanguineous parents have been associated with the disease[11], although this is a preliminary study requiring confirmation. These observations indicate the presence of a germline mutation (or mutations) in some individuals that predisposes to LCH and the associated malignancies. It would also be expected that genetic abnormalities would be detected in LCH lesions if these are transformed cells, and loss of heterozygosity has indeed been reported on chromosomes 1, 4, 6, 7, 9, 16, 17 and 22, detected by comparative genomic hybridization or microsatellite typing[30,31]. Although these data have been accrued independently of the symposia, another feature of tumour cells, their abnormal phenotype, has been documented by work stimulated by symposium discussions. Early on in histiocytosis research, the presence of placental alkaline phosphatase was demonstrated[25], but, more convincingly, high expression of *TP53* has been observed alongside other cell-cycle-related genes[32,33]. These data are certainly suggestive of an oncogenic process and the hypothesis can be advanced that LCH represents a spectrum of tumours ranging from benign to highly malignant. There are likely to be predisposing 'LCH susceptibility' genes and, in addition, the tumours might acquire somatic genetic abnormalities as they evolve from benign to malignant. Whether there are specific triggers for this process, in addition to smoking in adults, remains to be resolved.

How does LCH cause pathology?

An important feature of LCH is the irreversible damage to several organs that often occurs, especially the pituitary, lungs, liver and CNS. Individual meetings have considered the role of cytokines, chemokines, apoptosis, and tissue fibrosis and repair in causing the various manifestations of LCH (TABLE 1). The symposia have also devoted several sessions to discussion of aspects of the disease process that might lead to new therapies, including those that might prevent or ameliorate tissue damage.

Langerhans cells are the resident dendritic cells of the skin and are responsible for antigen uptake, processing and presentation. If inflammation occurs in the skin, the Langerhans cells become activated. They then take up and process antigens, and migrate to the draining lymph nodes, where they become interstitial dendritic cells and present antigen to T lymphocytes to initiate immune responses. These processes are controlled by cytokines and chemokines produced by basal keratinocytes, Langerhans cells themselves, endothelial cells and incoming inflammatory cells from the blood. The clinical signs and symptoms, as well as the morphology of LCH, indicate that disordered cytokine and chemokine production and responses are important in the pathogenesis of the disorder. The role of cytokines was discussed as early as the 3rd Nikolas Symposium[34].

Subsequent experiments by symposium participants and others have amply confirmed that LCH is characterized by a lesional 'cytokine storm', a term referring to both the high level and diversity of cytokines produced locally[35,36]. It is of special interest that the predominant source of haematopoietically relevant growth factors and regulatory and inflammatory cytokines in LCH lesions is actually the T cells. Up to 80% of the T cells in the LCH lesions prove to be memory helper T cells[37]. These express CD40 ligand (CD40L), a marker of activated T cells, whereas antigen-presenting cells express CD40. The CD40–CD40L interaction is known to activate T cells to produce cytokines, so it is likely that the interaction of $CD40^+$ LCH cells and $CD40L^+$ T cells in LCH potentiates the cytokine storm[38]. In any case, high levels of granulocyte–macrophage colony-stimulating factor (GM-CSF), tumour-necrosis factor-α (TNFα) and interleukin-3 (IL-3) are present in LCH and, together with other cytokines, function as chemoattractants to recruit eosinophils, neutrophils, macrophages and $CD34^+$ Langerhans cell precursors into the lesions[39].

This 'cytokine storm' in LCH lesions has several other consequences. First, even in the normal interaction of dendritic cells with T cells, cytokines secreted by dendritic cells after stimulation by pathogens[40] have an important role in inducing cytokine production by the T cells. Whatever the trigger for cytokine production by LCH cells, the cytokines will have a similar effect and provide an ideal microenvironment to prolong the viability of the interacting inflammatory cells by creating autocrine and paracrine loops. A second role of cytokines is to affect the differentiation of precursor cells, and altered differentiation might explain the features of the bone lesions so commonly seen in LCH. Appropriate cytokines can stimulate the development of macrophages, Langerhans cells or other types of dendritic cell from $CD34^+$ stem cells or circulating peripheral-blood monocytes[41,42]. Moreover, recent studies indicate that receptor activator of nuclear factor-κB ligand (RANKL) and macrophage colony-stimulating factor (M-CSF) induce normal bone-marrow progenitors to differentiate into osteoclasts. Moreover, multinucleate giant cells with the appearance of osteoclasts are a prominent feature of LCH lesions (FIG. 3).

In LCH, cytokines known to influence osteoclastogenesis, such as IL-1, IL-6, TNFα, RANKL, GM-CSF and M-CSF, are highly expressed[36,43]. LCH cells, and the T cells in close proximity to them, express RANKL. Moreover, LCH cells express

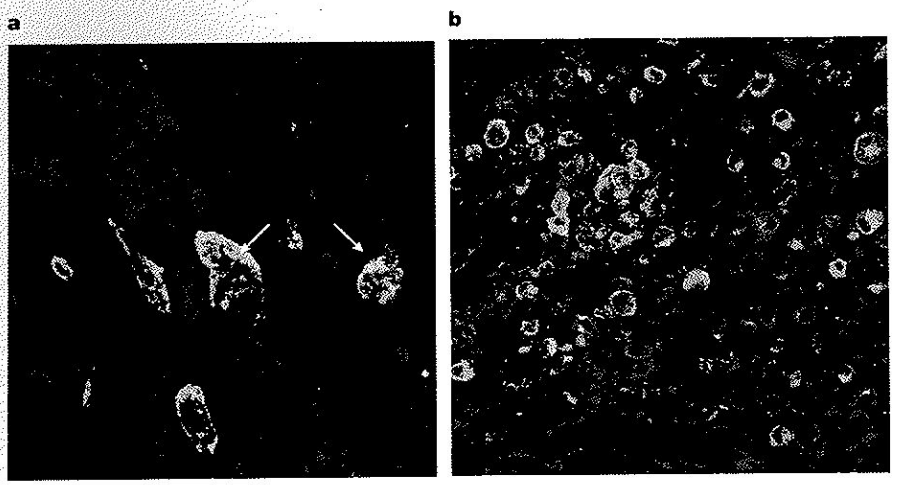

Figure 3 | **Immunohistology of Langerhans cell histiocytosis. a** | Section of Langerhans cell histiocytosis (LCH) tissue showing LCH cells stained with CD1a antibody in red and characteristic multinucleate giant cells (arrowed). Osteoclasts are stained in blue with antibody to cathepsin K. **b** | Section of LCH tissue showing LCH cells stained with antibodies to CD1a in red, tumour-necrosis factor-α in green and receptor activator of nuclear factor-κB ligand in blue.

M-CSF, whereas normal LCs do not[37]. Aberrant production of M-CSF by LCH cells together with RANKL–RANK interaction is therefore probably responsible for the large number of osteoclasts and the prominence of osteolysis in LCH[37] (FIG. 3). In addition, RANKL with GM-CSF generates dendritic cells, and the RANK–RANKL interaction provides a survival signal for these cells[42–44], which perpetuates the survival of LCH cells.

The above results stimulated discussion at the symposia on another aspect of cellular behaviour mediated by secreted factors — the migration of LCs, which is largely controlled by chemokines and their receptors. Chemokine and chemokine-receptor expression patterns might explain the predeliction of LCH for particular sites and the cellular composition of the lesions. Maturation of LCs is associated with the coordinated downregulation of receptors for inflammatory chemokines, for example CCR6, and the upregulation of receptors for constitutive chemokines such as CCR7. In normal physiology, this results in increased responsiveness of these cells to lymphoid chemokines, causing the migration of mature LCs to draining lymph nodes, where they are effective at activating naive and central-memory T cells[45,46]. Remarkably, despite the presence in LCH lesions of various inflammatory stimuli, such as TNFα, which should induce maturation, LCH cells remain immature, continue to express CCR6 and other markers of immaturity and do not upregulate CCR7 (REF. 37).

Why do LCH cells remain immature? *Ex vivo*, lesional LCH cells have the intrinsic ability to differentiate fully and mature[47], indicating that the lesional microenvironment is crucial to maintenance of the phenotype of LCH cells. *In vivo*, LCH cells lack expression of the correct chemokine receptors, and therefore cannot leave their peripheral-tissue sites. They accumulate locally because they remain sensitive to the ligand CCL20 (also known as MIP3α)[37]. In LCH, an autocrine loop appears to be established in which the LCH cells seem to be the main source of CCL20. They also express other inflammatory chemokines such as CCL5 and CXCL11 (also known as RANTES and I-TAC, respectively), resulting in attraction and accumulation of various other inflammatory cell types, especially T cells, into the lesions. The T cells use the same CCR6–CCL20 receptor–ligand pair, as well as CXCR3, the receptor for CXCL11.

Although the dendritic cells found in LCH lesions retain many features of normal skin LCs, such as expression of CD1a antigen, langerin and Birbeck granules, they are equally clearly abnormal[25,33]. Normally, cytokine production by LCs is triggered by pathogen-associated molecular patterns[40], while the factors that trigger cytokine production by LCH cells remain unknown. Furthermore, the lesional cytokine storm would be expected to induce differentiation from an antigen-processing to an antigen-presenting cell and migration of LCs to the draining lymph nodes. This does not occur in LCH. Therefore, the failure of LCH cells to differentiate and migrate produces a self-sustaining lesion, providing a microenvironment in which many cell types survive and precursors might differentiate to inappropriate effector cells and cause pathological damage.

Implications and future directions

The main difficulties in improving diagnosis and treatment of rare diseases are that governments and funding bodies often have other, higher priorities; individual doctors see too few patients to study the disease systematically. Collection of disease samples is also extremely difficult. For LCH, there are no known animal models and it has so far proved impossible to grow 'LCH cells' in short-term culture, much less produce any cell lines. Patients, relatives and doctors therefore suffer from relative 'scientific isolation'. The Nikolas Symposia have sought to overcome these problems by bringing together all these groups of individuals to discuss aspects of the disease more intensively and regularly than would otherwise be possible. The symposia have also attempted to avoid being just a 'talking shop'. On the last day of each meeting, an attempt is made to formulate key questions that have arisen from the discussion. Once they are back home, participants often attempt to resolve these questions by work funded from outside sources. These topics are also communicated directly to the Histiocyte Society and may be included in calls for proposals by that organization. At the last symposium, the question of how pathological Langerhans cells (LCH cells) differ from normal Langerhans cells was raised. Molecular methods for studying this at the level of the transcriptome (microarrays) and the genome need to be applied, and the meeting set in motion mechanisms to carry out this work. Recently, several patient support groups in Europe (Belgium, Greece and the United Kingdom) have joined forces to raise sufficient 'new' funds to initiate other substantive research projects. The first advertisment from the Histiocytosis Research Trust for the submission of research-grant proposals was placed in major scientific journals in autumn 2004.

Other 'rare disease' groups, notably the Dancing Eye (Opsomyoclonus) Syndrome Support Group and those dealing with disorders such as Fanconi anaemia, Blackfan–Diamond disease and severe aplastic anaemia, among other uncommon but chronic and debilitating diseases of young children, have also successfully used a model similar to that of the Nikolas Symposia, in which the formation of advocacy groups that foster scientific discovery and rational cures have been particularly effective. From

the point of view of scientific understanding, what has been achieved by the Nikolas Symposia? First, there is now a much better understanding of the clinical and pathological features of the disease than in 1989 (REF. 48). Second, scientists studying dendritic cells now realise that LCH is a human disease, which might help cast light on the functional and structural properties of normal Langerhans and associated cells. These insights might lead to a better understanding of the antigen-presenting arm of the immune system and to the best use of dendritic cells as weapons against other diseases, including cancer. Third, mechanisms of tissue damage in LCH are now better understood; this work will likely have relevance for understanding chronic inflammatory disorders[49]. However, LCH 'aficionados' realise that, even with the battery of powerful techniques now available to investigators, the underlying nature of LCH might be extremely difficult to pin down. These problems are regarded as a challenge by symposium contributors and increase their determination to pursue to its conclusion the Nikolas Symposium's logo, 'In Search of a Rational Cure'.

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doi:10.1038/nrc1632

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Acknowledgements
The authors thank the entire Kontoyannis family, especially Elizabeth, Paul and Nikolas, for their undying enthusiasm and practical support for the Nikolas Symposia. They would also like to thank D. Moustaka for her dedication as the secretary of the symposium series.

Competing interests statement
The authors declare no competing financial interests.

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