



The Carousel Network

**Chronic Neuroimmune Disease
Information and Support for Sonoma County**
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Autoimmunity: The Common Thread

Autoimmunity is not at all uncommon: it exists in all of us. Every one of us has some degree of autoimmunity naturally, and it does not seem to do us any harm. It is, in fact, only a minority of cases where autoimmunity actually produces damage in the body, producing disease. So there are two basic questions researchers in this field need to unravel: How does autoimmunity arise – what are the circumstances that trigger it? And what are the factors in the autoimmune response that cause disease?

The Carousel Network (TCN) offers information on the various diseases and disorders associated with chronic neuroimmune diseases, such as chronic fatigue syndrome, fibromyalgia, multiple chemical sensitivity, autoimmune thyroid disease, etc. The information is intended to help patients and caregivers make informed decisions about the patient's health, diagnostic testing, and treatment in conjunction with their health care practitioners. TCN does not diagnose patients nor recommend specific medical or palliative treatments.

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Autoimmunity: The Common Thread
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The topic Mrs. Ladd has asked me to discuss with you this afternoon is "Why Are Autoimmune Diseases Related." In getting started we must first clarify what we mean by autoimmunity or autoimmune disease? We're all familiar with the term immunity now that AIDS has become so prominent. To encapsulate the word, it means, essentially, resistance to disease. Usually we are speaking of infectious disease, and immunity comes through experience with the disease. If we've had mumps as children, we know that we are not susceptible to a second episode of mumps. We say that we are immune to mumps. If we have chicken pox as children, we know that we are immune to chicken pox, generally, for the rest of our lives. The same with measles — we know that we don't get them a second time. If we are vaccinated or immunized, we acquire our immunity through an artificial means. Therefore, we can acquire immunity, either through natural exposure to the disease or through artificial means, such as vaccination. Originally, then, immunity was thought of as the body's way of defending itself against disease.

One of the basic precepts of immunity, going back to the very early days of the 20th century, has been that if immunity is going to benefit us, it has to be directed to something foreign, something outside of the body. So it has always been a precept of immunologists that the immune response only concerns foreign material. When I began in this field - 40 years ago - almost everyone believed that immunity could be directed exclusively against foreign materials. That idea implies that there is some mechanism by which the body can distinguish what is *itself* and what is *not itself* - we now say the immune response shows self, non-self discrimination.

What happened about 40 years ago? Well, a number of key discoveries were made - some of them in my own laboratory - which turned that doctrine of self, non-self distinction on its head. We found that there are a number of instances in which the immune response is directed to something in the body of the host itself. It seemed implausible, even contradictory; but, in fact, that was exactly what we found: there are some circumstances where the immune response attacks the body of the host itself. The host may be an animal or it may be a human patient. That is what we call autoimmunity. Autoimmunity is nothing more than the immune response directed to the body of the patient.

Let me define a second term for you, autoimmune disease. These two terms do not mean exactly the same thing, and the difference may be important to us as we talk about some of these issues later this afternoon. Autoimmune disease is a disorder that occurs because of autoimmunity -- a disease that is caused by an immune response to the body of the patient himself or herself.

Now, in defining autoimmune disease that way, I imply that there is autoimmunity without autoimmune disease. In fact, we now know that autoimmunity is not at all uncommon and that it exists in all of us. Every one of us has some degree of autoimmunity naturally, and it does not seem to do us any harm. It is, in fact, only a minority of cases where autoimmunity actually produces damage in the body, producing disease. So there are really two basic questions that I, as an investigator, and my colleagues in this field need to unravel.

First question is: How does autoimmunity arise? What causes the body to produce an immune response to itself? What are the circumstances, what are the mechanisms, what are the triggers for the phenomenon that we call autoimmunity? That's one question. That's a very basic question that involves biology, chemistry, even biophysics. It requires a deep understanding of the immune system. We need to know a lot more about how the body produces immunity reactions. We know a great deal, but there are still enormous voids in our understanding. We must know that in order to understand how the body normally distinguishes self from non-self.

The second question is: What are the factors in the autoimmune response that sometimes cause disease? These are the two critical questions that are the topics of basic research. Sometimes the feeling is expressed that basic research is scientists fooling around in the laboratory doing things that are unimportant. We must understand that if we are ever going to develop effective treatments -- or, more important -- cures for preventing autoimmune disease, we must understand them. Just as we would never have been able to control infectious diseases until we found the bacteria or viruses that cause diseases, so we cannot deal effectively with autoimmune disease until we understand its cause.

Now, let's get to the question Mrs. Ladd put to us: Why are autoimmune diseases related? Here I have to give you a little bit of insider information about how medicine is organized in this country.

When medicine grew up in the middle ages, physicians had to divide diseases into various categories. The only way they could classify diseases was anatomically, that is, where does the disease occur? Physicians later divided themselves into doctors who are interested in diseases of the lungs, and

other doctors were interested in diseases of the skin. Other doctors were perhaps interested in disease of the intestinal tract or the reproductive tract or the urinary tract. Most medicine is still organized on the basis of the anatomy of the disease — on where the disease occurs. You go to a heart specialist (a cardiologist) if you have heart disease, to a neurologist if you have nervous system disease, to a dermatologist if you have a skin disease, and on and on.

The medical community organized itself that way because that was the level of sophistication at the time. But starting with Louis Pasteur about a hundred years ago, a change occurred. For the very first time we began to understand why disease occurs --not where it occurs, but why it occurs. And when we speak of why disease occurs, we speak of something else, and that is what we call etiology.

Etiology means cause. If we are concerned with curing disease and possibly even preventing disease, the etiology is extremely important information. Why have we been able to control so many infectious diseases? Because we now know the bacteria and the viruses and the parasites that cause these diseases, and we can develop antibiotics and other drugs that will specifically attack that organism. Discovering the etiology has allowed medicine to progress to its present state where we can successfully treat and even cure many diseases.

Within the lifetime of most of us, we have ways of effectively treating infectious disease. Until World War II, until antibiotics were introduced, we did not have methods that cured disease. We had treatments that alleviated the symptoms of disease, but we really didn't cure disease. With the introduction of antibiotics — penicillin, streptomycin, and other substances -- we now have a way of treating. And that's why it is so important to understand etiology.

There are a few other groups of diseases which are now defined by their etiology. Allergies are an example. If you have an allergy, it doesn't matter whether it's an allergy of the nose, (hay fever) whether it's in the lungs, (asthma) or whether it's atopic dermatitis, (a skin disease). You may go to an allergist because all of these diseases have the same etiology. They have different anatomies, but they have the same etiology. That's the way progress is being made by bringing together diseases with the same etiology. Autoimmunity is an etiology: it is a *cause* of disease. Anatomically, autoimmune disease is very diverse; and that's why we see specialists in so many areas of medicine studying autoimmunity. They may be rheumatologists who are interested in joints; they may be dermatologists who are interested in skin; they may be cardiologists who are interested in the heart; or gastroenterologists who are interested in the gastrointestinal tract. But the common etiology for all of these diseases -- for Crohn's disease of the gut; for lupus of the skin; for rheumatoid arthritis of the joints -- the common etiology that brings together all of these diseases is autoimmunity.

A major aim of the American Autoimmune Related Diseases Association is to help us understand that all of these diseases, diverse as they are, in their anatomical location, and in their clinical manifestation, are related because they have the same etiology; they are all caused by autoimmunity. In my opinion, the only way we're going to develop really effective treatments will be to treat the cause of the disease, not the symptoms. The symptoms are late; the symptoms are at the end of the train of events. We want to get on the train at the very beginning.

Now, what are some of the specifics of this relationship? Let's lay out some of the principles that we now understand about the etiology of autoimmune disease.

Unlike some diseases, autoimmune diseases do not generally have a simple, single cause. There are usually two major categories of factors that are involved in causing them: genetics and environment. Virtually every autoimmune disease combines these two factors. Let me explain.

First, genetics. Genetics is involved in the development of autoimmune disease, but autoimmune diseases are not typical genetic diseases. What is a typical genetic disease? Most of us have heard of sickle cell anemia — that's a genetic disease. It's a disease in which the victims have a specific genetic mutation. If you inherit this mutation from one parent, you have sickle cell trait: and if you inherit it from both parents, you have sickle cell disease. We know what the gene is, and we even know a great deal of how that works; so we know the etiology of that disease.

That's not, however, the way genetics works in autoimmune disease. In autoimmune disease, multiple genes are involved; we have genes that collectively increase the vulnerability or susceptibility to autoimmune disease. What is inherited is not a specific gene that causes a specific defect in metabolism; but several genes which increase vulnerability or susceptibility to autoimmune disease.

How do we know that there is a genetic basis of autoimmune disease? I can cite three kinds of evidence. The first is that autoimmune diseases tend to occur in families. If there's one case in the family, there's likely to be another.

However, it is not a particular autoimmune disease; it is generally a tendency to autoimmunity. One family member may have lupus, another family member may have Sjögren's disease, a third member of the family may have rheumatoid arthritis. That's one bit of evidence for genetic involvement,

and we've known this for a number of years. If we ask patients when they come to us, "Is there other autoimmune disease in your family?" - and we actually have to mention them because most people know very few - they will usually say, "Yes, my aunt had thyroid trouble. . . my grandmother had Crohn's disease. . . etc."

But we call this soft data in science because families share genes and that's some indication of genetics; but families share many other things too. So we need to look further.

The second thing we do is to look at twins. We compare two kinds of twins. There are twins that are genetically identical, and there are twins that are non-genetically identical. If something is caused by an environmental factor, there should be no difference between identical twins and non-identical twins. If there's a difference, it suggests that genetics plays a role. These studies have been done for a number of autoimmune diseases, and the answer has always come up about the same. Genetic components represent something approximating half of the risks. In other words, if you have a genetic predisposition to autoimmunity, you may have twice or five times as much chance of developing autoimmunity as someone else -- not 100 times, but not zero either. So genetics plays an important role.

One group of genetic factors is particularly important. One of the things that immunology has taught us through the years is obvious but needed some kind of physical basis — it is simply that every human being is different from every other human being (unless you have a genetically identical twin). Every person is a little different from everybody else; we know that for certain when we try to transplant tissues, like kidneys or hearts, in general you cannot accept a kidney or heart from someone else unless we dampen your immune response. There clearly are significant physical differences between people. And we call the substance that causes that difference histocompatibility complex. We call the genes that provide that difference "major histocompatibility complex genes." Everybody abbreviates that long tongue twister by just saying MHC; and every species has an MHC, a major histocompatibility gene. In a human we call it HLA.

HLA is the major group of genes that distinguishes one human being from another. It is important in transplantation, and we do HLA typing regularly. It's important to us in autoimmunity because susceptibility to autoimmunity is associated with the HLA type. It represents the most important single genetic trait in estimating susceptibility to autoimmune disease.

There are three kinds of information that tell us if autoimmune diseases are genetic. I've mentioned two. One is family clustering; the second is the association with HLA. What's the third?

The third is that autoimmune diseases occur in animals as well as in human beings. With animals we can do the breedings that are necessary.

We can infer the same must be true in humans. In animals the equivalent of HLA determines susceptibility. In animals this trait is actually predictive. In humans we aren't yet at that point because we don't have enough information from humans to say, "because of your HLA factor you're going to develop an autoimmune disease." We can, however, say that you have a greater likelihood of this happening.

So we're getting to a point where we can almost predict who is more likely or less likely to develop autoimmune disease. Now this, again, is an example of how very basic research on a molecular level or on a genetic molecular level is beginning to pay off in human medicine.

I would like to conclude with the second half of the story. I've said that genetics accounts for about half of the risk of developing an autoimmune disease.

The other half is the agent in the environment which triggers the process. Unfortunately, we just don't know many of the triggers. We know there are certain drugs that can induce lupus. We know there are certain environmental substances like silica that can induce scleroderma. We suspect that there are certain dietary substances, such as iodine, that can exacerbate thyroid disease. So we're beginning to define the other half of the story, the environmental half. It is going to be, I think, an equally fascinating chapter in the saga of autoimmune disease in the next decade.

So, in summary, that's what autoimmune diseases have in common. That's why we feel very strongly there should be an organization like the American Autoimmune Related Diseases Association that brings together all of the research and all of the investigators and all of the physicians as well as all of the patients interested in autoimmune diseases. Let us begin to get to questions of etiology so that we can get at the root causes of these diseases, rather than being left at the superficial level of just treating the symptoms after the disease has had its destructive effects.

Reprinted from the American Autoimmune Related Diseases Association, 22100 Gratiot Avenue, East Detroit, MI 48021-2227. 810.776.3900 www.aarda.org

On note on the genetically identical twins: According to Roger Williams, Ph.D. (Biochemical Individuality: The basis for the genotrophic concept, 1956, 1998, University of Texas), even "identical" twins are not strictly identical. Book information: www.anapsid.org/cnd/books/biochem.html.