

HISTIO *NEWS*



Research • Education • Support

REPORT ON RESEARCH

FROM THE PRESIDENT

The *Encyclopedia and Dictionary of Medicine, Nursing and Allied Health* defines research as "the systematic, rigorous investigation of a situation or problem in order to generate new knowledge or validate existing knowledge."

The Histiocytosis Association of America directly funds research in two areas: basic science and clinical science. Basic science research is the "through the microscope" kind that increases knowledge. Clinical science research directly involves the treatment of patients. Basic and Clinical research depend on each other. Information learned by basic scientists helps clinicians better understand and treat the disease. In turn, clinicians help pose new questions for research.

The Association has now directly funded eighty-nine projects in either clinical or basic research. But, did you know that there are other ways we encourage and accomplish research, ways that may not be immediately apparent to the public eye. For example, the Association staff is responsible for managing the administrative duties and tasks for the Histiocyte Society. We plan, organize and manage their yearly scientific symposia (whose primary goal is to generate new knowledge and validate existing knowledge), and oversee the management of the membership (for more details on this topic, see page 3 of this newsletter).

Other ways that the Association encourages research include:

- ✧ Recruiting scientists, physicians, and other medical personnel to become involved in the Histiocyte Society and their efforts,
- ✧ Raising awareness in the National Institutes of Health with the aim of obtaining government commitment to research into the histiocytoses,
- ✧ Directly participating in the research process as the appointed North American Data Collection Center for both the LCH-III and HLH-2004 Treatment Protocols,
- ✧ Collaborating with other international organizations to develop and maintain a unified research direction, and
- ✧ Educational outreach at scientific meetings such as the American Society of Pediatric Hematologists/Oncologists (ASPH/O), the International Society of Pediatric Oncologists (SIOP), the American Society of Hematologists (ASH) and the American Society of Clinical Oncologists (ASCO).

These efforts can only continue and be successful with the support of Association members. My thanks go out to those who have gotten involved; and those who haven't, why not call the Association and find out what you can do to help.

WHAT'S INSIDE

WELCOME2

ANNUAL MEETING OF THE HISTIOCYTE SOCIETY

Secretariat's Office	3
President's Report.....	4
Society Leadership.....	4-5
Meeting Overview	6
Agenda.....	10
Scientific Prizes	14
Special Reports.....	16

RESEARCH & EDUCATION

Research Project Updates	18
NIH Network.....	20
Clinical Trials.....	20
Perforin/NK Function.....	21
HAA Symposium.....	22
Scientific Publications	24

DONATIONS21

ANNOUNCEMENTSback

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The Histiocytosis Association of America is an international partnership of parents, patients, physicians and friends bound together by their mutual interest in histiocytic disorders.



In an effort to compensate for the shortage of information on the disorders and the small number of individuals and families dealing with them the Association provides a variety of educational and emotional support programs to its members, as well as other interested parties.

In addition, the Association promotes scientific and medical investigation into histiocytic disorders through its research program with the aim of establishing better treatments, cures, and prevention of the diseases.

BOARD OF TRUSTEES

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HISTIOCYTE SOCIETY SECRETARIAT'S OFFICE

Jeffrey Toughill and the staff at the Histiocytosis Association of America manage the Office of the Secretariat for the Histiocyte Society. It was nearly fifteen years ago that this partnership was forged in order to free Society members from administrative duties and allow them to focus solely on research and treatment of the histiocytoses. The partnership gives the Association a direct link to the physicians and research of the Society. The Secretariat is responsible for the every-day functions of the Society that include collecting membership dues, distributing materials, producing their annual newsletter, and planning and managing annual meetings.

GOALS

The goals of the Histiocyte Society are:

- ▶ To improve the state of knowledge of the histiocytic disorders and welfare of patients, and their families, with these disorders;
- ▶ To promote, facilitate and carry out research in histiocytic disorders;
- ▶ To facilitate and provide a forum for health care professionals for effective communication concerning these aims;
- ▶ To promote education and to educate physicians and scientists and others in matters related to the histiocytic disorders;
- ▶ To advise lay organizations in educational and other matters concerning histiocytic disorders; and
- ▶ To collaborate with organizations with common aims.

Ultimately, the Society's goal is to better understand the cause and pathogenesis of the histiocytoses, and disseminate that information to physicians caring for patients with these diseases.

SOCIETY MEMBERSHIP

Membership in the Society is open to medical professionals who are actively working in the field of hematology/oncology. Membership applications are reviewed annually for approval and require a current Society member's sponsorship.

Currently there are nearly 200 members from 30 different countries. Newsletters, membership directories, and online technologies facilitate information and communication among Society members. This network allows those interested in the histiocytic disorders to act as a cohesive group.

HISTIOCYTE SOCIETY OFFICE OF THE SECRETARIAT

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RESEARCH

The Society is actively involved in international research to develop improved treatment approaches for patients with Langerhans cell histiocytosis and other histiocytic disorders. The Histiocyte Society has established guidelines for the treatment of these disorders. The most recent include the:

- ▶ LCH-III: Langerhans Cell Histiocytosis Third Study;
- ▶ HLH-2004: Hemophagocytic Lymphohistiocytosis Study;
- ▶ LCH-CNS: Langerhans Cell Histiocytosis and Central Nervous System disease; and
- ▶ LCH-S-98: Treatment Protocol of the Langerhans Cell Histiocytosis Salvage Therapy Group.

These treatment protocols are distributed by the Society to physicians who are engaged in treatment of histiocytic disorders and who wish to participate by registering patients on the studies.

THE SOCIETY AND THE ASSOCIATION

The relationship between the Histiocytosis Association of America and the Histiocyte Society is unique and valuable. The members of the Histiocyte Society provide the Association with a door to information and assistance. Society members are eager and willing to speak at Association Educational Meetings and to review and proof Association materials for accuracy and clarity. In addition, the Society Executive Board invites Histiocytosis Association Board Members to attend their Annual Meetings so that the Association can always stay abreast of the latest and upcoming treatments for histiocytic disorders.

The following pages will guide you through the Histiocyte Society's XIX Annual Meeting and show you the efforts in which the members engage in the search for better treatments and a cure.

HISTIOCYTE SOCIETY EXECUTIVE BOARD

The Executive Board is the governing body responsible for operating and managing the Histiocyte Society. The Board meets twice a year, once during the Annual Meeting (usually held in September) and once in either February or March.

R. Maarten Egeler, *President*

Leiden University Medical Center - The Netherlands

Alexandra Filipovich, *Secretary*

Children's Hospital Medical Center - Cincinnati, Ohio USA

Nicole Grois, *Treasurer*

St. Anna Children's Hospital - Vienna, Austria

Jan-Inge Henter, *President-Elect*

Karolinska Hospital - Stockholm, Sweden

Jean Donadieu, *Member-at-Large*

Hospital Trousseau - Paris, France

Jorge Braier, *Member-at-Large*

Hospital Garrahan - Buenos Aires, Argentina

HISTIOCYTE SOCIETY PRESIDENT'S REPORT

Every year I am more and more impressed by the participants at the Histiocyte Society Annual Meeting, and especially this year in Philadelphia. One of my oldest friends in the field of histiocytic disorders wrote me about it; he congratulated the Society on a superb meeting and stated that the meeting was beautifully organized (thanks to Beth, Melissa, Kristy and Kristen from the Histiocyte Society Secretariat's Office in Pitman) with excellent science (thanks to all of the members of the Society).

Last year the Society held our mid-year Board meeting in Paris, thanks to Board Member Jean Donadieu who arranged the meeting. Besides the regular issues of new members, new members for committees, we discussed the never-solved issue of the financial climate of our Society. In light of the fact that the Society has just 150 to 200 members with a low membership fee, we do very well. Some members still have trouble affording the costs of the Annual Meeting Registration fee and the costs incurred to travel to and stay at a meeting. In order to make it a little easier for those colleagues, however, the Society Board proposed two travel stipends for colleagues who will present a poster or who have a oral presentation at the meeting. We know that the stipends will not cover their whole trip, but it is a starting point. Another financial "issue" is the clinical studies. Only with support of the Family Associations can we perform these studies. We just cannot find a better solution, but the two major clinical studies LCH in primarily Vienna and the HLH study in primarily Stockholm run on a yearly budget of \$130,000US. Furthermore, the Histiocytosis Association of America (also the Secretariat's Office in Pitman) is helping considerably with the enrollment of American patients. At the moment we do not have a solution for the coming years and will probably always rely on the support of the Family Associations. I have suggested that the next President of the Society rob a bank in Monaco, but this was found unacceptable by the whole

Board. Besides these issues however we are indeed not rich, but extremely healthy!

During our intense meeting, members of the Society take one evening to relax and enjoy being together at our Annual Banquet. This year's wonderful event was held in the Mütter Museum of Medical Oddities at the Philadelphia College of Physicians. We were also treated to a local Philadelphia favorite: a Mummers String Band!

At the dinner I compared our work within histiocytosis to Langerhans cell histiocytosis. We all know that LCH is a melting pot of cells, which is quite heterogeneous. I made a comparison! The main players in LCH are the Langerhans cells, the T-cells, the eosinophiles and the macrophages. The Langerhans cells in LCH are the key players and I would like to compare the Langerhans cells with our joined interest in histiocytic disorders. That is the reason that we are here. The eosinophiles should be compared to support. We have an extremely big support of the family associations all over the world. The macrophages and related cells, like multi-nucleated cells, are essential in the lesion. These cells, besides being responsible for a part of the signs and symptoms, they also clean debris. Because of their important role in LCH, I like to compare them to research. Essential for disease and essential for going to the next level. T-cells are heavily responsible for many of the signs and symptoms in LCH. Within the Society I would like to compare the role of the T-cells in LCH to the friendship with our group. T-cells are activated and unregulated and I feel that a big part of our success is based on open international collaboration and friendship. Whether I think of my friends in the field from Israel, Canada and the US, Sweden or Germany, Italy or Austria or Japan, I always feel extremely motivated when I have interactions with this group. I really cherish this friendship.

R. Maarten Egeler, M.D., Ph.D.

HISTIOCYTE SOCIETY SPECIAL COMMITTEES

WORKING GROUPS

The Histiocyte Society has established a number of small working groups that deal with particular areas of histiocytic disorders. In addition to other responsibilities, these groups gather patient data and create and manage treatment protocols.

HLH Study Group: Jan-Inge Henter, Chair
Karolinska Hospital—Stockholm, Sweden

Epidemiology Study Group: H. Stacy Nicholson, Chair
Oregon Health & Science University—Portland, Oregon USA

CNS Study Group: Nicole Grois, Chair
St. Anna Children's Hospital—Vienna, Austria

LCH-S Study Group: Sheila Weitzman, Chair
The Hospital for Sick Children—Toronto, Ontario Canada

LCH III Study Group: Helmut Gadner, Chair
St. Anna Children's Hospital—Vienna, Austria

Adult Histiocytosis Study Group: Maurizio Aricó, Chair
Ospedale dei Bambini—Palermo, Italy

Pathology Study Group: Ronald Jaffe, Chair
Children's Hospital—Pittsburgh, Pennsylvania USA

Malignant Histiocytosis Study Group: Peter Bucsky, Chair
Medical University of Lubeck—Lubeck, Germany

Late Effects Study Group: Riccardo Haupt, Chair
Gaslini Children's Hospital—Genova, Italy

THE SCIENTIFIC COMMITTEE

The Scientific Committee is made up of seven elected members of the Histiocyte Society. Their two-year terms are staggered. A member may serve no more than six (6) consecutive years if re-elected. The committee selects its own chairperson from its membership; that chairperson will lead the Committee and serve as liaison for communication with the Society President. The Committee is responsible for reviewing proposals for research and related activities according to guidelines as developed by the Board, and for making recommendations to the Board; they also present the Society Board with annual reports and plans concerning the Society's research activities.

Robert Arceci, Chair
Johns Hopkins Oncology Center—Baltimore, Maryland USA

E. Marion Schneider
Universitätsklinikum Ulm—Ulm, Germany

Jean Francois Emile
Paul Brousse Hospital—Villejuif, France

Bengt Fadeel
Karolinska Institute—Stockholm, Sweden

Michael Weintraub
Hadassah University Hospital—Jerusalem, Israel

Eishii Ishii
Saga Medical Center—Saga, Japan

Stephan van Gool
University Hospital Gasthuisberg—Leuven, Belgium

THE EDUCATION COMMITTEE

The Education Committee is made up of five elected members of the Histiocyte Society. Their two year terms are staggered. A member may serve no more than six (6) consecutive years if re-elected. The committee selects its own chairperson from its membership; that chairperson will lead the Committee and serve as liaison for communication with the Society President. The Committee suggests topics for educational sessions at meetings; reviews, grades, and selects abstracts for presentation at Annual Meetings; monitors the Histiocyte Society Constitution and By-laws for necessary changes and/or amendments; drafts changes and/or amendments for the Constitution and/or By-laws; and presents the Executive Board with an annual assessment of the Constitution and By-laws.

Maurizio Aricó, Chair
Ospedale dei Bambini—Palermo, Italy

Vasanta Nanduri
Watford General Hospital—Watford Hertfordshire, UK

Kevin Windebank
Sir James Spence Institute—Newcastle upon Tyne, UK

Finn Wesenberg
National Hospital—Oslo, Norway

Kim Nichols
University of Pennsylvania - Philadelphia, PA USA

XIX ANNUAL HISTIOCYTE SOCIETY MEETING OVERVIEW

The 2003 Histiocyte Society meeting, held in Philadelphia, commenced with a very enthusiastic group of approximately 100 scientists and research physicians. Maarten Egeler, MD, PhD, current President of the Society, gave a brief and inspiring history of the evolution of this organization, which began 19 years ago with a mere 20 members. The Society is now comprised of about 200 members, some of whom travel across the world to meet once a year and share their latest ideas and findings about the histiocytoses. Dr. Egeler's enthusiasm proved infectious, as we eagerly anticipated hearing about the latest developments in histiocytosis research.

A large meeting room was set up with 15 poster presentations. Physicians and scientists from Italy, Japan, U.S., Germany, Argentina, Canada, Brazil and Norway displayed and presented their research findings on a number of topics related to the histiocytoses.

The first guest speaker was Maurizio Arico, M.D. from Palermo, Italy. In his presentation, entitled "**Genetics of Langerhans Cell Histiocytosis**," he stated that LCH is usually nonfamilial; however, it is occasionally seen in twins or siblings and has been known to skip generations. Although it is believed that there is no LCH gene per se, there have been cases of "familial clustering."

Although the pathogenesis of LCH is still unknown, there are new possibilities for research that are being explored, including the study of the DNA repair process. Various other topics were discussed throughout the morning, including vaccinations, epidemiology, bone lesions, bone marrow transplant, and liver involvement in LCH.

It is estimated that 15-35% of children with LCH have liver involvement. Biliary cirrhosis associated with sclerosing cholangitis is a relatively uncommon problem, but when it occurs, it can have devastating consequences requiring liver transplantation.

A study was done on the incidence of LCH in Stockholm County, Sweden from 1992-2001. In a previous study done from 1975-1989 in Denmark, it was estimated that 5.4 out of a million per year children were diagnosed with LCH. In this new study, the number is estimated at 8.9 out of a million per year children, which suggests a 60% increase of patients with single-system disease, 70% increase of patients with multisystem disease, and a 50% increase in patients with risk-organ involvement. It is believed that the increased numbers are due to the fact that a small, well-defined cohort of children was studied, so the risk of "missing" patients is much smaller than with a nationwide study.

The **most frequent sites of LCH bone involvement** include skull, femur, pelvis, tibia, jaw, humerus, vertebra, and rib, in order of frequency. Radiologically, LCH is sometimes mistaken for malignancy. CT or MRI scans cannot distinguish



Jim Whitlock, Ken McClain, Scott Baker, Joseph Neglia & Michael Jordan

LCH versus malignancy in the bone. Only a biopsy conclusively provides a diagnosis of LCH.

The question of whether **vaccinations** can induce LCH was next presented. Although vaccinations are known to trigger primary and secondary immune responses, there is currently no argument to modify the vaccination program in LCH children who are not on immunosuppressive chemotherapy.

Next, **bone marrow transplantation used as salvage therapy for resistant multisystem LCH** was discussed. Immunoregulatory dysfunction and the related expression of tissue-destructive cytokines are believed to be the cause of refractory and progressive LCH, which continues to be difficult to treat and may not respond to standard therapy. Langerhans cells originate from bone marrow precursors. BMTs have been implemented in the past, but conventional myoablative conditioning regimens carry a high risk of fatal toxicity. However, reduced-intensity transplant conditioning drugs may improve outcome in some children, although clinical trials will be needed to determine whether this approach is better.

On the afternoon of the first day of meetings, Robert Arceci, M.D. from Johns Hopkins provided an update on the **Nikolas Symposium 2003 proceedings**. The major topic at this "think tank" in Greece was whether LCH is a neoplastic or immunodysregulatory disorder. According to Dr. Arceci, although LCH is known to affect all ages, the question is how it should be categorized. There is indication of genetic predisposition in some cases. LCH has some characteristics consistent with neoplasm, and some are consistent with an immunodysregulatory disorder. Isolated pulmonary LCH is not clonal -- it can wax, wane, and completely regress without treatment in some instances. However, LCH is clonal and proliferative. The possibility of a viral etiology for LCH is being investigated. Researchers have debated whether LCH is a neoplastic process, an immunodysregulatory disorder, or a

reactive process to a viral agent. Most evidence now supports a primary defect in the Langerhans cell that results in a clonal myeloproliferation of abnormal cells. Understanding the etiology of LCH will impact future diagnosis, treatment and possibly prevention of this illness.

Other afternoon topics included long-term consequences from LCH, neonatal multisystem LCH, HLH, and salvage treatment possibilities for LCH.

There are some estimates that as many as 75% of LCH patients develop **long-term sequelae**. A method of scoring has been devised to assess the degree of impairment caused by sequelae of disease and treatment. Long-term sequelae include symptoms such as morbid obesity, hearing loss, failure of muscular coordination, learning disabilities, psychological/behavior problems, and cosmetic problems. Utilization of this method of assessing sequelae can be useful in providing appropriate support and treatment strategies for patients.

Data from the Vienna Group was discussed, in terms of **neonates with LCH**. Within the first four weeks of life, skin is the cardinal manifestation of LCH, either isolated or part of multisystem disease. In a recent study in Vienna, 88% of the neonatal patients initially showed skin involvement. There seems to be a predominance of multisystem involvement in neonates, as well as a more unpredictable course and a higher incidence of risk-organ involvement. Given the possibility for clinically "silent" involvement of other organ systems, thorough clinical, laboratory and x-ray evaluation is recommended in all neonates with LCH.

The **pathophysiology of HLH** remains poorly understood. There is a good animal model. While progress has been made in treating this disorder during the last decade, future progress may likely depend on a greater understanding of how HLH develops. Mutations in the perforin gene have been associated with HLH in about 20 to 30% of cases. Perforin is important for the immune-mediated destruction of target cells.

Progress is being made in the understanding of HLH through animal models.

In the last presentation of the day, the topic was the association between 2CdA and Ara-C as a rescue treatment for refractory LCH. Along with 2CdA alone, this combination has been shown to have activity against refractory LCH, although the true response rate has still not been defined.

After an exciting first day, we convened early the next morning. The first presentation addressed **sclerosing cholangitis in children with LCH**. Sclerosing cholangitis is a chronic disease with inflammation and obliterative fibrosis of the bile ducts of the liver. It was first recognized in children in 1980. Its etiology remains obscure, but an immune mechanism is suspected. In LCH, it is believed to be a histiocytic infiltration leading to obliterative fibrosis of bile ducts and secondary biliary cirrhosis. Sclerosing cholangitis can precede the diagnosis of LCH. Approximately 90% of children with this are over age 3 months. It is often asymptomatic for a long time. Symptoms include fatigue, pruritus (itching), abdominal pain, jaundice, and hepatomegaly (liver enlargement). Liver function tests show an increased GGT level and increased serum bile acids. In a study of 56 cases, 40% developed liver failure with poor prognosis. No treatment has been proven to halt or reverse the disease progression.

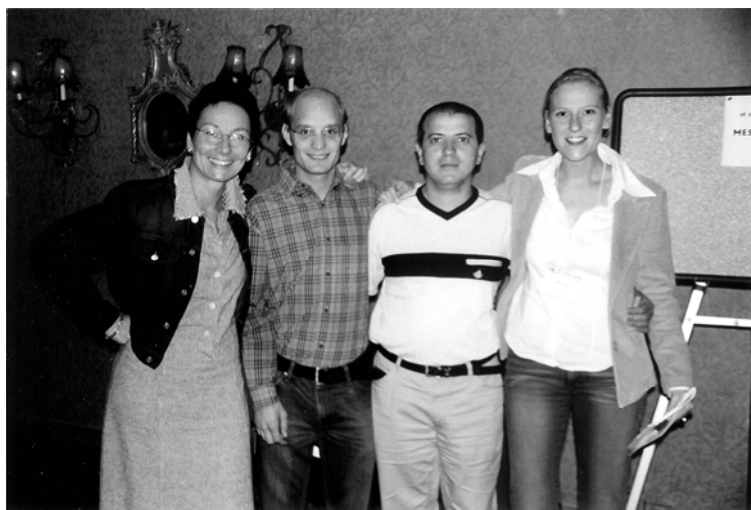
Steroids appear to have little influence, and chemotherapy has not been proven to help. However, ursodeoxycholic acid (UDCA) seems to help in the short term. Currently, the only effective therapy is liver transplantation and should be considered before evidence of liver failure. The 10-year survival rate post liver transplantation is 80%. Early diagnosis is essential to allow early treatment with UDCA that may halt disease progression.

Other topics presented throughout the day included a clinical trials update, uncommon histiocytic disorders, and the role of NK cell activity in HLH.

The LCH-III Treatment Protocol, which began in April of 2001, has eight participating subcenters in Spain, Germany, France, Scandinavia, USA/Canada, Italy, Spain and Argentina. The study center and database are located in Vienna, Austria.

The goal of this trial is to decrease mortality in patients with risk organ involvement. It introduces methotrexate as a new agent in the initial treatment and recommended an early switch to the salvage protocol when needed. It also prolongs treatment from 6 to 12 months. A total of 399 patients have been registered in this trial. The number of patients registered is below the expectation, and this compromises the study. There is a need for more registered patients and more randomization.

The LCH CNS Clinical Trial, instituted in March of 2000, was able to recruit only 23 CNS patients. Although melatonin was tried in 8 patients, incomplete data reporting and lack of



L to R: Nicole Grois, Manuel Steiner, Milen Minkov, Edda Unger
From St. Anna Children's Hospital, Vienna Austria

compliance forced the trial to end. This was the first cooperative effort of the Society for CNS-LCH. It has succeeded in increasing awareness of the problem, establishing collaboration with selected centers, and starting a collection of patient data which will help with future research. There will be a new LCH CNS 2003 trial; however, there are no treatment recommendations as of yet.

There are three types of CNS lesions:

- 1) hypothalamic/pituitary – most common;
- 2) tumorous/vascular lesions; and
- 3) neuro-degenerative lesions.

Recommended therapy for hypothalamic/pituitary lesions is systemic chemotherapy, as opposed to irradiation. 2CdA seems to work for these kinds of lesions. Tumorous/vascular lesions usually respond to the LCH III treatment protocol.

Therapy for neurodegenerative disease is difficult. Possibilities include nonsteroidal anti-inflammatory agents, cyclosporine, thalidomide, Trental, and tacrolimus. Children with DI (Diabetes Insipidus), who have not been diagnosed with LCH, should not be treated, since the underlying illness could be something other than LCH and would need to be treated differently. The underlying disease should be identified first. According to the speaker, "We will continue sharing ideas and experiences. We can only solve this when we work together."

In the **LCH-S-98 Salvage Protocol**, one of the objectives was to study the response to 2CdA in poor-risk and intermediate-risk patients who did not respond to the LCH-III protocol. A total of 88 patients were registered for this trial in Vienna. An approximately 30-to-40%-response rate was observed. The arm for high-risk patients is now closed to accrual. The trial for low-risk, chronically reactivating patients remains open. Hopefully a new protocol will be developed within the next year for high-risk patients.

Dr. Milen Minkov from Vienna, Austria next spoke about reactivation in patients with multisystem LCH at diagnosis. A trial for this group of patients is being discussed and considered as a means of preventing neurodegenerative disease.

The **HLH-94 (Hemophagocytic Lymphohistiocytosis) Treatment Protocol** trial was the next topic. This trial started in 1995, and a total of 428 patients were registered, with 223 studied. Most patients were registered from Germany, Czech Republic, Austria and Japan, with an increasing number from North America.

Requirements for participants were that they be less than 15 years old with no previous treatment. After bone marrow transplantation, the survival rate of FEL (Familial Erythrophagocytic Lymphohistiocytosis) patients is estimated to be 64%. These results are much better than expected when this trial began. After stem-cell transplant, of 55 survivors, approximately 83% have normal ability to function/play. Two-

thirds of transplant patients are long-term survivors.

The HLH-94 protocol has proved effective, and the major aims were accomplished. A new protocol, HLH-2004, has been developed. The goals are to improve survival and our understanding of the disease. The new treatment is based on the HLH-94 treatment with some minor modifications.

Proposed changes include:

- 1) cyclosporin being started at diagnosis, rather than at 8 weeks,
- 2) no treatment beyond week #40, and
- 3) stem-cell transplant as soon as possible.

"**Uncommon Histiocytic Disorders**" was then presented. The more uncommon histiocytic disorders include Juvenile Xanthogranuloma (JXG), adult xanthogranuloma, Rosai Dorfman, and Erdheim-Chester disease. These disorders, like LCH, are defined by an accumulation of histiocytes, but they differ pathologically.

Juvenile Xanthogranuloma (JXG) is one of the more common non-LCH histiocytic disorders and may involve skin only or extracutaneous sites. The majority of JXG patients present before age 2. Cutaneous JXG is usually a self-limited condition with gradual, spontaneous regression. The most common site of extracutaneous JXG is the eye. Symptoms can include glaucoma, hyphema (hemorrhage in the anterior chamber of the eye), erythema (redness) and tumor of the iris. JXG may also involve subcutaneous tissues, CNS, liver, spleen, kidney and lung. Bone involvement is rare. JXG may spontaneously regress and has an excellent prognosis, although fatalities have been reported. Surgical removal is curative for single lesions. Most children with multiple JXG require no treatment.

Adult xanthogranuloma commonly occurs as a single lesion, mostly in the head and neck region. Adult XG is less likely to resolve spontaneously.

Sinus histiocytosis with massive lymphadenopathy (SHML/Rosai Dorfman) most commonly presents with bilateral painless cervical lymphadenopathy with fever, night sweats, malaise, and weight loss. Extranodal tissue such as skin, soft tissue, upper respiratory tract, bone, eye, and retroorbital tissue can be affected in 43% of cases. Skin involvement occurs commonly; however, disease limited to skin is uncommon. The clinical course of SHML is unpredictable with periods of worsening and remission, which may last years. The outcome is usually good; however, approximately 5% of patients die of this disease. Treatment is necessary when a vital organ is involved or when airway obstruction occurs. Steroids and different chemotherapies have provided varying success.

Erdheim-Chester disease usually affects adults. It is a histiocytic infiltration of multiple organs, including bone, skin, orbit and lung. Symptoms can include bone pain, xanthomata (small skin lesions), exophthalmos (abnormal protrusion of the eye), diabetes insipidus and lung disease.

SOCIETY ANNUAL MEETING

A study was done of 58 cases of LCH in France and postmortem findings were presented next. The two major causes of death were related to hematological dysfunction and sclerosing cholangitis. New chemotherapy options could improve prognosis in patients with hematological dysfunction. Biliary cirrhosis/sclerosing cholangitis should be evaluated for liver transplant prior to the onset of signs of liver failure.

“Sequential LCH and Rosai Dorfman (RD) – A Case Report.” LCH is thought to be a dendritic cell process, while RD is thought to be macrophage related. The pathogenesis of both LCH and RD are unknown. Discussion centered on a child with recurrent multisystem LCH who subsequently was found to have RD. This finding suggests an etiologic relationship between the two diseases, and this relationship will be explored further.

Familial HLH is a fatal disease in infancy and early childhood, and BMT/SCT (stem cell transplant) is the only known curative treatment. It is difficult to distinguish whether the patient has the primary or secondary form of HLH, especially if there is no family history and no perforin gene mutation. It is believed that classification of NK function deficiency can be valuable for doctors in deciding whether a patient with HLH needs a BMT/SCT. The finding of this study is that patients with NK cell activity, type 3, will most likely need BMT/SCT.

Every year, the Histiocytosis Association of America, in conjunction with the Histiocyte Society, awards a prize for the best clinical article at each Annual Meeting. It is given in honor of Dr. Mark Nesbit, renowned pediatric oncologist, teacher, and supporter of the many families dealing with histiocytic disorders. The prize is awarded to a physician or scientist who is carrying out clinical research to the therapy, biology, or pathogenesis of one of the histiocytic disorders. The goal of the award is to stimulate and promote the activities of clinical scientists from all around the world to study specific aspects of these puzzling diseases. The winner for 2003, chosen by the Education Committee, is Manuel Steiner, M.D. from St. Anna's Children's Hospital in Vienna, for his research of multisystem LCH in neonates.

The Nezelof award was presented next. This award is given in honor of Dr. Christian Nezelof, renowned pathologist, investigator, teacher, founding member, and first President of the Society, to a physician or scientist who is carrying out basic research on the therapy, biology, or pathogenesis of one of the histiocytic disorders. The winner for 2003 is Michael Jordan, M.D., from the University of Colorado, Denver, for his research on HLH.

In closing, Histiocyte Society President Maarten Egeler thanked all of the presenters for their hard work and dedication to finding a cure. “Scientists and doctors working in other fields are contributing to our knowledge. Clinical studies and scientific research bring our level of understanding to higher and higher levels.”



From L to R: Dr. Bengt Fadeel, Dr. Jan-Inge Henter, Dr. Alexandra Filipovich, & Mr. Alexis Hult.

I believe that each year, major progress is made in the research of these disorders. I am always inspired and amazed by the sense of integrity, enthusiasm, and dedication that I witness in these Society meetings. I hope that we Association members will continue to fully support this much-needed research. They are depending on our financial support, just as we are depending on them to keep working hard on our behalf.

This is a true partnership. We are all striving toward the same goal – a cure!

Sandra Conway Warren, Website Editor
Histiocytosis Association of America, Histiocyte Society

This article is a synopsis of oral presentations given by various physicians and contains "opinions" in some cases. It is not intended to diagnose any condition or recommend treatment. If anyone has questions about what is written here, the disease, treatment or any other medical question, the treating physician should be consulted. Opinions in this article should not be interpreted as the official position of the

SPECIAL THANKS

Many thanks are extended to
Sandra Warren
for chronicling and reporting
the details of both the
Histiocyte Society Annual Meeting
and the
Histiocytosis Association of America National
Histiocytic Disorders Symposium.

MEETING AGENDA

Annual Meetings of the Histiocyte Society usually run for three days. Members of the Society, as well as others interested in the field, submit abstracts (a summary) of their recent work to the Society Education Committee for grading four months prior to the meeting. Abstracts deemed worthy are then placed into specific sessions for presentation at the Annual Meeting. These presentations are then given orally during four scientific sessions or visually during one poster session. There are an average of forty abstracts presented at a meeting. Additional lectures are given by guest speakers. These speakers are invited to attend by the Executive Board of the Society. The full text of the abstracts listed here will be available in the medical publication ***Pediatric Blood and Cancer*** (Vol. 43, Issue 2). You can find this journal at your local library or educational institution.

DAY ONE – THURSDAY, SEPTEMBER 18th

0800 – 0930

Scientific & Education Committee Meetings
Epidemiology/Late Effect Study Group Meeting
Poster Presentation Set-up

0930 – 0945

OPENING CEREMONIES
Histiocyte Society President R. Maarten Egeler

0945 – 1030

GENETICS OF LANGERHANS CELL HISTIOCYTOSIS
Maurizio Aricó, Guest Speaker
 Ospedale dei Bambini, Oncoematologia Pediatrica, Palermo
 ITALY

1045 – 1200

SCIENTIFIC SESSION I – CLINICAL LCH
 Jean Donadieu and Nicole Grois, *Moderators*

LIVER INVOLVEMENT IN LCH. The French experience.
 L Marti, C Thomas, JF Emile, F Bernard, D Plantaz, T Genereau, L Brugieres, G Leverger, J Donadieu, D Debray For the French LCH Study Group. Hopital Bicêtre. Le Kremlin Bicêtre CHU Nantes, CHU Montpellier, Hôpital Trousseau, Paris; CHU Grenoble, Institut Gustave Roussy, Villejuif; Hopital P Brousse, France.

THE INCIDENCE OF LANGERHANS CELL HISTIOCYTOSIS IN CHILDREN IN STOCKHOLM COUNTY, SWEDEN 1992-2001.

Jenny Karis, Cecilia Bernstrand, Bengt Fadeel, Jan-Inge Henter. Childhood Cancer Research Unit, Department of Woman and Child Health, and Division of Toxicology, Institute of Environmental Medicine, Karolinska Institute, Stockholm, Sweden.

RADIOLOGICALLY AGGRESSIVE LANGERHANS CELL HISTIOCYTOSIS BONE LESIONS (LCH) IN CHILDREN.
 Loretta Lau, Kyra Stuurman, Andreas Roposch, Wendy Doda, Sheila Weitzman. Division of Haematology/Oncology, The Hospital for Sick Children (HSC), Toronto, Canada

VACCINATION COULD INDUCE LCH.

J Donadieu, V Doireau, N Aladjidi, L Brugieres, O Oberlin, C Thomas, JF Emile for the French LCH Study Group. Hôpital Trousseau, Paris; Hôpital, Pau, Hôpital Pellegrin, Bordeaux; Institut Gustave Roussy, Villejuif; Hopital P Brousse, France.

BONE MARROW TRANSPLANT AS SALVAGE FOR MULTISYSTEM LANGERHANS CELL HISTIOCYTOSIS.

Kanchan Rao, Vasanta Nanduri, Penelope Brock, Paul Veys, David Webb. Great Ormond Street Hospital for Children, London, United Kingdom.

UNEXPECTED COURSE IN REFRACTORY MULTISYSTEM LANGERHANS CELL HISTIOCYTOSIS (LCH) FOLLOWING PERIPHERAL STEM CELL TRANSPLANTATION - A CASE REPORT.

Edda Unger¹, Susanne Matthes-Martin¹, Anita Lawitschka¹, Christina Peters¹, Nicole Grois¹, Milen Minkov¹, G. Surico², Manuel Steiner¹, Helmut Prosch¹, Helmut Gadner¹. ¹St. Anna Children's Hospital, Vienna, ²Department of Pediatrics, University of Bari.

1300 – 1315

NIKOLAS SYMPOSIUM UPDATE: Robert Arceci, *Speaker*

1315 – 1500

POSTER ABSTRACT PRESENTATION SESSION
 Kenneth McClain, *Moderator*

PROGRESS REPORT OF THE PROJECT: "CONSTRUCTION OF A RETROVIRAL VECTOR CONTAINING THE PERFORIN1 GENE".

R. Clementi¹, L. Dupré², A. Aiuti², G. Andolfi², R. Maccario³, F. Locatelli³, M. Aricò⁴, C. Danesino¹, and M.G. Roncarolo². ¹Genetica Medica, Università di Pavia e IRCCS S. Matteo, Pavia, Italy; ²HSR-TIGET, Milano, Italy; ³Oncoematologia Pediatrica, IRCCS S. Matteo, Pavia, Italy; ⁴Oncoematologia Pediatrica, Ospedale dei Bambini G.Di Cristina, Palermo, Italy.

LONGITUDINAL FOLLOW-UP OF PATIENTS WITH EPSTEIN-BARR VIRUS (EBV) -ASSOCIATED HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH): THE RELATIONSHIP BETWEEN EBV-HLH AND THE DEVELOPMENT OF CHRONIC ACTIVE EBV INFECTION.

S Imashuku, T Teramura, H Tauchi, Y Ishida, Y Otoh, M Sawada, H Tanaka, A Watanabe, Y Tabata, A Morimoto, S Hibi, J-I Henter, HLH Registration Center in Kyoto and Stockholm.

CLONALITY ANALYSIS OF LESIONAL T-CELLS IN PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS.

Masahiro SAKO, Nobuhiro KIMURA¹, Takefumi ISHII, Yuko OSUGI, Ichiro ICHINOSE¹ and Ken NAKAMURA² Department of Pediatrics, Osaka City General Hospital, Osaka, Japan, ¹Department of Internal Medicine¹, ¹st Department of Biochemistry², Fukuoka University School of Medicine, Fukuoka, Japan.

MEETING AGENDA continued

2-CHLORODEOXYADENOSINE (2-CDA) FOR THE TREATMENT OF REFRACTORY OR RECURRENT LANGERHANS CELL HISTIOCYTOSIS IN PEDIATRIC PATIENTS.

Kimo Stine, Robert Saylor, Suzanne Saccente, David Becton, Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, AR.

TREATMENT OF FAMILIAL HEMOPHAGOCYTIC LYMPHO-HISTIOCYTOSIS WITH A MONOCLONAL ANTIBODY AGAINST INTERLEUKIN-2-RECEPTOR.

K. Beutel, M. Schneider, G. Janka. Pediatric Hematology and Oncology, University of Hamburg, Germany; Department of Experimental Anesthesiology, University of Ulm, Germany

RISK FACTOR ANALYSIS IN RISK MULTISYSTEM LANGERHANS CELL HISTIOCYTOSIS.

Jorge Braier, Diego Rosso. Guillermo Chantada, Antonio Latella, Blanca Balancini, Mario Ripoli, Julio Goldberg. Hospital de niños J.Garrahan and CESAC N° 5. Buenos Aires, Argentina.

ANALYSIS OF SOLUBLE CD154 (SCD154) IN THE SERA OF PATIENTS WITH LANGERHANS CELL HISTIOCYTOSIS (LCH)

Rumiko Ishii, A.Morimoto, S.Ikushima, T.Inaba, T.Sugimoto, S.Imashuku, Japan LCH Study Group.

RESPONSE TO THERAPY IN A PATIENT WITH COEXISTING LANGERHANS CELL HISTIOCYTOSIS (LCH) AND NEUROBLASTOMA EMPHASIZES THE NEED FOR THE ADDITION OF LCH-DIRECTED THERAPY.

Ronald M. Grant, Michael Capra, Ted Gerstle, Sheila Weitzman. The Hospital for Sick Children (HSC), Toronto.

THE NATURAL HISTORY AND LONG-TERM COMPLICATIONS OF PATIENTS WITH BONE LANGERHANS CELL HISTIOCYTOSIS

Kyra Eva Stuurman, Loretta Lau, Wendy Doda, and Sheila Weitzman. Division of Haematology/Oncology, The Hospital for Sick Children (HSC), Toronto, Canada

EDUCATION OF FAMILIES AFFECTED BY LANGERHANS CELL HISTIOCYTOSIS AND HEMOPHAGOCYTIC LYMPHO-HISTIOCYTOSIS: A MULTIDISCIPLINARY APPROACH.

Ruth Anne Herring, Michelle Lawson, Kenneth McClain, Terry Stanfield, Dana Swan. Texas Children's Cancer and Hematology Center, Houston.

SINUS HISTIOCYTOSIS WITH MASSIVE LYMPHOPATHY (ROSAI-DORFMAN DISEASE): TWELVE YEARS MULTI-CENTER EXPERIENCE.

Cristian Sanchez, Beatriz De Camargo, Wellington Mendes, Guadalupe Rey, Jorge Braier. Hospital J.P. Garrahan, R. Gutierrez, Buenos Aires. Argentina; Hospital do Cancer, Sao Paulo Brazil.

HEPATOSPLENIC CANDIDIASIS IN A PATIENT TREATED FOR LANGERHANS CELL HISTIOCYTOSIS DURING 10 YEARS.

Marit Hellebostad¹ and Arne Borthne², Departments of Paediatrics¹ and Paediatric Radiology², Ulleval University Hospital, Oslo, Norway

IDENTIFICATION OF AN HETEROZYGOUS PERFORIN MUTATION IN A PATIENT WITH LANGERHANS CELL HISTIOCYTOSIS.

R. Clementi, P. De Filippi, S. Scappaticci, C. Danesino, M.Aricò. Biologia Generale e Genetica Medica, Università di Pavia, and Oncoematologia Pediatrica, Palermo, Italy.

BENIGN DISEASE OF OSTEOLYSIS.

Naoko Kinugawa, Makoto Suzuki, Norio Suzuki, Toshiji Shitara, Yoshiaki Tsuchida, Atsushi Takahashi, Hiroyuki Kuwano. Department of Pediatrics, Showa University School of Medicine, Division of Hematology/Oncology and Division of Pediatric Surgery, Gunma Children's Medical Center, The first Department of Surgery, Gunma University Graduate School.

REDUCED INTENSITY ALLOGENEIC BONE MARROW TRANSPLANTATION FOR CHEMOTHERAPY RESISTANT LANGERHANS CELL HISTIOCYTOSIS WITH SCLEROSING CHOLANGITIS.

Takashi Kanazawa, Chitose Ogawa, Mitsuru Seki, Naoko Kinugawa*, and Akihiro Morikawa; Department of Pediatrics and Developmental Medicine, Gunma University Graduate School *Department of Pediatrics, Showa University School of Medicine.

1515 – 1645

SCIENTIFIC SESSION II: PRESIDENTIAL SYMPOSIUM ORAL ABSTRACT PRESENTATIONS

R. Maarten Egeler, *Moderator*

A “COMMON LANGUAGE” FOR ASSESSMENT OF LONG TERM MORBIDITY FROM LANGERHANS CELL HISTIOCYTOSIS.

Vasanta Nanduri, Gill Levitt, Penelope Brock, Jon Pritchard Great Ormond Street Hospital for Children, London and Royal Hospital for Sick Children, Edinburgh, United Kingdom.

LANGERHANS CELL HISTIOCYTOSIS (LCH) IN NEONATES.

M. Minkov, M. Steiner, H. Prosch, N. Grois, E. Unger, G. Janka, H. Gander. St. Anna Children's Hospital, Vienna, Austria.

LANGERHANS CELLS IN LCH EXPRESS INCREASED AMOUNTS AND UNIQUE TYPES OF CYTOKINE GENES.

Xiaotian Yan, John Hicks, Leif E. Peterson, and Kenneth L. McClain. Texas Children Cancer Center/Hematology Service, Pediatric Pathology, Department of Medicine, Baylor College of Medicine, Houston, TX.

LANGERHANS CELL HISTIOCYTOSIS, A PRIMARY VIRAL INFECTION OF BONE? HUMAN HERPES VIRUS 6 (HHV-6) LATENT PROTEIN DETECTED IN LYMPHOCYTES FROM PEDIATRIC PATIENTS.

Glantzbecker Michael, Dormans John, Carpentieri David
Department of Orthopaedics and the department of Pathology,
The Children's Hospital of Philadelphia, Philadelphia, PA and
the University of Pennsylvania School of Medicine,
Philadelphia, PA.

A MURINE MODEL OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS.

Michael B. Jordan, John Kappler, and Philippa Marrack.
University of Colorado Health Sciences Center, National
Jewish Medical and Research Center, and The Howard
Hughes Medical Institute.

ASSOCIATION BETWEEN 2-CdA AND Ara-C AS A RESCUE FOR PEDIATRIC PATIENTS WITH LCH, HEMATOLOGICAL DYSFUNCTION AND FAILURE TO STANDARD THERAPY

F Bernard, C Thomas, R. Chiron, Y Bertrand, M Munzer, J
Landman Parker, B Pellegrino, M Ouache, Y Perel P
Chastagner, C Vermylen, J Donadieu CHU, Montpellier ;
Nantes ; Hôpital Debrousse, Lyon. CHU Reims ; Hôpital
Trousseau, Paris ; Hôpital Necker Paris ; CHU Pellegrin
Bordeaux ; Hopitaux de Brabois, Faculté de Médecine de
Louvain, Bruxelles

DAY TWO – FRIDAY, SEPTEMBER 19th

0830 – 0930

SCLEROSING CHOLANGITIS IN CHILDREN: AN OVERVIEW.

Dominique Debray, *Guest Speaker*
Hôpital Bicêtre, Service d'Hépatologie Pédiatrique
Le Kremlin Bicêtre, FRANCE

0930 – 1230

UPDATE ON CLINICAL TRIALS

LCH-III, LCH CNS, HLH-94, and LCH-S

1330 – 1500

SCIENTIFIC SESSION III – LABORATORY LCH ORAL ABSTRACT PRESENTATIONS

Gritta Janka and E. Marion Schneider, *Moderators*

ANALYSIS OF THE -160C>A POLYMORPHISMS IN THE E-CADHERIN GENE IN PATIENTS AFFECTED BY LANGERHANS CELL HISTIOCYTOSIS.

Paola De Filippi, Catherine Klersy, Cesare Danesino,
Emanuela De Juli, Marco Paulli, Alessandra Viglio e Maurizio Aricò.

ANALYSIS OF THE POLYMORPHISMS IN THE MANNOSE BINDING LECTIN GENE IN PATIENTS AFFECTED BY LANGERHANS CELL HISTIOCYTOSIS.

Paola De Filippi, Catherine Klersy, Cesare Danesino,
Emanuela De Juli e Maurizio Aricò.

THE ROLE OF MULTINUCLEATED GIANT CELLS IN LCH.

Cristiana Costa, Nicola E. Annels, Claudia Faaij, Pancras
Hoogendorn, R. Maarten Egeler. Leiden University Medical
Center, Department of Paediatrics and Department of
Pathology, Leiden, The Netherlands.

TRANSCRIPTIONAL REGULATION OF MONOCYTE MATURATION BY C/EBP α AND JUN β .

Alan D. Friedman, Huaitian Liu, Jeffrey R. Keefer, and Qian-fei
Wang. Division of Pediatric Oncology, Johns Hopkins
University, Baltimore, MD USA.

COINCIDENT EXPRESSION OF THE CHEMOKINE RECEPTORS CCR6 AND CCR7 BY HISTIOCYTES IN HISTIOCYTOSIS.

Mark Fleming, Jack Pinkus, Sarah Alexander, Carmen Tam,
Massimo Loda, Stephen Sallan, Kim Nichols, David
Carpentieri, Geraldine Pinkus, Barrett Rollins. Dept. of Medical
Oncology, Dana-Farber Cancer Institute, Dept. of Medicine,
Brigham & Women's Hospital, Harvard Medical School,
Boston, MA.

ANALYSIS OF THE C77G POLYMORPHISM IN THE CD45 GENE IN PATIENTS AFFECTED BY LANGERHANS CELL HISTIOCYTOSIS.

Paola De Filippi, Sally Boxall, Cesare Danesino, Elma Z.
Tchilian, James McCormick, Peter C.L. Beverley, Stephan
Strobel, Ritu Dawes, Catherine Klersy, Rita Clementi,
Emanuela De Juli, Aline Ferster, Diana L. Wallace e Maurizio
Aricò.

1500 – 1600

UNCOMMON HISTIOCYTIC DISORDERS

Sheila Weitzman, *Guest Speaker*
The Hospital for Sick Children, Pediatric Oncology
Toronto, Ontario Canada

1600 – 1730

GENERAL ASSEMBLY BUSINESS MEETING

1830

ANNUAL DINNER BANQUET

HISTIOCYTE SOCIETY PRESIDENTS

Christian Nezelof	1985 – 1987
Blaise Favara	1987 – 1989
Stephan Ladisch	1989 – 1992
Helmut Gadner	1992 – 1996
Göran Elinder	1996 – 1998
Kenneth McClain	1998 – 2001
R. Maarten Egeler	2001 – 2004

DAY THREE – SATURDAY, SEPTEMBER 20th

0830 – 0915

MEET THE EXPERT SESSIONJan-Inge Henter, Kenneth McClain, *Panel Members***POSTMORTEM FINDINGS IN PEDIATRIC LANGERHANS CELL HISTIOCYTOSIS CASES**

Laura Galluzzo, Guadalupe Rey, Jorge Braier, Elena De Matteo, Julio Goldberg. Hospital Nacional de Pediatria Garrahan, Hospital de Niños Ricardo Gutierrez, Buenos Aires, Argentina.

ANALYSIS OF THE CAUSES OF DEATH THROUGH MEDICAL CHART IN LCH. A French study of 58 cases

H Ibrahim, C Thomas, JF Emile, C Schmitt, F Bernard, D Debray, F Doz, C Behar, P Lutz, G Michel, T Genereau, L Brugieres, Parker, J Landman-, J Donadieu. for the french LCH study group. CHU Amiens, CHU Nantes, Hopital P Brousse, CHU Nancy, CHU Montpellier, Hopital Bicetre, Institut Curie, CHU Reims, CHU Strasbourg, CHU Marseille, Hopital St Antoine, Institut Gustave Roussy, Villejuif; Hôpital Trousseau.

SEQUENTIAL LANGERHANS CELL HISTIOCYTOSIS AND ROSAI-DORFMAN DISEASE: A CASE REPORT

James A. Whitlock, Derek Welch and Mary Ann Thompson
Departments of Pediatrics and Pathology, Vanderbilt University Medical Center, Nashville, TN.

0915 – 1000

INTERPLAY BETWEEN THE SAP-AND SLAM GENE FAMILIES IN IMMUNE RESPONSES**Cox Terhorst**, *Guest Speaker*

Chief, Division of Immunology: Beth Israel Deaconnes Medical Center, Harvard Medical School, Boston MA.

1000 – 1130

SCIENTIFIC SESSION IV – HEMOPHAGOCYTIC SYNDROMES**ORAL ABSTRACT PRESENTATIONS**Robert Arceci and Alexandra Filipovich, *Moderators***NATURAL KILLER CELL FUNCTION AND PERFORIN EXPRESSION IN PATIENTS WITH JUVENILE RHEUMATOID ARTHRITIS AS COMPARED TO MACROPHAGE ACTIVATION SYNDROME AND HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS.**

Joyce Villanueva, Alexandra Filipovich, Susan Lee, Murray Passo and Alexei Grom. Division of Hematology/Oncology, William S. Rowe Division of Rheumatology, Children's Hospital Medical Center, Cincinnati, OH.

NATURAL KILLER CELL ACTIVITY SUBTYPES PROVIDE THERAPEUTIC GUIDANCE IN HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Chengyun Zheng, E Marion Schneider, AnnaCarin Samuelsson-Horne, Martina Löfstedt, Ingrid Lorenz, Gritta Janka, Jan-Inge Henter. Childhood Cancer Research Unit, Dept of Women and Child Health, Karolinska Institutet, Stockholm, Sweden; Experimental Anaesthesiology, University Clinic Ulm, and Dept of Hematology and Oncology, Children's University Hospital, Hamburg, Germany.

THE 50delT MUTATION OF THE PRF1 GENE SHOWS EVIDENCE OF A FOUNDER EFFECT FOR HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH) IN AFRICAN-AMERICAN PATIENTS

Susan Molleran Lee, Yasuhiro Tabata, Joyce Villanueva, Kejian Zhang, Janos Sumegi and Alexandra H. Filipovich
Division of Hematology/Oncology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio.

NAD(P):QUINONE OXIDOREDUCTASE 1 (NQO1) MUTATION IN EXON 6 MAY CONTRIBUTE TO FAILURE OF VP16 TREATMENT IN HLH.

E. Marion Schneider, Uwe Gerstenmaier, Ingrid Lorenz, Michaela Müller-Rosenberger, Gritta E. Janka-Schaub.
Sektion Experimentelle Anästhesiologie, Universitätsklinikum Ulm, Abteilung Hämatologie und Onkologie, Universitätskinderklinik, Hamburg, Deutschland.

CLINICAL FEATURES OF HLH PATIENTS WITH OR WITHOUT PERFORIN GENE MUTATIONS

Ikuyo Ueda, A Morimoto, T Teramura, N Suga, E Ishii, Y Kurokawa, K Koike, M Sako, S Imashuku, Japan HLH Study Group

UPDATE OF THE PERFORIN MUTATIONS IDENTIFIED IN A GROUP OF ITALIAN PATIENTS.

R. Clementi, V. Conter, C. Micalizzi, F. Locatelli, R. Maccario, C. De Fusco, C. Danesino, M. Arico'. Genetica Medica, Università di Pavia e IRCCS S. Matteo, Pavia; Ospedale S. Gerardo, Monza; Istituto Gaslini, Genova; Oncoematologia Pediatrica, Policlinico S. Matteo, Pavia; Ospedale Pausilipon, Napoli; Oncoematologia Pediatrica, Palermo, Italy.

1130 – 1200

Closing Ceremonies/Nesbit and Nezelof AwardsR. Maarten Egeler, *Moderator***POST-MEETING ANNOUNCEMENT**

The Histiocyte Society Salvage Protocol is now officially closed; it is still available for the treatment regimen, but not for patient registration.

THE CHRISTIAN NEZELOF PRIZE IN BASIC SCIENCE

In order to stimulate the activities of scientists and clinicians from around the world studying the histiocytic disorders, the Histiocyte Society sponsors an annual prize for the best scientific abstract at the Annual Meeting. The Award will be given in honor of Dr. Christian Nezelof, renowned pathologist, investigator, teacher, founding member and first President of the Society, to a physician or scientist who is carrying out basic research on the therapy, biology or pathogenesis of one of the histiocytic disorders.

Dr. Christian Nezelof studied medicine in Paris, France during and after the Second World War. In 1948 he specialized in Pediatrics at the Hospital des Enfants Malades. In the early fifties, as a young pediatrician, he published the first clinical report on cystic fibrosis in France.

In 1956 he worked in the Department of Pathology at the Sick Children Hospital in London under the direction of Professor Bodian, a famous British pathologist who first described cystic fibrosis in children.

On returning to France he completed training in Pediatric Pathology. During the period of 1960-1968 Dr. Nezelof served as a full-time pathologist at Necker-Enfants Malades, where he became Chairman of the Department of Pathology in 1968.

In parallel, from 1970, for 15 years he was Head of INSERM Research Unit and created the Groups of Pediatric Pathology located at the Necker-Enfants Malades Hospital.

In the field of histiocytosis, his seminal contribution was that Letterer-Siwe, Hand-Schuller-Christian and eosinophilic granuloma are linked to the same cell, having a common ultrastructural marker designated as the Langerhans body (Birbeck granule). In his paper "Histiocytosis X:



Dr. Christian Nezelof (in 2002)

Histogenetic arguments for Langerhans cell origin", he noted the dendritic lineage of this disease. Not long afterwards the term Langerhans cell histiocytosis was introduced.

Histiocytic disorders continued to be one of his major fields of interest. In 1982, Dr. Nezelof described the successful growth in nude mice of a tumor after injection of cells from the pleural effusion of a child with malignant histiocytosis. After this manuscript entitled: "Tumor cell line characterization of a malignant histiocytosis transplanted into nude mice" his team described successful establishment *in vitro* of the Malignant Histiocytosis DEL cell line.

The Society thought it entirely consistent with Dr. Nezelof's great interest in new developments of basic pathophysiology, bridged with his key-role in supporting others, that this prize be given in his honor. The awardee need not be a physician, but the focus of the work should be on some aspect of the pathophysiology of the histiocytic disorders.

Judgment is based on a written abstract describing work done by the candidate him/herself. It is understood that the winning abstract may have co-authors, but that the first author must be the leader of the project and the one who is awarded the Nezelof Award.

The Program Committee provides a time during the Annual Meeting for presentation of the winning paper. The decision, made by a special committee of the Histiocyte Society, is based on originality, completeness, scientific accuracy, and contribution to science.

This year the \$500US prize was awarded to Dr. Michael B. Jordan of the University of Colorado Health Sciences Center in Denver, Colorado for his presentation "A murine model of hemophagocytic lymphohistiocytosis".



Dr. R. Maarten Egeler with Nezelof Award Recipient Dr. Michael Jordan

THE MARK NESBIT PRIZE IN CLINICAL SCIENCE

The Histiocytosis Association of America, in conjunction with the Histiocyte Society, offers an annual prize for the best clinical abstract at the Histiocyte Society Annual Meeting. It is given in honor of Dr. Mark Nesbit, renowned pediatric oncologist, teacher, and supporter of the many families dealing with histiocytic disorders.

The prize is awarded to a physician or scientist who is carrying out clinical research to the therapy, biology, or pathogenesis of one of the histiocytic disorders. The goal of the award is to stimulate and promote the activities of clinical scientists from all around the world studying specific aspects of these puzzling diseases.

Dr. Mark Nesbit completed his medical training at George Washington Medical School in 1959. The remainder of his medical training was completed at the University of Minnesota where he specialized in pediatric hematology and oncology.

In 1967 he joined the faculty at the University of Minnesota, achieving the rank of Professor of Pediatrics in 1973. Dr. Nesbit assumed the position of Director of the Division of Pediatric Hematology and Oncology at the University of Minnesota where he built one of the most productive and nationally recognized programs during his 14 year tenure.

Professor Nesbit has been a leader in the development of clinical research for the treatment of leukemia and has a special interest in histiocytosis, bone tumors and the late complications of cancer survivors. In addition, Dr. Nesbit has helped countless young investigators with their careers in the field of pediatric hematology and oncology.

Of the contributions made by Professor Nesbit towards better understanding of the histiocytic disorders, we highlight the following three:

- 1) Histiocytic disorders have been a continual interest from the onset of Professor Nesbit's career. His first publication was entitled: "Histiocytosis X",
- 2) Dr. Nesbit played an important role in the organization of the Histiocyte Society. Besides his active input in the Epidemiology Study Group of the Histiocyte Society, he served on the Education Committee. His interest and initiative for increasing the activity and visibility of the Histiocyte Society has been an important part of the Society's evolution, and
- 3) Dr. Nesbit was an active member and participant of the Histiocytosis Association of America Board of Trustees. His activities in the Association made him a national source of information on the diagnosis and treatment of histiocytosis. In 1990, Professor Nesbit received the Outstanding Investigator Award from the Histiocytosis Association. In conclusion, Dr. Nesbit has made substantial contributions to research in the field of histiocytosis. His dedication to the organization of



Dr. R. Maarten Egeler with Nesbit Award Recipient Manuel Steiner

interested investigators has resulted in a strong research agenda to better understand the etiology, diagnosis, treatment and long-term outcome of children with Langerhans cell histiocytosis. His compassion for patients and their families has always been evident by his willingness to consult with both physicians and family members.

The Histiocytosis Association of America and the Histiocyte Society thought it entirely compatible with the support of and work of Dr. Nesbit within the world of the histiocytoses to offer this prize in his name. The candidates for this award need not be physicians, but the focus of their work should be on some aspect of the histiocytic disorders, be it in clinical medicine or allied pursuits such as nursing, psychology, social work, occupational therapy, etc.

Judgment is based on a written abstract presented at the Annual Meeting of the Histiocyte Society describing work done by the candidate him/herself. It is understood that the winning abstract may have co-authors, but that the first author must be the major contributor who is awarded the Nesbit Award.

The Society's Program Committee provides time during the Annual Meeting for presentation of the winning paper. A decision, made by a special committee of the Histiocyte Society, is based on originality, completeness, scientific accuracy, and contribution to science.

This year the \$500US prize was awarded to Dr. Manuel Steiner of St. Anna Children's Hospital in Vienna, Austria for his presentation "Langerhans cell histiocytosis (LCH) in neonates".

LANGERHANS CELL HISTIOCYTOSIS STUDY COMMITTEE REPORT

Prof. Dr. Helmut Gadner, *Study Chairman*; Dr. Nicole Grois and Dr. Milen Minkov, *Study Coordinators*

PROGRESS OF THE LCH III STUDY

The official start of the LCH III Study was April 1, 2001. Due to extensive national requirements the start of the study was delayed in France, Spain and U.K. Therefore, the patient recruitment by August 31, 2003 was lower than expected.

- 397 patients have been enrolled in the study.
- Instead of 186 expected multisystem patients only 157 were enrolled, 86 of these were "RISK" patients, and 71 patients were "LOW RISK" patients.
- 240 patients were single system patients, of these, 75 patients were multifocal bone patients and 67 patients had single system disease with special site involvement, defined as lesions in the craniofacial bones or skull base with intracranial tumor extension or vertebral lesion with intraspinal extension.

In the low risk group only 42 patients (60%) were randomized which is significantly lower than the expected randomization rate of 72%.

In 19/42 randomized patients no follow up information was reported, therefore, even the response to therapy at week 6 could not be evaluated.

78/86 multisystem risk patients were randomized (91%), but in only 28 from 67 evaluable patients the response at week 6 and 12 was available.

For the first interim analysis 46 patients would have been needed. Therefore, the interim analysis had to be postponed. It is the goal of the study center in collaboration with the subcenters and participating clinics to increase patient recruitment and to improve the compliance with respect to randomization and especially follow up reporting.

REACTIVATIONS IN MULTI-SYSTEM LCH

Among multisystem-LCH (MS-LCH) patients treated on the clinical trials DALHX, LCH I and II survival reaches about 80%. Disease reactivation, however, in survivors may cause considerable morbidity.

In a retrospective analysis the course of 563 MS- patients enrolled on the 3 clinical trials were analyzed with respect to frequency and pattern of disease reactivation. The probability for complete disease resolution after first-line therapy (non-active disease = NAD1) was lower in patients who had risk organ (RO) involvement at diagnosis (p 0.65 at 5 years) than

in patients without RO involvement (p 0.93 at 5 years). This difference was due to the high mortality rate in patients with RO involvement at diagnosis. However, the median time from diagnosis to NAD1 was 6 months (88% of all NAD1's were observed within 2 years) independent of RO involvement at diagnosis.

In the 335 patients who achieved NAD1 the overall risk for reactivation at 5 years after diagnosis was 46%.

Single system reactivation (SS-R) in the bone was the most frequent pattern (16% risk at 5 years), followed by non-bony (mostly cutaneous) SS-R and multisystem reactivation without involvement of RO (MS-R RO-), each with 11% risk at 5 years.

Reactivation in RO (MS-R RO+) was a rare event (5% risk at 5 years) and only seen in patients with RO involvement at diagnosis.

The probability of a second disease resolution after reactivation (NAD2) at 5 years after the first reactivation was 96% for patients with SS-R and 89% for patients with MS-R.

The time interval from the first reactivation to NAD2 was similar to that from diagnosis to NAD1. Only 2 fatalities due to disease progression were reported within the context of first reactivation.

The probability for a second reactivation at 5 years after NAD2 was 51% in patients who had multisystem first reactivation and 43% in patients with single system disease at first reactivation. The probability for reactivation in RO was only 2% at the second reactivation. The overall probability for multiple reactivations is very low with 3% for a third reactivation, and under 1% for fifth reactivation.

With the current patient accrual and the current poor compliance with respect to follow up reporting (a drop out rate of about 50% at 5 years after diagnosis in the analyzed cohorts) a randomized study to test the best therapy for LCH patients upon reactivations seems to be difficult. Further discussions within an extra LCH study group meeting were planned for February 2003 to clarify the inclusion criteria and possible treatment strategies for the different disease settings at reactivation.

LCH COMMITTEE REPORT CONTINUED

LCH CNS 2003 STUDY

In June 2003 the LCH CNS 2003 protocol was released. This protocol constitutes a continuation of the LCH CNS 2000 study in a condensed version.

It is the goal of the study to:

1. implement a uniform diagnostic program, and
2. to collect information on
 - a. the natural history and pathophysiology of the disease, and on
 - b. the outcome of patients treated with various therapeutic approaches.

The diagnostic program includes guidelines and intervals for the performance of magnetic resonance imaging (MRI), motor efficiency tests, psychometric tests, neurophysiological tests (brain stem evoked potential, visual and event related potentials), endocrine evaluation, cerebrospinal fluid studies, etc.

No guidelines for specific therapy are included in the protocol at this point.

It is the aim of the study group to frame uniform therapeutic recommendations for the different groups of LCH CNS disease, i.e. hypothalamic pituitary disease, extraaxial tumorous lesions and intraparenchymal neurodegenerative disease.

The data collected in the LCH CNS Study will form the basis for future therapeutic approaches. Therefore, complete reporting of patients with LCH CNS is essential.



*LCH Study Reference Center at
St. Anna Children's Hospital in Vienna, Austria
From L to R: Dr. Helmut Prosch, Dr. Milen Minkov,
Dr. Nicole Grois, Elfriede Thiem, Edda Unger, Manuel Steiner*

HLH STUDY GROUP REPORT

Submitted by Jan-Inge Henter, Chair

The HLH Study Group is mainly aiming at improving diagnosis and treatment for patients suffering from FHL/HLH. We also want to improve knowledge on the biological mechanisms causing the disease. The HLH-94 treatment protocol has been a therapeutic success. It has also provided a lot of research data, in particular on NK-cell activity in HLH.

The HLH-2004 Study of the Histiocyte Society was opened on January 1, 2004. At the same time the HLH-94 study was closed for enrollment of new patients, but it stays open for follow-up of patients already enrolled in the study. There will be only minor alterations in the treatment regimen. The HLH-94 protocol appears to be effective and appreciated. Most patients registered are from Europe and Japan. The registration in the US/Canada is improving.

A report on the outcome of the patients recruited the first four years has been published (Blood 2002 Oct; 100: 2367-2373). In brief, the cure rate is around 50% (around 80% survive until BMT, and around 65% survive the BMT). In addition, biological studies on genetics and cytotoxicity will be associated with the protocol.

A retrospective study on genotype-phenotype will be initiated, as a complement to the prospective data gathered in the new protocol. In addition to the study subcenters (Scandinavia, Germany, Benelux, United Kingdom, Italy, USA and Japan), local coordinators for Spain (I Astigarraga), Austria (M Minkov) and South America (J Braier) will be associated with the new protocol.

HISTIO NEWS

The next issue of *Histio News* will include regular features like:

In Memory

In the News

Donation Listings

Somebody Special

Fundraising Event Stories

If you would like to submit materials for the next issue, please contact Kristen at email address kristen@histio.org or by calling 1 856-589-6606. Please limit all submissions to 500 words.

RESEARCH PROJECT FINAL PROGRESS REPORT

BIOLOGIC CORRELATES OF RESPONSE TO THERAPY IN LANGERHANS CELL HISTIOCYTOSIS

Submitted by Kenneth L. McClain M.D. Ph.D.

I. Study Objectives:

1. Correlate the relative amount of transcripts for genes of the tumor necrosis factor alpha family and other cytokines relevant to the biology of LCH to treatment results. Since the work was begun we have identified three other important aims that will also be addressed in this report:
2. Identify similarities and differences between the expression of cytokine genes in normal CD1a+ Langerhans cells (LC) from skin and compare that profile to LC from biopsies of patients
3. Compare gene expression of LC from patients with single site, multifocal site Low Risk, and multifocal site High Risk specimens.
4. Compare gene expression profiles of CD3+ T cells from the single site, multifocal site Low Risk, and multifocal site High Risk specimens.

Project Goal: Develop new hypotheses for the pathophysiology of LCH based upon expression profiles of LC and T cells in the different patient categories

II. Study Objectives (in lay terms):

We are measuring the amount of RNA (messages from the DNA) for genes that control the interaction of cells of the immune system that have been shown to be important for LCH. The relative amounts of the gene expression (RNA) is compared to the type of LCH patient: that is "Low Risk" or "High Risk" patients meaning: "easy to treat" or "hard to treat".

III. Relevance to Histiocytic Disorders (in lay terms):

This information will help to further classify the types of treatment that may be best for LCH patients and advance our understanding of how the disease is caused.

IV. Findings: **{First studies with a 36 gene custom array}**:

There was no difference in the relative intensity of genes expressed at the highest levels from normal LC and those from LCH tissue in microdissected cells : M- CSF, TGF- β Receptor, IL-1 α , Next highest: TRAF2, CD40, GM-CSF, IL-1 Receptor, STAT-6, TNF-Receptor p55. When whole tissues were used as the source of RNA the expression pattern showed more TNF-R p55, RANK-Ligand, GM-CSF, TNF-R p75, RANK, TRAF3, CD40-L, TNF- α , TGF- β -R, M-CSF-R, IL-2, NF κ B, IL-4R. There were relative differences in the genes expressed in different tissues from the same patient. Dramatic differences in the gene profile from lesions of patients with only bone involvement versus organs of patients with multi-system involvement were found. **{Second generation studies with a 96 gene commercial cytokine array}** With the expanded number of substrate cytokine genes in the GEArray blot similarities and clear differences were found. A core group of genes including insulin-like growth factor 2, platelet-derived growth factor alpha, and interleukins-9, -11, -17, and-17 beta were expressed in both normal and

pathologic LC with similar intensity except for IL-9 which was distinctly more highly expressed in the latter. Unique expression of IL-13 and TNF α were found in bone and spleen lesions. One bone lesion also had high expression of interferon alpha, fibroblast growth factor, bone morphogenic protein3B, transforming growth factor B3, TNFSF13 (April), and vascular endothelial growth factor type C. **{Third Generation Studies-In Progress}** We have extended the work supported by the HAA with funding from our department. CD3+ T cells and CD1a+ LC cells from patients with single bone lesions (Low Risk), multiple bone lesions (Medium Risk), and High Risk organ lesions have been isolated and analyzed. Distinct profiles of cytokine and growth factor genes are evident for the different clinical groups. Briefly, low risk lesions had modest amounts of IL-9 & lymphotoxin A; Mod. risk high levels of IL-10, and High Risk-highest levels of IL9and lymphotoxin A from the CD3+ T cells. LC from the Low Risk group expressed the highest levels of IL-11, IL17B and IL-9; Mod Risk highest levels of IL-10 and TGF-Beta; and High risk low or modest levels of the previously noted genes and high amounts of leptin. *These results are being validated with more specimens by immunocytochemical staining and gene expression.*

- V. Study Problems, Obstacles or Concerns: Initially we tried to obtain cells from tissue fixed with formaldehyde, but no RNA could be isolated. Then we used paraformaldehyde-fixed tissue which allowed us to generate the first results noted above. The second generation studies came from work with frozen tissue specimens which give much better quality RNA. The major obstacle is obtaining specimens. The major concern is to validate these results with other methods.

- VI. Presentations at Histiocyte Society Annual Meeting and The American Society of Pediatric Hematology/Oncology: 2002 & 2003 (Each Abstract was presented at both meetings).

Gene Expression In Langerhans Cell Histiocytosis
Kenneth L. McClain¹, Yi-Hong Cai¹, John Hicks², Leif E. Peterson³ and Stephen D. Ginsberg
Langerhans and T Cells in LCH Express Increased Amounts and Unique Types of Cytokine Genes
Xiao-tian Yan¹, John Hicks², Leif E. Peterson³ and Kenneth L. McClain¹.

- VII. A manuscript that has been submitted to Pediatric and Developmental Pathology. A second manuscript is planned soon to summarize the latest results.

- VIII Future Plans: Once we have validated the profiles of gene expression in the T-cells and LC we plan to develop an *in vitro* model using LC generated from monocytes. It is hypothesized that this will prove a more consistent way to evaluate the role of various cytokines in changing LC behavior.

RESEARCH PROJECT ONGOING PROGRESS REPORT

STUDY OF GENETIC DEFECTS UNDERLYING HLH: INVESTIGATION OF CELLULAR ABNORMALITIES ASSOCIATED WITH DEFECTIVE NK CELL FUNCTION AND RESULTANT DYSREGULATION OF T CELL POPULATIONS.

Alexandra H. Filipovich, M.D., Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio

Our proposal listed 4 specific aims. Progress has been made in addressing three of them.

I. Specific Aim. 1) Description of the immunologic phenotypes of newly diagnosed patients with HLH.

The major findings to date are summarized in the manuscript "Characterization of diverse PRF1 mutations leading to decreased natural killer cell activity in North American Families with Hemophagocytic Lymphohistiocytosis", which has been accepted for publication in the Journal of Medical Genetics. This study describes 50 North American families tested for NK number and function, perforin expression and PRF1 mutations. Half of the cases fit phenotype b. and were found to have biallelic PRF1 mutations (Table 1 of manuscript). In addition to the predicted phenotype several interesting findings emerged. The first was the unexpected finding of a homozygous PRF1 mutations in P35, a 7 year old boy born of a consanguineous marriage who exhibited normal NK function despite markedly decreased perforin expression in cytotoxic cells. The second was the observation that all African American patients with HLH had perforin deficiency and shared the same mutation, 50 del T. HLH in African American patients presents at a very young age (1-3 months) compared with other patients who have HLH on the basis of PRF1 mutations. This observation was submitted as an abstract "The 50delT Mutation of the PRF1 Gene Shows Evidence of a Founder Effect for Hemophagocytic Lympho-histiocytosis (HLH) in African-American Patients" to the 2003 HS annual meeting in Philadelphia and selected for oral presentation.

Building on the experience from our research supported by the HAA and HAC (Histiocytosis Association of Canada) we have been able to set up the first clinical genetic testing program for PRF1 mutations in North America. This test is available through the Molecular Genetics lab at our hospital which is a CAP/CLIA approved facility with attendant genetic counseling services. In affected families, prenatal and pre-symptomatic screening can be performed, as well as carrier detection.

II. Specific Aim. 2) To compare gene expression microarrays in resting and activated peripheral blood samples from patients with HLH that are PRF1 -/- and PRF1 +/-.

RNA Samples have now been prepared on 4 paired sets (unstimulated and mitogen-activated) of normal control blood and 9 paired; samples from patients with HLH or different phenotypes, (including 3 patients with different PRF1 mutations). Findings show that those genes in the patients with HLH are overexpressed or underexpressed 5-fold normalized against healthy pediatric controls. The 4004 most aberrantly expressed genes illustrate two important findings. First, aberrations in gene expression are readily detected in unstimulated peripheral blood and relatively few genes become upregulated with in vitro activation (especially compared to

normal samples). This may reflect the intense in vivo activation that the patients' immune samples experience. Second, gene expression patterns vary between the patient with HLH who has normal perforin genes vs. the patient with perforin deficiency with reciprocal down vs. up-regulation of a provocative set of genes associated with apoptosis and T cell function amount. For example, perforin (indicated as very underexpressed in the patient with PRF1 mutations) is upregulated in the patient presumed to have another genetic cause of HLH. Also found to be very upregulated, as one would expect, are the genes for TNF receptors and ligands, and IL1 receptors and ligands.

Since submission of this proposal the Division of Rheumatology at our institution has been awarded a P01 grant from the NIH to apply gene expression microarray to pediatric rheumatologic disorders. I am a co-investigator on Project 4 which looks to examine gene expression in the macrophage activation syndrome, a potentially fatal complication of systemic onset juvenile rheumatoid arthritis which is very similar to HLH. Successful funding of that work relied extensively on preliminary data collected during the previous HAA grant: "Cytotoxic Defects in HLH family members and Patients with Macrophage Activation syndrome. Publications resulting from that work include: "Natural Killer Cell Function in Patients with systemic-Onset Juvenile Rheumatoid Arthritis and Macrophage Activation syndrome", Grom et al Jpeds Mar 2003 (attached) and the oral abstract presentation at this year's Histiocyte Society meeting by Villanueva et al: "Natural Killer Cell Function and Perforin Expression in Macrophage Activation Syndrome and Hemophagocytic Lymphohistiocytosis".

III. Specific Aim. 3) To examine other potential cellular abnormalities related to NK cell dysfunction. Progress has been made with 2 of the subaims. The expression of CD56 bright (immunoregulatory) vs. CD56 dim (effector, perforin-expressing) NK cells has been examined. In the majority of patients with HLH there are virtually no immunoregulatory NK cells compared with pediatric controls. Interestingly, similar abnormalities exist in patients with the macrophage activation syndrome – suggesting a similar maturation defect in both conditions. This observation was presented at the 2003 Histiocyte Society meeting and is being prepared for publication. Second, we have developed the assay to begin studies of NK target cell conjugates by flow cytometry (targets have been transduced to express green fluorescent protein).

As a consequence of the research previously funded in my lab by the HAA and HAC, Dr. Kim Risma, a postdoctoral fellow has chosen to join our laboratory and has received a fellowship stipend from FOCIS (Federation of Clinical Immunology Societies). Her proposal was entitled: "Mechanistic Evaluation of Defective Perforin –Mediated Cytotoxic Killing in Patients with Hemophagocytic Lymphohistiocytosis". Dr. Risma will be continuing studies in Specific Aims 3 and 4 in the coming year.

WHAT TO EXPECT FROM CLINICAL TRIALS

When a person considers participating in a clinical trial, there are several things he or she should be aware of in order to have realistic expectations and adequate knowledge of possible risks and benefits:

- What is the purpose of the trial? Is the intent to find a cure, or simply a treatment, or perhaps preventative measures or a diagnostic test? Don't sign up for a clinical trial unless your expectations are in line with the study's objective.
- Is an experimental clinical trial appropriate for you? Have you tried the standard treatments and failed to benefit from them? Are you willing to try a treatment for which little is known, rather than try a treatment that has risks and possible benefits that are well understood?
- What are the known risks and benefits of the experimental treatment? How many people have been in the experiment before you? Did they experience any harm?
- Is the experimental product only slightly different from other available treatments (e.g., a slightly revised version of an existing drug), or is it a completely new approach to treatment?
- Who is paying for the study? Is it supported by government funds or a commercial firm? Does your doctor have a commercial interest in the therapy (e.g. a patent, royalties, etc.)? Note: Some universities have "Conflict of Interest" committees who review these factors and decide whether a commercial conflict may influence the outcome of the study.
- Is this a "placebo controlled" trial, or will the experimental treatment be compared to the standard treatment for your disease? Is there a chance that you will receive the placebo and if so, how much risk does this represent?
- If you are harmed by the experimental treatment, who will pay for your medical care?
- What will happen when the study is finished? Will you be able to continue using the treatment, or will it be stopped even though you feel you are benefiting from the product? Will the manufacturer promise you can have continued access?
- While the vast majority of experimental treatments are free, will you or your insurance be liable for any costs related to your medical care while you are participating in the clinical trial?

This information came from the National Organization for Rare Disorders (NORD).

For more information visit: <http://www.rarediseases.org/>.

NATIONAL INSTITUTES OF HEALTH ESTABLISHES RARE DISEASES CLINICAL RESEARCH NETWORK

To address the challenges inherent in diagnosing and treating rare diseases, the National Institutes of Health (NIH) announced the establishment of the Rare Diseases Clinical Research Network.

With \$51 million in grant funding over five years from several NIH components, the network will consist of seven Rare Diseases Clinical Research Centers (RDCRCs), and a Data and Technology Coordinating Center (DTCC).

Approximately 25 million people in the United States are affected by an estimated 6,000 rare diseases or conditions.

"Because of the small number of affected patients in any one location, rare disease research requires the collaboration of scientists from multiple disciplines and the capacity to share access to geographically distributed national research resources and patient populations", said Judith L Vaitukaitis, M.D., Director of the National Center for Research Resources (NCRR), one of the NIH funding components.

"The network will facilitate increased collaboration and data sharing between investigators and patient support groups working to improve the lives of those affected by diseases in the future", said Stephen Groft, Pharm.D., Director of NIH's Office of Rare Diseases.

This information came from the website of the National Institutes of Health Office of Rare Diseases. For more information visit: <http://rarediseases.info.nih.gov/>.



From L to R, top row: Christine Harris, Beth Anne Miller, Jeffrey Toughill; bottom row: Melissa Hawk, Kristy Lajkovicz

BASIC ISSUES: PERFORIN AND NK FUNCTION IN HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

Commentary by Dr. Alexandra Filipovich

1. Scientific evidence suggests that there are probably 3 to 4 different genetic defects that cause HLH. So far, only one of these defects has been found – mutations in the perforin genes.
2. In North America, approximately 50% of familial HLH cases are caused by perforin deficiency due to mutations in the perforin (PRF1) genes. Thus, in families where the HLH is caused by genetic defects in the perforin genes it is quite likely that abnormalities in perforin expression can be found in the laboratory when studying NK cells from affected patients or carriers (e.g. parents). This possibility must always be confirmed by genetic sequencing of the perforin genes in family members. In families where the mutations have been defined this information can be used for prenatal screening and preimplantation diagnosis.
3. In families where the gene defect(s) have not yet been discovered, definite carrier testing and prenatal diagnosis are not yet possible. In some of these families (less than half) subtle abnormalities in NK function and/or perforin expression are seen on laboratory testing in parents even though they have normal perforin genes. This suggests to us that there are defects in other (related) genes that have to do with the control of perforin in NK cells – we believe this is an important clue. In still other families with HLH where we believe it is familial because there have been more than one affected child or the first case occurred very early in life, we can find no abnormalities in the parents (presumed carriers) in NK function or perforin expression – this does not mean that they are not carriers! In these families we suspect that there are other genetic problems that lead to HLH.
4. Almost all children with familial HLH will have absent or decreased NK function regardless of the specific genetic cause. There are a few rare exceptions where NK function may be calculated as within normal limits on at least one occasion. These are rare exceptions.
5. Children who develop HLH under one year of age (some say under two years of age) are statistically very likely to have familial HLH, even though we may not be able to find the precise cause at the present time.
6. In some cases of familial HLH, symptoms can occur for no apparent reason. In other familial cases there may be reason to suspect that a virus, such as EBV has triggered the symptoms in the patient who is already genetically prone to develop HLH disease. Finding footprints of a virus, such as EBV, does not exclude the possibility of familial HLH, especially in very young children.

Nowadays, very sensitive techniques exist to detect EBV even in very young children; however, one needs to know when and where to look, and which tests to use. The importance of identifying EBV infection is an order to control the virus directly, in addition to using the standard HLH 94 treatment.

RESEARCH PROJECTS: RESULTING PUBLICATIONS

“Aberrant Chemokine Receptor Expression and Chemokine Production by Langerhans Cells Underlies the Pathogenesis of Langerhans Cell Histiocytosis”

Nicola E. Annels, Cristiana E.T. da Costa, Frans A. Prins, Annemieke Willemze, Pancras C.W. Hogendoorn, and R. Maarten Egeler

Langerhans cell histiocytosis (LCH) is characterized by a clonal proliferation and retention of cells with a Langerhans cell (LC) - like phenotype at various sites within the body. The present study set out to elucidate whether aberrant expression of chemokine receptors or dysregulation of chemokine production in LCH lesions could explain abnormal retention of these cells. Immunohistochemical analysis on 13 LCH biopsies of bone, skin, and lymph node all expressed the immature dendritic cell (DC) marker CCR6 on the lesional LC's and absence of the mature DC marker CCR7. Furthermore, regardless of the tissue site, LCH lesions markedly overexpressed CCL20/MIP-3 α , the ligand for CCR6. The lesional LC's appeared to be the source of this CCL20/MIP-3 α production as well as other inflammatory chemokines such as CCL5/RANTES and CXCL11/I-TAC. These may explain the recruitment of eosinophils and CD4⁺ CD45RO⁺ T cells commonly found in LCH lesions. The findings of this study emphasize that, despite abundant TNF- α , lesional LC's remain in an immature state and are introduced to produce chemokines, which via autocrine and paracrine mechanisms cause not only the retention of the lesional LC's but also the recruitment and retention of other lesional cells. We postulate that the lesional LC's themselves control the persistence and progression of LCH.

Langerhans-cell histiocytosis ‘insight into Dendritic Cell biology’

Jon D. Laman, Peiter J.M. Leenen, Nicola E. Annels, Pancras C. W. Hogendoorn and R. Maarten Egeler

Langerhans-cell histiocytosis (LCH) is caused by an uncontrolled pathogenic clonal proliferation of dendritic cells (DCs) with Langerhans-cell (LC) characteristics. LCH cells are arrested in an immature, partially activated stage and show a deviant regulation of cell division. Their aberrant interactions with T cells and the lesional microenvironment are typified by high level production of diverse cytokines. Chemokine and chemokine receptor patterns probably explain LCH predilection sites and lesion composition, reminiscent of chronic granulomatous inflammation. Recent advances in LCH immunology suggest that clonal changes in DCs might underlie the aberrant immune interaction with T cells, leading to a unique pathological picture, which combines features of carcinogenesis and chronic inflammation.

NATIONAL HISTIOCYTIC DISORDERS PATIENT AND FAMILY SYMPOSIUM

On the morning of September 22, 2003, at the Crowne Plaza Philadelphia Hotel, a very unique and diverse group of people convened to talk about a rare disorder that has affected the lives of every person present.

This group of approximately 150 included internationally known and acclaimed research physicians, oncology nurses, parents, children, extended family members of patients, adult patients, staff members of various international histiocytosis groups, and the Histiocytosis Association staff.

Of interest is the fact that this meeting in 2003, as well as the inaugural meeting of the Histiocyte Society in 1985, was held in Philadelphia.

Maarten Egeler, MD, PhD, President of the Histiocyte Society, opened the meeting with a brief history of the Histiocyte Society, current research, and the more recent accomplishments, including the ongoing development of the first international study for adults with LCH and the opening of a new HLH protocol in 2004.

According to Dr. Egeler, "This is a rare disease. We have to work together, because our questions and problems are the same."

Nicole Grois, M.D. of Vienna, Austria began her presentation about the clinical trials by saying, "We feel responsible to tell you what we are doing, because of your tremendous support of our work."

She explained what clinical trials are and how they have evolved. A database is maintained in Vienna, Austria to make sure the studies are performed correctly, and this is run by statisticians and physicians.

A total of 2154 LCH patients have been registered since 1983, when the DAL-HX trial was instituted. This was the cornerstone trial of current treatment. The LCH-I trial, begun in 1991, had 517 patients registered, LCH-II had 924, and LCH III, opened in April of 2001, has 352 patients registered to date.

The CNS trial of 2000 had only 43 patients registered and subsequently closed. A few years ago, clinical trial registrations were almost entirely European accrual; however, North America is now participating more often.

Dr. Grois then outlined how a clinical trial/treatment protocol is created:

- 1) Approximately eight Histiocyte Society research physicians form a study committee and plan the protocol. They look at results from the previous trials and consider many ideas.
- 2) These ideas are then written up and edited.



Independence Hall in Philadelphia

- 3) Data is collected from patient sheets included with the protocol registration sent in by physicians. The study group checks the forms for completeness and correctness of information.
- 4) The data is then entered into the database. There are eight subcenters throughout the world, and each subcenter sends their data to the database in Vienna, Austria.
- 5) The data is analyzed and evaluated.
- 6) Reports and presentations are then prepared by the study group.
- 7) The findings are published in medical journals.

Many physicians are overworked and don't take the time to register their patients and send histiopathological confirmation. Many don't follow up with subsequently required information. At least 20% of patients registered in the trials have no follow-up information.

It costs approximately \$100,000/year to run the study center in Vienna. These costs include travel expenses, maintenance of the database, and office maintenance. Last year, the Histiocytosis Association of America provided \$30,000 toward this international effort.

In closing her presentation, Dr. Grois looked out across the crowded room and said, "Knowing you motivates us to remember why we do this work. We need to encourage and motivate physicians to register their patients. It's very important that we continue to work together."

Dr. Maurizio Arico from Palermo, Italy then presented information about adults with LCH. According to Dr. Arico,

Symposium continued

approximately 4% of adult patients have thyroid disease, and he believes there is a historical link between LCH and thyroid disease. Approximately 5% of adult patients develop malignancy before, during or after LCH diagnosis. The five-year survival rate in adult patients with localized disease is estimated to be 100%, in multisystem disease 91.7%, and in patients with only pulmonary involvement 87.8%.

An international trial for adults with LCH is currently being developed. The requirements for registration will include:

- 1) new diagnosis,
- 2) over age 18,
- 3) definitive diagnosis of LCH, and
- 4) no prior antineoplastic treatment for LCH.

No pregnant women can be registered, no patients with severely impaired lung function, no associated conditions determined by the physician that could impact the outcome of the trial, and no pre-treatment. (However, pre-treatment with steroids will be accepted.)

This trial, called the LCH A-I trial, will be organized into three groups:

- 1) Single system – including multifocal bone and excluding isolated CNS disease,
- 2) multisystem, and
- 3) isolated pulmonary disease.

An announcement about this trial will be forthcoming.

Subsequent sessions included the topics, "Effective Patient-Physician Communication" and "Psychological and Emotional Effects of a Rare Disorder." These sessions were presented by a combination of research physicians, nurses, and social workers, including

James Whitlock, M.D. of Vanderbilt University Hospital;

Ken McClain, M.D. of Texas Children's Hospital;

Maarten Egeler, M.D. of Leiden University, The Netherlands;

Kim Nichols, M.D. of Children's Hospital of Philadelphia (CHOP); and

Diane Baniewicz, R.N., Mary McSherry, L.S.W., and Stephanie Fooks Parker, L.S.W. of CHOP.

Family and patient stresses include lifestyle changes, financial strain, changes in family priorities, sibling issues, anxiety, fatigue, difficulty sleeping, loss of appetite, procedures that are painful and/or scary, loss of innocence, having to stay in a strange place, fear of death, fear of the unknown, loss of community, loss of self-esteem, scars, and hair loss. Coping with these stresses can include professional counseling, antidepressants, financial support

through the hospital's patient assistance program or family and friends, support from one's church, and support and information from the Histiocytosis Association of America.

The panel made several recommendations for those families needing emotional support:

- 1) Establish and maintain a routine,
- 2) maintain normal discipline,
- 3) be honest with your child,
- 4) take time for other family members, and
- 5) ask for help when you need it.

Ken McClain, M.D. then talked about the accomplishments in research that were made possible because of funding generated by families and patients.

The Histiocyte Society is currently dissecting abnormalities in the cells that lead to histiocytic disorders. The physicians are studying growth factors, and they believe that osteoclasts may be abnormal in this disorder. They are dissecting cells to extract RNA to see which genes could be expressed at higher levels. They are looking at numerous tissue biopsies and genes. Genetic perforin 9 and 10 have been determined within the last few years to have mutations in HLH.

"We are in search mode, and we are making quite a bit of progress." Dr. McClain stated that there is no money available in the federal budget because this is considered a rare disease. We must continue to raise funds for research. According to Dr. McClain, "Health case numbers drive the money."

A number of questions from the audience were then fielded by the panel of experts. The gathering of patients and families then dispersed into four smaller specialty groups, which met in adjoining conference rooms. These four groups were comprised of adults with LCH, families whose children have HLH/FHL, families of children with LCH, and patients with other histiocytic disorders. Each group was staffed with a panel of several research physicians. The rest of the afternoon was full of questions, answers, and active dialogue between patients and physicians.

This kind of cooperation and sharing of information is truly unique and quite exciting to behold. The Histiocytosis Association of America has indeed succeeded in forging a strong bond and working relationship with the Histiocyte Society, a bond that we hope will continue to strengthen through the years, a relationship that we know will have a tremendous impact on the lives of those affected by the histiocytic disorders.

Sandra Conway Warren, *Website Editor*
Histiocytosis Association of America
Histiocyte Society

The Histiocytosis Association strongly encourages those who receive grant awards to publish the results of their work. Publication of information is important to physicians around the world who are treating patients and doing research. Sometimes the information that is learned from research projects helps other physicians to formulate new scientific ideas and better treatments. Below is a recent list of some of the publications in which the Histiocytosis Association was involved in supporting, either financially or organizationally. Copies of these articles can be ordered directly from the publishers through your local library. *The Histiocytosis Association Office does not have copies for distribution.*

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Boston, M. and C.S. Derkay. "Langerhans' Cell Histiocytosis of the Temporal Bone and Skull Base." *American Journal of Otolaryngology* 23(4): 246-248, 2002.

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UW of New England: *BJ's Wholesale: Doreen R. Clerc; Filene's Basement: Mira Olic, Richard Frassa, Janet West, Andrea Bondietti, Ansuya Gohil, Jannie Daniels, Djwunna Jiggetts, Rosa A. Ceballos, Juana E. Garcia, Rahsarn L. Nelson, Titilayo Salako*

Valley of the Sun UW: *America West Holdings Corp.; Banner Health System: Sharon Miller; The Dial Corp.: John Ferrarin Honeywell, Anne Chevaleau Ruffin, Matthew Greenman, Kathleen Master, Franklin Merkley, Heidi Pursley, Joseph Searle, John Snow, Douglas Spencer; Intel Corporation: Suzanne Reddie; City of Phoenix, General Dynamics Decision Systems*

Undesignated gifts received from May 1, 2003 to November 30, 2003

AT&T- The Northern Trust Co.

AT&T Community Giving Prog.

Aetna Foundation: *Richard M. Toll*
America's Charities: *Girls and Boys Town Workplace Giving, Jodi K. Nelsen*

City of Orlando: *Richard L. Levey*

Comm. Health Charities of CA

Spencer Andrews

David and Paula Benham

Blevins Construction, Inc.

Ronald C. Coleman

PSEG - Brian Connor

Dee Goodrich

iGive.com

Mary and James Harmon

Lockheed Martin Employees' Fdn.

Patricia and Dana Jandreau

Manhasset Middle School Eighth Grade

Student Gov. Treasury

Sears Roebuck & Co.

South Hills Village Associates

Lexie F. McCraney

Gerald and Barbara Moore: *Benjamin Moore & Co. Matching Gift Program*

CAL FED Workplace Giving: *First*

Nationwide Mortgage: Michele L. Damon, M. H. Faecke and Deborah Sprick

Goggans Construction Co.

Hemera Technologies Corp.

IBM Corporation

Jr. Woman's Club of Wyoming Fdn.

Merck Employee Giving Cpgn.

Network For Good:

Kathryn Flynn, Ellen Nearman, Chris Hallahan, Kenny Yee, Friends of Tom Standing

The Ruth Church McKay Fdn.

Allison Smith Terrey

VG's Food Center

Scicom Data Services

Greg and Sue Smokovitz/ Accenture -

Community Meeting Charitable Org.

Steve and Adele Sopko

Heather Swantek

Dean and Bev Walhof

Wells Fargo Community Support:

Patricia Alexander, Lisa Hirsch-Handley, Cindy Morimoto

Kathleen F. White

Alice Winge

World Reach, Inc.: *Tim Cox*

**Please note that this issue of
HISTIO NEWS does not list donations
resulting from fundraising events.**

**All donations collected through
fundraising events will be reported
in the next issue of the newsletter
which will focus on fundraising.**

SUPPORT THE HAA

MARY KAY COSMETICS!

Carol Swanson, an Independent Senior Sales Director with Mary Kay, would like to extend a generous offer to all Histiocytosis Association members. Carol will donate 25% of the total purchase price from all orders placed at her personal Mary Kay website that reference the Histiocytosis Association of America. In addition to her generous donation Carol will pay all tax and shipping costs for each order. To take advantage of this wonderful opportunity please visit

<http://www.marykay.com/carolswanson>.

When ordering be sure to write "Histiocytosis Association" in the comment box at the bottom of the order form.

Carol's grandson Ben has been battling Histiocytosis for two years since he was diagnosed at the age of six months. To learn more about Ben please visit www.stokman.com.

REGIONAL MEETING UPDATE

Please note that the Regional Meeting scheduled for October 2004 in Chicago has been cancelled due to the unavailability of funding.

HISTIOCYTOSIS AWARENESS PINS

In an effort to promote knowledge of histiocytosis the HAA has designed a limited edition Awareness Pin. Pins are navy blue with silver trim, measuring approximately 1 and ¼ inch long. They are made in the classic "Ribbon Awareness" style. These unique pins are selling quickly, be sure to order yours soon! Each pin sells for \$10, including shipping.

HAA LOGO T-SHIRTS

New HAA logo t-shirts are now available. They are white with a blue HAA logo and are available in the following sizes:

**Children's small, medium, and large
Adult small, medium, large, and extra-large**

To order either a pin or t-shirt with your Visa, MasterCard, or American Express, please call the HAA office at:

856-589-6606

or send a check to:

**Histiocytosis Association of America
72 E. Holly Avenue, Suite 101 • Pitman, NJ 08071**

Be sure to include the number of pins or t-shirts and/or sizes as well as an address to which the item(s) should be shipped.



**Histiocytosis Association of America
72 East Holly Avenue, Suite 101
Pitman, New Jersey 08071 USA**

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