have found several hot spots in a genomewide scan for susceptibility genes in the Pimas and are now trying to pin down the genes involved.

There are encouraging signs that susceptibility genes picked up by these scans could provide good targets for antidiabetes drugs. Certain variations in the gene for a transcription factor called PPAR-γ have been linked to a modest increase in diabetes risk, and researchers now know that members of a relatively new class of drugs, known as the thiazolidinediones, work at least partly by stimulating PPAR-γ activity.

Yet other drugs are urgently needed to treat the diabetes epidemic, because people are unlikely to cut back on food intake and start exercising anytime soon. Indeed, CDC has just found that more than half of the U.S. population exercises little or not at all.

–JEAN MARX

NEWS

Lupus: Mysterious Disease Holds Its Secrets Tight

Caused by an unruly immune system, lupus manifests itself in a variety of symptoms; researchers are beginning to learn what the triggers are

Lupus. Even the origin of the name is uncertain. According to one tradition, the disease was named lupus—wolf in Latin—because people afflicted with it had lesions that resembled wolf bites. According to another, a classic rash on the face created a wolfish appearance. It was not until 1851 that a physician gave it a medical appellation: systemic lupus erythematosus. Today, this complex disease remains a mystery in more than name.

The deepest puzzle lies at its core: Something in the lupus patient causes the immune system to go awry and turn its armamentarium of cell-killing forces against the host. For the more than 1 million people in the United States with lupus, symptoms can appear in a bewildering variety of forms, ranging from mild to lethal. The damage can affect almost any organ in the body, causing arthritis, fatigue, blood clots, heart disease, osteoporosis, kidney failure, and other life-threatening illnesses. Symptoms flare and recede over time, and more often than not, the disease produces a slow decline, including cognitive loss. Even professionals have trouble diagnosing it, and by the time a diagnosis is confirmed, the patient may have developed irreversible kidney damage.

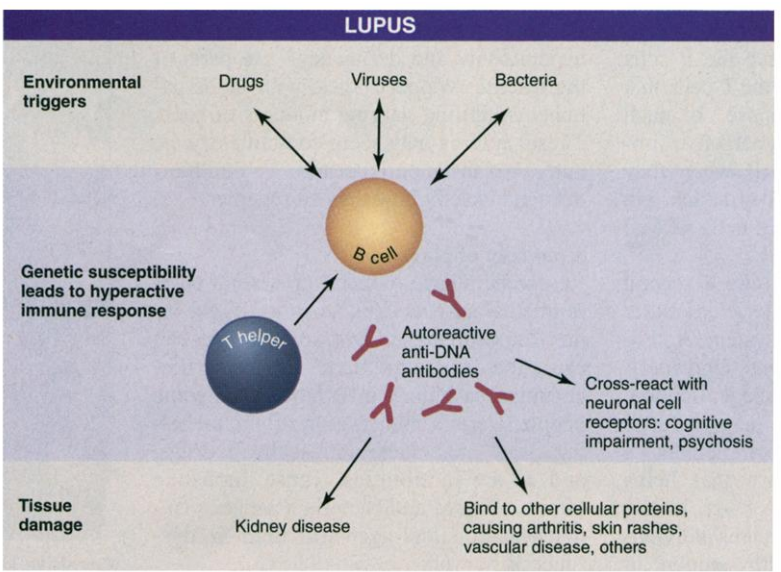
The complexity of the disease also impedes clinical research. One symptom may be "cured," only to be replaced by another that may be worse. Clinical trials are tough because it is hard to accumulate significant data if each patient seems unique, and clinicians grumble that drug developers are leery of lupus trials because the patients may have unrelated medical problems that look like side effects. Doctors have been able to offer relatively few therapies, and those that are available, including corticosteroids and cytotoxic compounds, are also very risky.

But an explosion of new data promises to bring lupus research out of the doldrums. Molecular biology has unlocked a trove of information about factors that regulate the immune system. Using new mouse models of the disease, researchers have begun to identify the biochemical mechanisms by which lupus causes tissue damage, and they have identified a series of candidate genes that appear to be involved in lupus. Desperately needed money for clinical trials may also be on the way. In the past 2 years, new lupus organizations have opened shop, vowing to put all their money into peer-reviewed science (see sidebar on p. 690).

"We're going to see a lot of activity" in lupus research, predicts Peter Lipsky, scientific director at the National Institute for Arthritis and Musculoskeletal and Skin Diseases (NIAMS). He also predicts an intensified focus on emerging drug targets. Equally encouraging, Lipsky notes, is that scientists from disciplines other than immunology are entering the field, drawn by genetic and physiological discoveries. "You have a lot of new people in the mix: nephrologists, cardiologists, neurologists, hematologists." A few biotech companies are also testing the waters, raising hope that less toxic drugs may soon be available.

War within

Anyone who investigates lupus encounters a striking fact, says Michael Lockshin, an immunologist who directs the Barbara Volcker Center for Women and Rheumatic Disease at the Hospital for Special Surgery in New York City: 90% of the patients are women. Black women are three times as likely to get lupus as white. And lupus strikes primarily between the ages of 15 and 40, during peak fertility. Because of this pattern, estrogen, the female sex hormone, has long been considered a key risk factor. But Lockshin says he has heard too many simple arguments blaming estrogen. Men get autoimmune diseases, too, Lockshin points out—including lupus. In some autoimmune diseases, males and females are equally affected. In others, males predominate. "There are so many anomalies" in the patterns of autoimmune disease, says Lockshin, that researchers should look beyond sex hormones.



Self-destruction. Environmental factors such as viruses interact with inherited risks to create a flood of "self" antibodies that harm tissues.

ILLUSTRATION: CARIN CAIN

Although scientists have proposed a smorgasbord of causes—and debate them endlessly—they agree on some fundamentals. Environmental factors such as estrogen and viruses are important, but just as critical are inherited genetic traits that make an individual's immune system susceptible to dysregulation. Among twins of lupus patients, for example, monozygotic twins are about 10 times more likely to get the disease than dizygotic twins.

Animal studies suggest several ways this complex interaction between environment and genetics might lead to chronic disease. The dominant view

Research Funding: New Kids on the Block

When Robert W. "Woody" Johnson's child was diagnosed with systemic lupus erythematosus, he checked out the state of lupus research—and found it wanting. Johnson—owner of the New York Jets, investment banker, and heir to a biomedical fortune—concluded that people were "just scratching the surface." Private grants were small, and the money was going mostly to "people already sitting around the table." The field needed his guidance and support, he decided. So Johnson plunked down $12 million and started the Alliance for Lupus Research (ALR). This New York City adjunct of the Arthritis Foundation of Atlanta, Georgia, opened for business 2 years ago and has now given 15 grants worth $500,000 each. Johnson's goal is to raise $50 million.

LUPUS RESEARCH SUPPORT
($ millions per year)

NIH total	70
NIAMS	30
Arthritis Foundation	2+
Alliance for Lupus Research	3.8
SLE Foundation	1
Lupus Research Institute	1.4
Lupus Foundation of America	0.1
Mary Kirkland Center for Lupus Research	1.4

ALR is the splashiest of several new arrivals. At the same time, the SLE Foundation of New York City launched a spinoff dedicated to lupus research called the Lupus Research Institute (LRI). According to LRI president Margaret Dowd, the organization awarded its first 12 research grants last year, worth $225,000 each, with review by a 16-member scientific panel. It's gearing up to make new grants this year and to raise $35 million. Yet another outfit opened its doors last year: The Mary Kirkland Center for Lupus Research, based at Cornell University's medical complex in New York City, under the direction of Michael Lockshin. A $7 million grant from a lupus-affected family is being used to support the clinical center and studies by several independent scholars.

All three lupus research organizations claim they want to stir things up, fund risky projects, and spur government agencies to invest more heavily in lupus. LRI, for example, says it will back ideas that might not win high peer-review ratings at the National Institutes of Health (NIH)—especially new ideas in basic research. "There really hasn't been a major new therapy in lupus for 40 years," Dowd says. Johnson takes a businesslike approach: "We don't want to duplicate what NIH does," because ALR wants to focus on results that can be used immediately. "Our objective is simple: cure, treatment, and prevention—just the way aspirin treats a headache." **–E.M.**

holds that people inherit a risk for lupus: Their immune systems are genetically structured to respond too aggressively to foreign stimuli, pushing into overdrive the B cells that generate antibodies and the T cells that magnify the antibody response. In such lupus-prone individuals, hyperactive immune cells may not turn off when they should, leading to an expanded attack that goes after an individual's own cells as well as foreign material.

Researchers increasingly cite a second pathway to lupus as well: a deficient rather than a hyperactive immune system. Anthony Rosen of Johns Hopkins University, Mark Walport of Imperial College, London, and others argue that people develop lupus because they have flaws in "complement," a multistage immune response that helps clear dead material from the body. In this scenario, a complement-deficient individual might build up an unhealthy amount of debris in the blood and tissues. This uncleared waste could then trigger the immune system into an exaggerated response, leading to destructive attacks on a wide variety of tissues. Both of these basic trends—hyperactivity and deficiency—are parts of the disease, Walport notes, with lupus patients exhibiting varying amounts of each. These patterns may seem contradictory, he notes, but that's only because we don't understand exactly how they fit together.

A panoply of players

Researchers have rounded up several environmental suspects that seem to trigger lupus. Exposure to sunlight, for example, can cause the disease to "flare," triggering life-endangering kidney inflammation in some people. Certain prescription drugs, including heart medicines, antipsychotic drugs, and a few antibiotics, cause lupuslike effects. Viruses and bacteria have been fingered as potential agents of immune dysfunction as well.

Immunologist John Harley and colleagues at the Oklahoma Medical Research Foundation in Oklahoma City have assembled one of the strongest arguments so far implicating a common infectious agent: the mononucleosis bug, Epstein-Barr virus (EBV). Against his better judgment, Harley says, he began this investigation in the mid-1990s after a grad student nudged him. They were intrigued by an amino acid sequence in EBV that is repeated with one change in an unusual antibody (known as anti-Sm) found in about 30% of lupus patients but almost never in people who don't have the disease. Because "EBV has been blamed for everything," Harley says, "even if we were right, I knew it would take 10 years" to persuade peers that it is a factor in lupus, and "we would probably lose our grant."

Harley took the plunge anyway and has published studies with Judith James and others showing associations between anti-Sm and EBV infection. Demonstrating significance, though, is tricky. About 95% of all adults are infected with EBV. So Harley's group focused initially on children, who are less often infected. They found that 99% of lupus-affected children had been infected by EBV, but only 70% of healthy controls had. They also demonstrated that animals injected with anti-Sm developed lupuslike disorders. "I'm not sure [these findings] have been generally embraced by the community," cautions NIAMS's Lipsky.

Friend or foe?

To understand how lupus does its damage, immunologists are focusing on anti-Sm, which is known to target part of the cell's gene transcription machinery, and another unusual antibody found in the blood of patients that is directed at a patient's own DNA. Although anti-Sm is found in a minority of lupus patients, nearly all lupus patients have

Cognitive key. Betty Diamond's lab discovered that anti-DNA antibodies attach to neurons, possibly causing loss of memory and mental acuity.

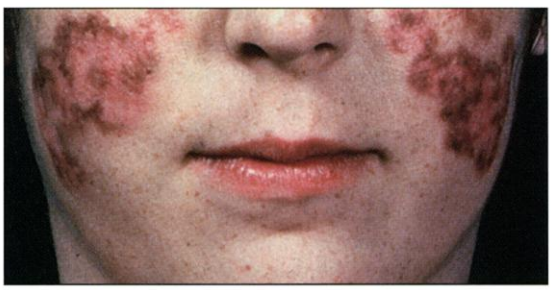
CREDIT: (BOTTOM) LUPUS RESEARCH INSTITUTE

anti-DNA antibodies. But these antibodies are also found in healthy people. It's a confusing pattern.

"To my thinking, if you could understand the anti-DNA response, you could understand what's involved in human lupus," says David Pisetsky, chief of rheumatology at Duke University in Durham, North Carolina, who demonstrated that healthy people also make anti-DNA, most of it directed at nonmammalian DNA, for example, from bacteria. Pisetsky hypothesizes that in lupus patients, "there is something aberrant in the response to foreign DNA" that causes them to produce poorly constructed antibodies aimed at their own cells. Support for the theory is incomplete, however.

Although some researchers think that anti-DNA antibodies are directly responsible for the harm done by lupus, finding the mechanism has been difficult. A couple of recent reports, both from Albert Einstein College of Medicine in New York City, point to some possibilities. Immunologist Chaim Putterman and colleagues reported in the *Journal of Immunology* in January that in a mouse study, anti-DNA antibodies bound specifically a protein (alpha-actinin) on the surface of kidney cells. This may explain why lupus is so devastating. Contrary to earlier assumptions, this suggests that attacking molecules attach directly to kidney cells rather than to stray DNA particles on the surface, enabling the cells' destruction. Kidney failure is one of the deadly consequences.

Betty Diamond, an immunologist at Albert Einstein, and her colleagues think that anti-DNA antibodies may also explain one of the least explored problems of lupus patients, a gradual loss of memory and mental sharpness. They reported in *Nature Medicine* last year that anti-DNA antibodies can bind to a peptide on a key neural cell receptor known as NMDA, important in an area involved in memory and decision-making. Both mouse and human brain cells in test tubes died more quickly as a result of this binding. Although researchers caution that these results are preliminary, Lipsky thinks they're "exciting" because "we don't understand anything" about lupus-induced loss of cognition, and "now we have an idea of how it might work."



CREDIT: NMSB/CUSTOM MEDICAL STOCK PHOTO; TABLE SOURCE: AMERICAN COLLEGE OF RHEUMATOLOGY

DEFINING THE DISEASE

Four of 11 Symptoms Constitutes Systemic Lupus Erythematosus:

- Malar or "butterfly" facial rash
- Discoid rash
- Photosensitivity
- Oral ulcers
- Arthritis with inflammation
- Serositis (inflammation of tissue around lung, heart)
- Renal disorder: proteinuria, cellular casts
- Blood disorder: leukopenia, lymphopenia, thrombocytopenia, or hemolytic anemia
- Neurologic disorder: seizures, psychosis
- Immunologic disorder: anti-DNA, anti-Sm antibodies
- Abnormal antinuclear antibody titer

Susceptibility genes

The complex genetics of lupus are also yielding to molecular biologists' tools. "We are on the verge of a huge explosion of genetic knowledge," says Harley, head of the Lupus Multiplex Registry and Repository, a NIAMS-funded group in Oklahoma City, Oklahoma, that gathers DNA from lupus families.

Using such databases, researchers have linked lupus to several regions on chromosome 1 and found slightly less robust evidence of genes on chromosomes 4 and 6. Although the genes have not yet been identified, immunologist Robert Kimberly of the University of Alabama, Birmingham, describes three as "strong candidates." One affects an element of the immune system called the class II major histocompatibility complex; a second encodes proteins in the immune cascade known as complement; and the third affects immunoglobulin γ receptors IIa and IIIa. "At least a dozen [genes], probably more" are under active investigation, notes Kimberly, who, like others, credits Edward Wakeland of the University of Texas Southwestern Medical Center in Dallas and colleagues for "elegant work" in identifying susceptibility regions.

How all these genes interact is not clear. Some may be involved in turning on high-energy T and B cell activity. Others may set the threshold for "tolerance," the process by which the immune system learns to accept proteins as "self" rather than attack them as alien. Others are known to support the function of complement. All may "conspire together to give the full-blown disease," Walport says. "We are just beginning to understand the interplay of these genes," adds Lipsky, noting, "this will keep us working for a while."

Genetic studies may eventually lay bare the biochemical network that elicits the autoimmune response in lupus patients. Already, several groups of researchers hunting for powerful immune system proteins have collected clues about antibody targets and receptors that affect the growth and vitality of B cells.

Biotech companies are not waiting for all the details. Several firms have launched clinical trials testing novel proteins for lupus therapy. These approaches range from the subtle to the overpowering: One tack, for example, is to suppress existing B cells and allow the bone marrow to replenish the supply, presumably with less virulent ones. Another experiment, run by La Jolla Pharmaceuticals of La Jolla, California, aims to use four selected oligonucleotides to intercept antibodies that are thought to cause kidney inflammation. Alexion Pharmaceuticals of New Haven, Connecticut, is testing a monoclonal antibody that blocks complement C5, in a attempt to reduce kidney inflammation. Others are devising ways to block several receptors that stimulate B cell growth, including a key receptor for a protein known as BAFF or BLyS.

Preliminary animal tests have been encouraging. Human Genome Sciences Inc. of Rockville, Maryland, announced last fall that it had federal approval to begin human trials of its anti-lupus agent, a monoclonal product it calls Lymphostat-B, directed against the BLyS receptor.

Matthew Liang, an expert in research methodologies at Harvard School of Public Health in Boston, and several lupus specialists are talking about ways to coordinate clinical approaches to defining symptoms and clinical outcomes. One of the goals is to make results easily comparable from one center to another. This could also make it easier to collect data for drug trials. Other clinicians are drawing up hit lists of immune system proteins that could be targeted for drug therapy.

Many researchers will gather next month at a meeting in Düsseldorf, Germany, being organized by Liang and others. From this meeting, they hope to sally forth with a tightly orchestrated battle plan that will not only come up with good new ideas but also spark the interest of private investors. Before they make a new appeal for support, however, they believe they must achieve a consensus. And Liang warns that advancing this goal—like everything to do with lupus—will be "very difficult" and complex.

–ELIOT MARSHALL