That's not the way genetics works in autoimmune disease. In autoimmune disease, several genes are involved. We have genes that together increase the likelihood that we'll inherit an autoimmune disease. How do we know that there is a genetic basis of autoimmune disease? There are three kinds of information that tell us whether autoimmune diseases are genetic.

Family Clustering

The first is that autoimmune diseases tend to occur in families. If there's one case of autoimmune disease in the family, there's likely to be another. However, it is not a particular autoimmune disease that runs in families, but it is a tendency to autoimmunity. One family member may have lupus, another family member may have Sjögren's disease, a third member 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, "Are there other autoimmune diseases in your family?"–and we actually have to list these diseases for them because people don't know these are all autoimmune diseases–they will usually say, "Yes, my aunt had thyroid trouble...my grandmother had Crohn's disease..."

Twin Studies

Scientists also look at twins. We compare two kinds of twins. There are twins who are genetically identical, and those who are non-genetically identical, called fraternal twins. 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 play a role. These genetic studies have been done for a number of autoimmune diseases, and the findings are generally the same. Genes play a role in about half of the risk for developing an autoimmune disease. 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. So genetics plays an important role.

HLA Factor

The second piece of information that explains how our genes affect the likelihood that we'll inherit an autoimmune disease is called our association with HLA. HLA is the major group of genes that distinguish one human being from another. The substance that causes the significant physical differences between different people is histocompatibility complex. We call the genes that provide that difference "major histocompatibility complex genes" or MHC. Every species has an MHC, a major histocompatibility gene. In a human, we call it HLA.

When we transplant tissues, like kidneys or hearts, we do HLA typing regularly. In general you cannot accept a kidney or heart from someone else unless we dampen your immune response. It's important to us because susceptibility to autoimmunity is associated with the HLA type. It represents the most important single genetic trait in estimating susceptibility to autoimmune disease.

Not Just a Human Disease

The third clue that genes are involved in autoimmune diseases is that they occur in both animals and human beings. We can breed animals to provide us with the genetic information we need. We can infer that the same findings must be true in humans. In animals, the equivalent of HLA determines susceptibility; and having this trait can actually predict getting an autoimmune disease.

In humans, we aren't yet at that point because we don't have enough information 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 an autoimmune disease.

Environmental Factors

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 do not know very 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 AARDA 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 autoimmune diseases.

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Autoimmunity
the common thread

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What Does Autoimmunity Mean?

What do we mean by autoimmunity or autoimmune disease? We're all familiar with the term immunity now that AIDS has become so prominent. It means, essentially, resistance to disease. We can acquire immunity, either through natural exposure to the disease or through artificial means, such as vaccination. Usually we are speaking of infectious disease, and immunity comes through contracting the diseases. 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 or measles or chicken pox. If we are vaccinated or immunized, we acquire our immunity through an artificial means. Children are vaccinated against polio, diphtheria and tetanus. Originally, immunity was thought of as the body's way of defending itself against disease.

One of the original ideas about immunity was that if immunity is going to benefit us, it has to be directed to something foreign or outside the body. Immunologists believed that immunity could be directed exclusively against foreign materials. That idea suggests that there is some mechanism by which the body can distinguish what is itself from what is not itself. Today we call that immune response self, non-self discrimination.

However, 40 years ago, a number of key discoveries 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 toward something in the body of the host itself, not outside the body. It seemed unlikely, even contradictory. But 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. 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.

Natural Immunity

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 in order to unravel the mysteries of autoimmunity, researchers are asking how autoimmunity arises.

What causes the body to produce an immune response to itself? What are the circumstances, the mechanisms, and the triggers for the phenomenon that we call autoimmunity? The answers lie in understanding the immune system. We need to know a lot more about how the body produces immunity reactions. We know a great deal, but not enough. We must understand how the body normally distinguishes self from non-self.

Researchers also need to know the factors in the autoimmune response that sometimes cause disease. Just as we would never have been able to control infectious diseases until we found the bacteria or viruses that cause diseases, we cannot deal effectively with autoimmune disease until we understand its cause.

How Medicine Grew Up?

In order to understand why autoimmune diseases are related, it's helpful to know how the field of medicine is organized in this country. When medicine grew up in the Middle Ages, physicians divided diseases into various categories. They classified diseases according to where in the body the disease occurred. They didn't know what caused disease, just where it occurred. Physicians later divided themselves into doctors who were interested in diseases of the lungs, the skin, the intestinal tract, the reproductive tract or the urinary tract. Most medicine is still organized this way. 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.

What Causes Autoimmunity?

Starting with Louis Pasteur about a hundred years ago, we began to understand why disease occurs–not where it occurs. And when we speak of why disease occurs, we speak of the cause or etiology of the disease. If we are concerned with curing disease and possibly even preventing disease, the etiology is the most 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.

Groups of diseases can now be classified by their etiology or cause. Allergies are an example. If you have an allergy, it doesn't matter whether it's an allergy of the nose, that is, 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. Progress is being made by bringing together diseases with the same etiology.

Autoimmunity is an etiology: it is a cause of disease. Because autoimmune disease affects many organs of the body, that's why we see specialists in so many areas of medicine who study autoimmunity. They may be rheumatologists who are interested in joints; they may be dermatologists who are interested in the skin; they may be cardiologists who are interested in the heart; or they may be gastroenterologist 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 joint– is autoimmunity.

A major aim of the American Autoimmune Related Diseases Association (AARDA) is to help us to understand that all of these diseases, different as they are, in their location on the body, in how they make us sick, are related because they have the same etiology. They are all caused by autoimmunity. The only way to develop effective treatments is to treat the cause of the disease, not the symptoms.

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.

The Genetic Factor

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, a genetic disease. That's a disease in which the victims of the disease 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.