

Lupus Courier

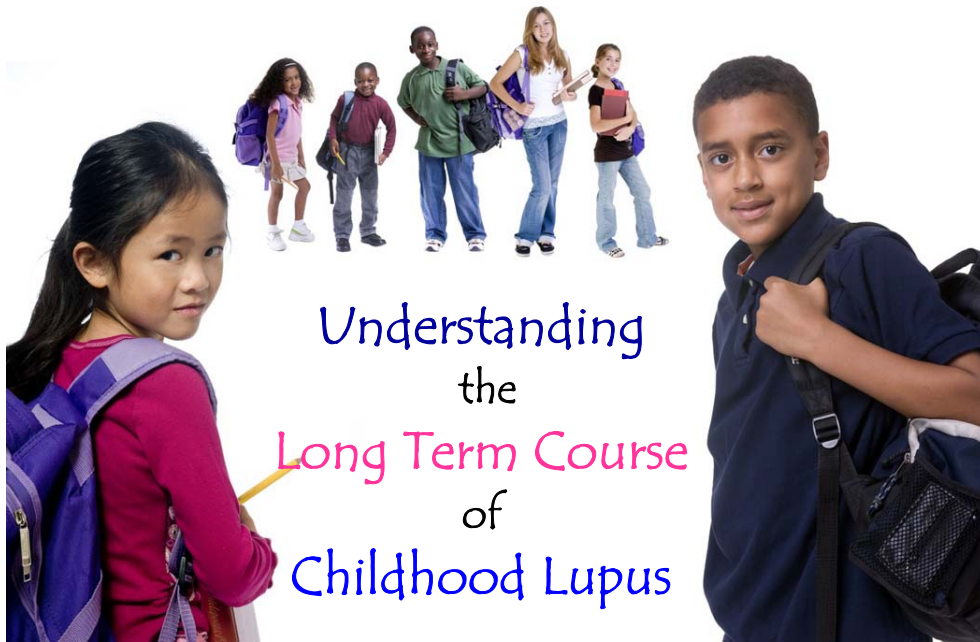


LUPUS SOCIETY OF ALBERTA



PHYSICIANS' EDITION

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Understanding the Long Term Course of Childhood Lupus

Dr. Rob Rennebohm, Pediatric Rheumatologist with the Alberta Children's Hospital and Clinical Professor with the University of Calgary Faculty of Medicine, described lupus as an **immune mistake disorder** which develops because a person's immune system starts to make mistakes, attacking parts of the person's own body, such as skin, joints and/or kidneys.

In a lecture hosted by the Lupus Society of Alberta on January 31, Dr. Rennebohm said that the long term course of lupus depends on several factors, including the extent to which the patient's immune system is capable of self-correcting its mistake. Dr. Rennebohm described the mistake-prone immune system as the "**Fire Setter**" which "sets fires" in various organs in the patients' body, at whatever level of intensity it is prone to do so.

Some fire setting immune systems set vicious blazing fires, others set only mild fires, others moderate fires. The immune system attacks things it should be leaving alone, as if it mistakenly sees an invader in those tissues, and dutifully attacks the tissues.

The course of the disease and treatment depend on the individual immune system's capacity to self-correct, to stop setting fires within the body. Some fire setting immune systems have great capacity for self-correction, while others have less capacity. Children seem to have greater capacity for self-correction than do adults. Some ethnic populations, such as African-Americans, tend to have immune systems that not only have poor capacity for self-correction, but are also prone to make the mistake at a higher level of intensity, setting and maintaining vicious, destructive "fires" within the body.

In the early years of his work as a Pediatric Rheumatologist and researcher, Dr. Rennebohm observed that 2 patients who were close in age and presented with the same initial clinical manifestations and who were treated in an identical fashion had different courses of disease. One patient, a 10 year old girl, was able to be tapered off medication and went successfully into remission with no return of disease symptoms.

The second patient, age 11, did not tolerate the same tapering schedule and could not be successfully tapered off of medication until the 4th year of treatment. Dr. Rennebohm asked himself: "Why did the first patient tolerate tapering, go into remission, and never relapse --- while the second patient failed to do so, despite the same initial symptoms and the same initial treatment?" He was satisfied that the initial therapy was successful and that the second patient was compliant, taking medication as prescribed. He theorized that the second patient's immune system was immunogenetically predisposed to make the lupus mistake for a longer time, because it had more difficulty self-correcting. Dr. Rennebohm concluded that the second patient had much less capacity for self-correction than the first patient.

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Dr. Rennebohm decided that as the treating rheumatologist, he should not take credit for the first patient's relatively short disease duration and should also not take the blame for the second patient's more difficult and prolonged clinical course and concluded that the natural pace of self-correction is individual and immunogenetically determined.

In order to treat the disease in the most effective way, he described his responsibility: "to try to imagine as accurately as possible what initial medications and dosages would be needed to counteract the intensity of the immune system's mistake at that time, then try to imagine as accurately as possible the likely pace and course of the immune system's self-correction, and taper accordingly. Then, interpret along the way whether I was tapering too quickly, too slowly, or just right."

Dr. Rennebohm's 30 years of pediatric rheumatology have led him to conclude that the long term course of lupus depends on the following 4 factors:

1. The extent to which the individual patient's immune system is prone to make the lupus mistake.
2. The level of intensity at which the patient's immune system is inclined to make that lupus mistake.
3. The extent to which the patient's immune system is capable of self-correcting its mistake.
4. The extent to which our medications are capable of actually changing the long term course, as opposed to simply, but importantly, suppressing the clinical manifestations of the disease.

A patient whose immune system is only minimally prone to make the lupus mistake is likely to make the mistake only once. A patient whose immune system is very prone to make the lupus mistake is likely to make the mistake, or set fires, repeatedly or continually. A patient whose immune system is prone to make the mistake at only a mild level of intensity will experience only mild disease. A patient whose immune system is prone to make the mistake, or set fires, at a very high level of intensity will experience very intense, severe disease manifestations or "fires."

Dr. Rennebohm said that unfortunately, we do not currently have medications that permanently stop the immune system from making lupus mistakes.

Most current therapies simply suppress the fires (in the skin, joints, kidneys, e.g.) that the patient's immune system has set and is fueling, or, at best, only partially slow or temporarily stop the fire setting.

Accordingly, once these medications are tapered or stopped, the fires build up again – if the immune system, by that time, has not yet self-corrected, that is, corrected its fire setting mistake.

There are varying degrees of self-correction, including the opposite – further loss of control. Some immune systems self-correct but then make the same mistake again, but self-correct again. Some immune systems will self-correct, make the same mistake again, but not self-correct as well the second time.

Medications which suppress the immune system may substantially suppress the symptoms (the fires) and modestly diminish the intensity of the immune mistake, i.e. slow down the fire setter. Prednisone treatment lowers the severity of symptoms, but does not change the ultimate disease duration or the immune system's mistake pattern. Methotrexate, Imuran and Cellcept further lower the severity of symptoms and allow the reduction of pred-

nisone dosage, but these medications will not change the disease duration or the pace or extent of self-correction. In severe lupus, even aggressive treatment with Cyclophosphamide may fail to shorten the disease duration.

Two therapies that may have potential to permanently stop the fire setting are stem cell transplantation and Rituximab. Rituximab is an antibody against B cells which are found in the immune system and works by killing B cells, stopping the immune system from setting fires. The scientific goal is that when the B cells regenerate they will not go into attack mode, setting fires. Dr. Rennebohm has concluded that immunogenetic factors largely explain why one child is more likely to develop lupus than is another child and whether one child is

more likely to develop severe lupus rather than mild lupus.

Immunogenetic factors also probably explain why some patients follow a prolonged and difficult course of disease, where their immune systems do not quickly self-correct, while others follow a much shorter course, with greater capacity for self-correction.



Childhood Lupus *continued*

Early, aggressive treatment is very important, because it improves ultimate outcome and provides comfort and protection through the course of active disease. Early, aggressive and sustained treatment continually suppresses the fires, which protects the patient and provides comfort until the immune system self-corrects. The treatment may not be capable of altering the intensity and duration of the fire setting but by dousing the fires, it helps the patient tremendously.

Treatment decisions include choosing the correct initial drug(s) and dosage(s), tapering at the best rate and choosing the best combination of medications. Treatment should be designed, conducted and adjusted in the context of a thorough understanding and recognition of the different paces and degrees of spontaneous immune self-correction. Treatment should be based on a careful, objective, imaginative, insightful, rigorously and compulsively studied appreciation of the variety of natural courses and paces of immune system self-correction that can occur.

Dr. Rennebohm stressed the importance of teaching the concepts of the fire-setter, the fires, the capacity for self-correction and goals of treatment to the patients and their families, so that they can appreciate the spectrum of possible courses their disease could follow, as well as correctly appreciate why their particular disease is behaving the way it is, appreciate why and how the treatment decisions are made and appreciate the importance of good compliance and close follow-up.

Throughout the course of the disease, it is possible but not proven that excellent nutrition, gently invigorating exercise, and good psychosocial health can reduce the intensity of disease and promote self-correction, at least somewhat, thereby permitting less use or lower doses of immunosuppressive drugs. Likewise, poor nutrition, no exercise, and poor psychosocial health possibly promote increased disease intensity and possibly hamper self-correction. Dr. Rennebohm encourages his patients to take good care of their bodies and minds so they are in positions of strength to fight the fires and give their immune systems the best chance to self-correct.

[This article was prepared by Christina Seger, Past President of LSA in conjunction with Dr. Rennebohm]

The Future Directions of Lupus Research

Presented by:

**U.S. Department of Health and Human Services;
National Institutes of Health; National Institute of
Arthritis and Musculoskeletal and Skin Diseases**

Chapter 4:

Pediatric Lupus, Special Populations, Epidemiology, and Health Services Research

Lupus is a disease that affects people of virtually every age, race, ethnic background and socioeconomic status. Yet some groups are affected more commonly and/or severely than others. For example, children and adolescents under the age of 18 make up only 20 percent of lupus patients, yet the disease in children is often associated with more severe renal and hematologic involvement than it is in adults. As many as 60 percent of children with lupus have renal involvement (lupus nephritis).

Lupus is believed to be three times more common in African Americans than in white women. It is also more common among women of Hispanic/Latino, Asian and Native American descent. Black and Hispanic/Latino women tend to develop symptoms at an earlier age than other women do. African Americans and Hispanics also have more severe organ system involvement; that is particularly the case for lupus nephritis.

Research on these high-risk populations is a major focus of lupus investigators. By studying the factors that lead to disease or more severe disease in these populations, scientists will gain a greater understanding of these health disparities and how to address them. But even more importantly, research in one group has potential implications for all groups, by providing scientists clues into the mechanisms of and eventually treatments for the disease.

Pediatric Lupus Breakthroughs

- The recognition that lupus is similar in children and adults, yet children tend to have more severe renal and hematologic manifestations.
- Recognition of the role of type I interferon signature and abnormal myeloid cells play in active pediatric lupus.
- The establishment of the Childhood Arthritis and Rheumatology Research Alliance (CARRA), a network to study pediatric lupus and other childhood rheumatic diseases.

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- The establishment of the APPLE trial in pediatric lupus. This trial has increased the understanding of institutional, regulatory, budgeting, site, coordinating center and design issues.

Because of their disease severity and young age, lupus is a particular burden for children. Thus, any research that leads to improved understanding, treatment and quality of life in children has significant, life-long implications.

Yet research in children has the potential to do much more than help children; more generally, studying children is valuable for a number of reasons. Children are more likely to be referred to pediatric or adult rheumatologists earlier in the disease process than adults are, because the disease often becomes severe more quickly in children. Children can be followed very long-term because of their young age, offering insights into the course of the disease over time and the long-term benefits and risks of the disease and its treatment.

Pediatric disease is similar to adult lupus. Aside from the severity of renal and hematologic manifestations, disease manifestations in children do not differ qualitatively from those of adult-onset disease. Thus, many findings about disease in children are likely to be applicable to individuals of all ages. Children are less likely to have comorbid conditions or to have been or be on other medications. They also have a better tolerance to medications in general and less hepatic damage from lupus treatment.

Children with lupus, at ages prior to, and going through puberty, provide a unique view to understanding how hormones affect various aspects of lupus.

Genetic studies may be more revealing in children, because stronger genetic contributors lead to earlier disease onset. Studying inheritance is possible because most children have at least one living parent, which allows for the study of DNA in both parent and child.

Similarly, there is a wave of information emerging about autoinflammatory diseases and the genes associated with them that usually have onset in childhood or adolescence. These include Familial Mediterranean Fever (FMF), TNF Receptor-Associated Periodic Syndrome (TRAPS), and most recently, Neonatal Onset Multisystem Inflammatory Disease (NOMID). Each of these diseases is rare, but is so characteristic that it would be helpful to study them for a better understanding of other autoimmune diseases.

Children's immune systems and microbial immunity are still developing until age 18 to 21. Lymphoid tissue grows until puberty; IgA antibodies reach adult levels only after puberty and thymic involution does not begin until puberty. Children and adolescents have somewhere in the range of 10¹⁴ (100 trillion) T-cell receptors, whereas adults have just 10⁷ (10 million) so an enormous amount of pruning occurs at adolescence and beyond. Studying children allows scientists to compare normal immune system development to lupus etiology.

Studying differences in microbial immunity between children in developed and developing countries may provide clues to autoimmunity as well. For example, immunity to common viruses, such as EBV and cytomegalovirus (CMV) occurs much earlier in developing countries. In Western countries, greater than 90 percent of individuals have immunity to EBV and CMV in early adulthood. In developing countries with underserved populations, however, immunity to both viruses occurs much earlier; 90 percent or greater may have immunity by age 5.

Such differences could potentially affect the development of autoimmune disease.

Studying the role of environmental triggers may, in some way, be more revealing in children and adolescents since these populations tend to have a lower threshold for some environmental triggers. Studies looking for an association between lupus and microbes that commonly infect a large section of the population may be more likely to pay off in children, in whom the differences between exposed and unexposed individuals is greatest.

For example, both Lyme disease and toxic shock syndrome were first recognized in children.



The course of pediatric lupus varies geographically, raising questions about possible environmental exposures that may be triggering and/or exacerbating lupus in those areas.

However, challenges to studying children do exist. The primary drawback of studying children is the relatively low number of pediatric patients, which makes it difficult or impossible to find enough children in a single center to study. Multi-center studies could potentially draw together more patients; however coordinating and harmonizing several centers is challenging. Additional challenges include: institutional, regulatory, budgetary and design issues; limited or non-existent access to patient materials and technologies for translational and mechanistic studies; difficulties in conducting long-term studies when children transition from pediatric to adult care.

It is important to increase the number of pediatric patients in adult studies to show stratification by age. Already some clinical trials that are mainly for adult patients are accepting older children. For example, one of the trials investigating mycophenolate in adults allows enrollment of children from age 12. It is essential to find ways to access young patients who would be appropriate for those studies and to develop ways to alert pediatric rheumatologists to the availability of those studies to appropriate patients.

Research Objectives

- Examine the genomics of lupus in children.
- Examine the immune development and microbial immunity in the development of lupus.
- Elucidate the role of environmental factors in pediatric lupus.
- Improve access to clinical trials for pediatric lupus patients through clinical networks.
- Develop core services such as tissue repository, immune reagent development cores, genomics, proteomics and metabolomics capabilities, informatics, pathology, etc.

Special Populations Breakthroughs

- The discovery that there is underascertainment/underreporting of deaths in death certificates of patients with lupus.
- The finding that African American ethnicity, lack of health insurance, and older age are associated with underreporting.

- The finding that African admixture is an important risk for the occurrence of lupus.
- The finding that African American children with lupus nephritis experience progression to end-stage renal disease despite aggressive treatment.
- The finding that African American children with either lupus nephritis or neuropsychiatric involvement experience high mortality rates despite aggressive treatment.
- The finding that Hispanic ethnicity is a risk factor for the occurrence of initial damage.
- The finding that poverty, not ethnicity, is a consistent predictor of mortality in lupus.

Lupus occurs disproportionately in certain ethnic populations. Until recently, studies of minorities and lupus focused on African Americans as the main minority population in the United States, but an increasing Hispanic population, now the largest minority and fastest growing – not only in the Southwest or the Northeast, but in Colorado and the Southeastern United States – has brought more attention to the unique problems of that group.

The largest study of lupus in ethnic populations to date, the Lupus in Minorities: Nature vs. Nurture (LUMINA) study, was designed to understand why minorities are affected more frequently and more severely by lupus. is considered, poverty, and not ethnicity, is a consistent predictor of mortality in lupus.



The Future Directions of Lupus Research

LUMINA is a multi-ethnic longitudinal study of outcome in three geographic areas: Alabama, Texas and Puerto Rico. Highlights of the study's findings include:

-Hispanics from Texas tend to develop damage more rapidly; however, over time, the damage is comparable to that accrued by African Americans.

-Hispanics from Texas and Hispanics from Puerto Rico have different disease manifestations, course, and outcome. Patients from Puerto Rico have much milder disease but also have much better socioeconomic status.

-Caucasians accrue less damage from lupus than do Hispanics or African Americans.

-African Americans are more likely than Caucasians and Hispanics to die from lupus, although when poverty is considered, poverty, and not ethnicity, is a consistent predictor of mortality in lupus.

Aside from the study's ethnicity-specific findings, the LUMINA study has demonstrated that hydroxychloroquine seems to prevent the occurrence of damage in lupus and increase survival by as much as 60 percent. This finding is particularly important because in the past hydroxychloroquine was used only in patients with mild to moderate, but not severe, disease.

Studies in other ethnic minority populations have offered additional insights. For example, a study by British researchers showed that African admixture was a risk factor for the occurrence of lupus among residents of the Caribbean island of Trinidad, while the incidence of lupus in Africa itself is not that common. Research has shown that both Hispanics and African Americans have a rapid progression of kidney disease. It is not known whether this rapid progression is related to poor access to care or lack of compliance with prescribed care or whether it actually represent a less favorable response to treatment.

An argument for a less favorable response to treatment is reflected in a pediatric study, looking at predominantly African American children. Children with lupus nephritis and neuropsychiatric involvement had a higher rate of progression to end stage renal disease and a higher mortality rate than children with lupus nephritis alone despite aggressive treatment.

Yet studying lupus deaths is difficult due to significant under-ascertainment of lupus in death certificates. Underreporting has been associated with certain factors such as African American ethnicity, lack of health insurance and older age.

To fully understand the role of poverty in disease in minorities, researchers must understand what aspects of poverty are related – for example, is it that they cannot get health care or that they do not take the medication? Statistically, poverty becomes such a strong variable that it overshadows everything else.

Providing the best treatment for minorities and, in fact, all patients with lupus, requires not only aggressively treating the severe manifestations such as lupus nephritis, but also not losing sight of basic lifestyle factors. For example, smoking is a major risk factor for atherosclerosis, which is already a common problem in patients with lupus, yet many lupus patients smoke. Programs to help people with lupus stop smoking could help minimize complications of the disease.

Also, it is vital to find a systematic way to inform clinicians about proven medication benefits. For example, if a treatment like hydroxychloroquine prevents the accrual of damage, it should be introduced as a therapy for everybody with lupus as close to the diagnosis as possible.

Research Objectives

- Better define the distribution of lupus and its impact at the population level.
- Disentangle the contribution of socioeconomic vs. genetic factors to the occurrence, course, and outcome of lupus.
- Identify lupus patients at risk of poor intermediate and long-term outcomes and intervene on risk factors.
- Identify strategies to improve lifestyle habits among lupus patients, including smoking cessation.
- Study lupus in other minority groups such as Native Americans, who tend to have severe disease and antibodies that do not always correlate with that in lupus patients of other ethnicities.

Epidemiology

Accurate estimates of the number of people who have a disease – as a whole and within specific groups – are important for a number of reasons, including understanding the disease and its impact; predicting groups and individuals who are most likely to develop lupus and, thus, are candidates for screening and preventive care; and providing care and services to people with the disease. Getting accurate estimates and updating them periodically can also enable researchers to determine if disease incidence is increasing and if so, start taking steps to understand why.

Getting accurate estimates and updating them periodically can also enable researchers to determine if disease incidence is increasing and if so, start taking steps to understand why. But estimates about the number of individuals with lupus vary widely, depending on the study from which the estimate was derived. Different study techniques, methodologies, populations and definitions of what constitutes lupus can lead to vastly different prevalence estimates. The range is large and tells us little about the true magnitude of the problem.

What most researchers agree on is that lupus is more common in women than men and that African Americans, Afro-Caribbeans, Hispanics, Asians, and Native Americans are affected more commonly than Caucasians. But even the degree of that discrepancy is disputable. The estimates range from a five to nine or 10 times increase among those high-risk populations. Prevalence and incidence figures for other groups and specific lupus-related problems can be even more problematic. Following are some examples:

Asians, and Native Americans are affected more commonly than Caucasians. But even the degree of that discrepancy is disputable. The estimates range from a five to nine or 10 times increase among those high-risk populations. Prevalence and incidence figures for other groups and specific lupus-related problems can be even more problematic. Following are some examples:

Lupus pregnancy and neonatal lupus

As with lupus in general, there are not consistent estimates of the prevalence of lupus pregnancy or neonatal lupus. Neonatal lupus is a rare, lupus-like disease in a neonate that begins during pregnancy due to the transfer of autoantibodies from mother to child through the placenta.

In neonatal lupus there are differences in incidence estimates depending on the aspect looked at – congenital heart block vs. the presence of anti-Ro and/or anti-La antibodies vs. cutaneous involvement. Even so, there is more incidence data on the disease than prevalence data. The prevalence of neonatal lupus is difficult to determine when disease presents beyond the neonatal period (0-6 months) and long-term follow-up of children with mothers that have lupus, to a certain extent, is lacking.

Estimates of other problems in pregnancy related to lupus are also lacking. Most figures have been of spontaneous abortion, fetal death and total losses in pregnant lupus patients.

Estimates of other problems in pregnancy related to lupus are also lacking. Most figures have been of spontaneous abortion, fetal death and total losses in pregnant lupus patients. Lupus-related problems in pregnancy may not necessarily result in a fetal loss, but rather fetal growth restriction, preeclampsia and preterm birth. The estimates of these vary widely. All of these problems are increased in women with lupus compared to women without the disease, but studies showing the relationship between lupus and these pregnancy complications were conducted before hydroxychloroquine came into wide use as a lupus treatment and particularly throughout pregnancy. Researchers are interested in learning how use of hydroxychloroquine in recent years may have impacted these figures.



The Future Directions of Lupus Research *continued*

Exogenous agent-induced lupus

Encompassing a form of lupus referred to as drug-induced lupus (DIL), exogenous agent-induced lupus is a lupus-like syndrome that occurs in response to an agent such as a drug, UV light or an infectious agent. In some cases, agents may modify the course of lupus by unmasking or accelerating disease. Examples of such agents that have been studied (but not necessarily all proven to cause or accelerate the development of lupus) include silica, heavy metals, hair dye and smoking. The incidence and prevalence of this condition is not known.

Given the relatively low incidence rates of lupus in the general population, classical incidence and prevalence studies of environmentally-induced lupus would be difficult to conduct, especially in the absence of widespread disease registries. There is a need to develop carefully designed epidemiology (case-controlled) studies to improve the understanding of known and proposed environmental risk factors. New and improved instruments and technologies to measure environmental exposure in populations need to be developed. The current approach has relied upon recall data, and methods are needed to improve the accuracy and consistency of such data collected across different study populations.

**Mission of The Lupus Society of Alberta:
To provide education and support
on lupus and lupus related issues
and enable research to find
effective treatments and cures.**

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