

When the Body Attacks Itself

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Autoimmune diseases
afflict women much more
frequently than men

Sex discrimination can happen anywhere—in the classroom, in the workplace and even inside the body. Take autoimmune diseases, for example: recognized autoimmune disorders afflict an estimated one in 20 Americans, but women can be 10 times more likely to develop clinical symptoms than men. Some 75 percent of

rheumatoid arthritis sufferers are women. Similarly, women constitute between 70 and 80 percent of those with lupus (also known as systemic lupus erythematosus, or SLE) and between 80 and 90 percent of those with multiple sclerosis (MS). Why the gender bias?

The immune system normally works to defend the body against infections by identifying and eliminating invading viruses, bacteria and other disease-causing microbes. But in people with autoimmune disorders, the body turns on itself: the immune system mistakenly attacks other cells, tissues and organs. Why should a female's immune system be more prone than a man's to attack her own tissues? Or why should her tissues be more susceptible to autoimmune attack than a man's?

To address these questions, we need to understand more about how the immune system learns to identify which cells belong to the body and which are foreign. One of the key players is the T lymphocyte. These white blood cells, called T cells for short, police the body and attack any cells they recognize as foreign. Recent studies from my laboratory and others indicate that the process that normally instructs the T cells to differentiate between "self" and "nonself" may be flawed in people with autoimmune diseases. Further, it appears that the errors that hobble T cell training have different consequences depending on sex: males somehow circumvent the defects, which suggests that drugs based on male hormones may offer women some protection from the ravages of autoimmune diseases.

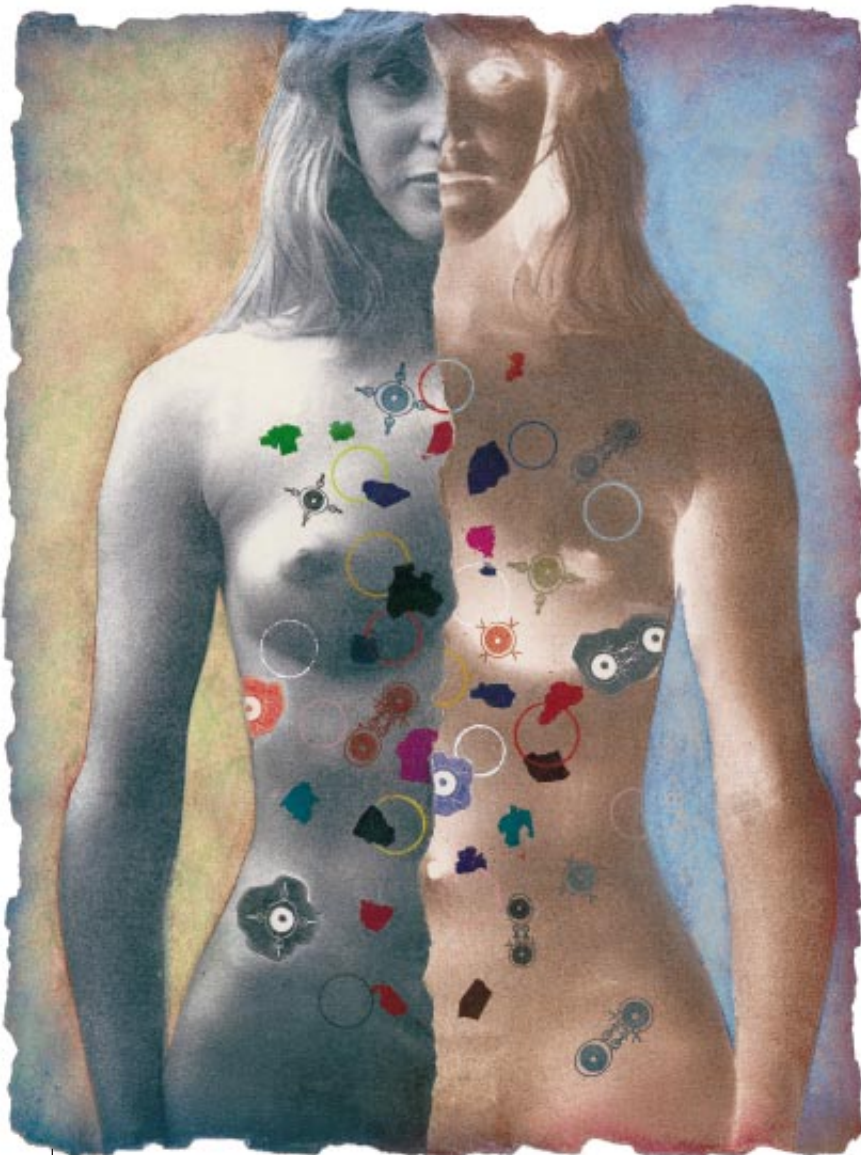
Autoimmune diseases attack a variety of tissues and organs in the body. In rheumatoid arthritis, the immune system targets the joints; in type I,

or juvenile, diabetes, the insulin-secreting cells in the pancreas are attacked; psoriasis and vitiligo target the skin; multiple sclerosis and myasthenia gravis attack the nervous system; Graves' disease destroys the thyroid gland; Crohn's disease targets the gut; and diseases such as lupus, scleroderma and Sjögren's syndrome attack multiorgan systems, including the skin, joints, kidneys, lungs and heart.

Because autoimmune disorders are so diverse, the symptoms vary depending on the syndrome. Someone with rheumatoid arthritis usually experiences pain, swelling and stiffness in the joints, whereas someone with Crohn's disease experiences diarrhea and severe abdominal pain. But many of the autoimmune diseases—particularly lupus, type I diabetes and MS—begin with more nonspecific symptoms, such as fatigue, which can make them difficult to diagnose early on.

Anatomy of Autoimmunity

To help diagnose autoimmune diseases, physicians often use laboratory tests that detect autoantibodies. Autoantibodies are proteins, one of the major types of molecules that make up all cells, that are mistakenly produced by the immune system and that recognize the body's own tissues. (In contrast, regular antibodies recognize only invaders.) At present, there are no cures for autoimmune disorders. Treatment involves using anti-inflammatory medications such as acetaminophen or ibuprofen to control the pain and, if the disease is severe, immunosuppressive drugs such as prednisone or cyclosporine to dampen the activity of the immune system. Unfortunately, immunosuppressive drugs prevent T



In women (and men) with autoimmune diseases, immune cells that normally protect the body from infection attack the body instead.

cells from multiplying, thereby hampering the immune system's ability to fight off infections, an effect that causes problems on its own. Although the various autoimmune diseases present different clinical pictures, they share a fundamental biological cause: T cells that destroy other cells of the body as if they were invaders.

Attack of the Killer T Cells

As part of the body's defense team, T cells patrol the bloodstream and tissues searching for any foreign proteins that might signal an infection. Early in their development, T cells must learn to recognize which proteins might be foreign and which are normal cellular proteins. In infants the training process centers in the thymus (hence the name T cells),

an organ that lies between the lungs near the top of the breastbone. But T cell education continues in the bloodstream throughout a person's life. T cells are taught to distinguish between self and nonself throughout the body by specialized immune cells called antigen-presenting cells.

Antigens are bits of protein that can invoke an immune response. Antigen-presenting cells expose T cells to protein fragments that come from invading bacteria and viruses and teach them to attack whenever they encounter such foreign proteins. This process primes T cells to destroy any cells in the body that might be infected by a disease-causing virus or microbe. But antigen-presenting cells also display fragments of proteins derived from the body's own cells. In this case, the antigen-presenting cells train

the T cells to ignore healthy cells that are part of the body. Normally, any T cells that show a tendency to attack cells that are displaying self-antigens are quickly eliminated.

In 1991 my colleagues and I determined that the antigen-presenting cells in patients with type I diabetes are not adequately educating T cells to distinguish between foreign antigens and self-antigens. The antigen-presenting cells fail to present protein fragments properly for T cell inspection—a sign of cellular immaturity. Since then, we have discovered that people with many different autoimmune diseases possess a similar defect in antigen presentation. Patients with lupus, rheumatoid arthritis and MS all possess immature antigen-presenting cells. Such immaturity may hold the key to autoimmune disease. If antigen-presenting cells are immature and do not properly display self-antigens, they can fail to instruct T cells to leave the body's tissues alone. Ours was the first evidence in humans to suggest that the fault lies not in the T cells but in their teachers.

Finding the Defect

Why don't antigen-presenting cells mature in people with autoimmune disorders? To answer that question, we turned to an animal model of autoimmune disease, the nonobese diabetic (NOD) mouse. These mice develop symptoms of several different autoimmune diseases, including diabetes and Sjögren's syndrome. And like humans with autoimmune disease, NOD mice have immature antigen-presenting cells that fail to teach T cells to recognize the body's tissues. When we examined female NOD mice—80 to 90 percent of which exhibit signs of autoimmune disease—we found that the animals had a defect in their antigen-processing pathway. Before antigen-presenting cells can display protein fragments for T cell inspection, they have to process them internally. This involves cutting up the proteins into the right-size fragments and shipping them to the surface of the antigen-presenting cell, where the T cell can find them easily.

By 1997 my colleagues and I had found that NOD mice have a single mutation that effectively cripples antigen processing in antigen-presenting cells. The defect actually shuts down two genes that are critical for antigen processing and the maturation of lymphocytes, including T cells. When these genes are inactivated by mutation, antigen-presenting cells don't mature as they should,

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and they fail to display properly the protein fragments that teach T cells what to attack—and what not to attack. Although people with autoimmune disorders also have impaired antigen processing, we have not yet linked mutations in the human versions of these defective mouse genes with a human autoimmune disease. Even if such mutations were found, autoimmune diseases are very complex and will probably involve problems in multiple genes. Although no single mutation is likely to underlie all autoimmune diseases—or even any particular one—each new discovery could point the way toward more effective treatments for these disorders.

What about Sex?

NOD mice show the same kind of gender bias as humans when it comes to developing symptoms of autoimmune disease. Although the mutation we discovered is present in both male and female NOD mice, only 10 to 15 percent of male NOD mice develop diabetes. So how could this defect hamper the maturation of antigen-presenting cells and antigen presentation preferentially in females, leaving males largely unaffected? Most male mice seem to be able to get around the mutation and generate enough mature antigen-presenting cells to avoid disease.

We suspect that hormones somehow play a role in sparing males from the harmful effects of this mutation—or in condemning females to experience them. But we are not yet sure which hormones are involved. Is testosterone protecting males from the potentially deleterious effects of the NOD mutation? Or do female hormones, including estrogen, somehow aggravate the condition in females? In NOD mice, experimental evidence suggests that testosterone could have protective effects against diabetes. Years ago researchers found that castrated male NOD mice increased their incidence of autoimmune disease. Moreover, the scientists found that giving testosterone to females actually diminished their development of disease. How testosterone could have such an effect is not known.

The clinical picture in humans is more complex. For many of the autoimmune disorders, females do not experience symptoms until they reach puberty, again suggesting that hormones play a role. But for juvenile type I diabetes, onset usually occurs before puberty. And some women with MS do not experi-

ence symptoms until after menopause. Observation of women with autoimmune disorders suggests that fluctuations in hormone levels—during menstruation and pregnancy—can either exacerbate or alleviate their symptoms. Women with rheumatoid arthritis often go into complete remission during pregnancy, a time when estrogen levels are high. Yet patients with lupus rarely experience remission of symptoms during pregnancy. In fact, early studies reported that pregnancy could cause disease flare-ups in women with lupus.

It is also possible that other factors unrelated to female hormones can improve or worsen autoimmune symptoms in women. In the case of pregnancy, the presence of foreign fetal cells in a woman's body suggests at least an altered state of immune recognition. And the effects can last much longer than just nine months. Recently researchers at the Fred Hutchinson Cancer Research Center and the University of Washington found that after pregnancy, women with scleroderma had fetal cells circulating in their blood more frequently and in higher numbers than healthy mothers did. Fetal cells often escape from the uterus and circulate through a mother's bloodstream, sometimes for decades after a pregnancy. Perhaps such foreign cells might somehow antagonize normal immune system function. On the other hand, their presence might be a result of immune system dysfunction, rather than a cause.

Little Pink Pills?

Autoimmune disorders are not the only maladies to display a gender bias: heart disease, for example, affects many more men than women. Studies have shown that estrogen, to some degree, protects premenopausal women from heart disease—a major reason why menopausal women often choose to go on estrogen therapy. Even men who are at risk for heart disease might benefit from taking drugs that mimic estrogen's heart-protecting effects.

So why not develop an equivalent treatment for women with autoimmune disease? Scientists in the pharmaceutical industry could design a drug that has the protective properties of testosterone but lacks its masculinizing side effects. Such studies are not yet being done, perhaps because clinical trials for chronic disorders such as autoimmune diseases are expensive and take many years to complete. Further, because many of the

autoimmune diseases remit and relapse spontaneously, it is difficult to tell when recovery is the result of a specific therapy. Five years ago, when the Food and Drug Administration approved beta-interferon (a drug that alleviates the progression of MS by an unknown mechanism), it was the first new drug approved to treat autoimmunity in 20 years.

Some postmenopausal women now take testosterone to increase their sex drives, but there are no data indicating whether any of these women had autoimmune disorders—or whether the testosterone alleviated their symptoms. To be most effective for treating autoimmune diseases, such drug therapies would need to be initiated before the disease is full-blown—at birth, if possible. By screening blood samples for autoantibodies, physicians can identify children who are one year old, or maybe younger, at risk for juvenile diabetes.

Beyond Genes

If all the autoimmune diseases are caused by the same—or similar—genetic and cellular disruptions, why does diabetes destroy the islet cells of the pancreas, whereas MS attacks the nervous system? It appears that the affected tissues themselves may become more susceptible to autoimmune attack. Tissues such as the pancreas that secrete hormones might produce and release antigens that attract the attention of marauding T cells. Further, such target tissues might be weaker and less able to defend themselves against T cell attack than other tissues. In the future, we may understand better how mutations in the various genes that control antigen processing might interrupt the development of the immune system in women with autoimmune diseases. And we would like to determine exactly how most men are protected from the deleterious effects of these mutations.

In the meantime, these studies should give hope to people, particularly women, with autoimmune disorders. The results suggest that even when a defective gene prevents the immune system from fully maturing, the proper drugs might be able to change the course of the disease. If we can learn how most males avoid autoimmune disorders, females, too, may one day be spared. 5A

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Are Autoimmune Diseases Colorblind?

Do autoimmune disorders discriminate on the basis of race, as well as sex? In the case of lupus (systemic lupus erythematosus, or SLE), the numbers are fairly striking: the disease is three times more common in the African-American population than in the Caucasian population. Lupus affects approximately one in 300 African-American women and one in 1,000 white women over the age of 18.

Type I diabetes and multiple sclerosis, on the other hand, appear to be more common among Caucasians than African-Americans, Native Americans or Hispanic-Americans. And rheumatoid arthritis is found in all races, with certain Native American populations having an increased incidence, says Elaine Collier of the National Institute of Allergy and Infectious Diseases.

Making definitive statements about the effects of race on autoimmune diseases, it turns out, is by no means easy. "Each disease is different," Collier remarks. "There's not really any overriding theme, except that genetics seem to play a role in determining risk." So researchers tend to focus on a single disease as they try to tease apart the genetic and environmental factors that may influence disease incidence and outcomes and try to determine whether race, on its own, has any effect on who gets the disease and how it will affect an individual's health.

Understanding the factors that contribute to the development and progression of autoimmune diseases should help researchers develop more targeted and rational treatment protocols. The first part of the problem is confirming that racial differences exist. "Getting statistics on how many people have each disease is hard," Collier comments. "Based on that, it's harder to say how many people in any particular race have the disease." The nature of autoimmune diseases also makes them difficult to pin down, statistically speaking. "For good epidemiological studies, you need a very large number of cases, and these are rare diseases," points out Marc C. Hochberg of the University of Maryland. And to study race, the population must be sufficiently diverse. "The Mayo Clinic in Minnesota has a good database [of patient information]," Hochberg says, "but the population is almost 100 percent Caucasian."

Many studies rely on data collected from medical centers in and around large cities, such as Baltimore, Pittsburgh, Boston or New York, states C. Kent Kwoh of Case Western Reserve University and the Veterans' Affairs Medical Center in Cleveland. In 1995 Kwoh (then at the University of Pittsburgh Graduate School of Public Health) and his colleagues reviewed medical records obtained from area rheumatologists, hospitals and the Pittsburgh Lupus Databank and confirmed that the incidence of lupus in African-American females is three times higher than in white females. But that study, reported last year in the journal *Arthritis and Rheumatism*, is just the "tip of the iceberg," Kwoh says. "First we had to document that there are racial differences. Now we need further studies to find out why those differences exist."

One factor that certainly influences the course of any disease is the patient's socioeconomic status. "It's been known for centuries that being poor is bad for your health," observes Matthew H. Liang of Harvard Medical School. "But knowing that isn't really helpful: we can't eliminate poverty." So Liang and his colleagues set out to identify the "modifiable" factors related to socioeconomic status that might contribute to the severity of lupus.

The researchers collected information from 200 patients with the disease, including each person's race, age at diagnosis, socioeconomic status, diet, compliance with treatments and access to health care systems. Their conclusions? The researchers reported

last year in *Arthritis and Rheumatism* that when they compared patients who were in the same socioeconomic class, none of the outcomes they measured, including health status and degree of organ damage, were associated with race. Instead the patients who fared the worst, healthwise, were those who were least able to handle their disease—by taking care of themselves and feeling confident that they could deal with disease flare-ups, for example.

Such studies offer hope, says Hochberg, who also works on lupus, because the risk factors that appear to be highly correlated with the progression of lupus are under the patient's control. With better education and adequate access to health care providers, patients can learn how to comply with their treatment protocols, eat healthier diets and generally take charge of their disease—changes that should help improve their condition, regardless of race.

So where do the differences between African-Americans and Caucasians come from? Collier and other researchers assert that genetic differences might influence the susceptibility, onset and progression of autoimmune diseases in different races. "Genetics reveals first principles," says John B. Harley of the University of Oklahoma and the Oklahoma Medical Research Foundation. "The genetic differences between individuals constitute why one person will get a disease and somebody else won't."

Harley is currently coordinating the identification of families in which more than one family member has lupus for a nationwide Lupus Multiplex Registry and Repository. So far he has contacted and collected DNA samples and clinical information from 1,000 individuals in 160 different families. Using these samples, Harley and his colleagues hope to identify genes that might be involved in lupus. At the American College of Rheumatology conference last winter, the researchers reported identifying a region on chromosome 1 that appears to correlate with lupus in African-Americans but not in Caucasians. The region contains many genes involved in the immune response, and the investigators still have quite a bit of work to do before they can identify which gene in the area is involved in lupus.

Others searching for lupus genes have also wound up studying chromosome 1. One of these genes appears to correlate with a high incidence of lupus nephritis—loss of kidney function—which occurs more frequently in African-Americans with lupus than in whites. Another genetic region appears to play a role in lupus in African-Americans, Asians and Caucasians, suggesting that the biological basis of the disease might be similar for different races.

In the end, such studies will help define the subtle differences that might exist in the way that people of different races acquire disease—why they get it, how they respond to treatment and how the disease progresses. Armed with this knowledge, scientists should be able to design more effective therapies for treating all people who have autoimmune disorders.

—Karen Hopkin, special correspondent

For more information on autoimmune diseases, contact: American Autoimmune Related Diseases Association at 800-598-4668 or at <http://www.aarda.org> on the World Wide Web.

National Institute of Allergy and Infectious Diseases at 301-496-5717 or at <http://www.niaid.nih.gov/publications> on the World Wide Web.

National Institute of Arthritis and Musculoskeletal and Skin Diseases at 301-495-4484 or at <http://www.nih.gov/niams/healthinfo/> on the World Wide Web.

National Institute of Diabetes and Digestive and Kidney Diseases at 301-654-3810 or at <http://www.niddk.nih.gov> on the World Wide Web.

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