

# Health & Science

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## New clarity for a baffling disease

*Although Lupus patients continue to face a difficult path, physicians who treat them see reasons for hope.*

Stories by Kathleen F. Phalen

**T**HE LATIN ROOT OF THE WORD "LUPUS" means wolf. That makes it an appropriate name for this mysterious disease. For those who have it, it means that their body's own killer instinct has turned inward, mistaking their own organs and tissues for prey — attacking and devouring them.

Formally known as systemic lupus erythematosus, lupus is an inflammatory autoimmune roller coaster of flares and remissions. It is a disease of more questions than answers, of veiled origins and misdiagnoses, and of less than ideal treatments. "There was no fundamental treatment change in 20 years," says Israeli Jaffe, MD, a rheumatologist at Columbia Presbyterian Eastside in New York.

Even so, there's a possibility. "There may be new things on the horizon," Dr. Jaffe says. "Today patients are diagnosed earlier. That's good. It used to be routine to end up on dialysis. The quality and duration of life have improved."

Still, the Centers for Disease Control and Prevention recently reported a 60% increase in lupus deaths since 1979 — a statistic scientists discuss cautiously, fearing its misinterpretation.

"Outcomes tend to be worse for minority populations. I caution that what they've documented needs to be confirmed," says Susan Manzi, MD, MPH, associate professor of medicine and eni-

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ILLUSTRATION BY RUNA LEE

## Holding the line on lupus flares

**F**OR SHERRY BARBER, SYMPTOMS STARTED when she was 24. She'd fall asleep at her desk; she couldn't walk a mile to her Clarendon, Va., Metro stop; her hands ached and she was plagued by chronic pain. Still, she blamed her busy life and two jobs.

"It was easy at the time to dismiss the symptoms," says Barber, now 29. "I thought I had carpal tunnel, and I was tired because I was working so much."

But the pain intensified, and even simple tasks were impossible. Within four months she was in the hospital. That's when Barber was di-

agnosed with lupus. "Women my age are frequently dismissed as hypochondriacs," she says. "It takes so long and so much work to get a doctor to believe us."

After a couple of flares and treatments that depressed her, made her hair fall out and caused her to become bloated, she is now participating in a clinical trial. The drug, LJP 394, was developed by La Jolla Pharmaceutical Co. and is designed to target B cells and reduce renal flares.

Patients get an IV injection once a week. "It seems to have the ability to suppress B cells," says Andrew Wiseman, PhD, La Jolla Pharma-

ceutical founder. "And results show a 73% reduction in lupus flares. ... We hope to finish phase III this year and with good data go to the FDA."

Right now Barber is stable, but because the trial is blinded she does not know if she's actually getting the drug. Why did she participate? "I hope we can get more people to understand the disease," she said.

Present treatments are like trying to kill a fly with a nuclear bomb, says Mahesh Krishnan, MD, MPH, a nephrologist with Virginia Nephrology Group in Fairfax, Va., which is involved in the LJP 394 trial. "The advantage of LJP is that it is like a cruise missile strike targeting the B cell, which produces antibodies." ♦

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dermatology at the University of Pittsburgh School of Medicine and co-director of the Lupus Center of Excellence at the University of Pittsburgh Medical Center. "Are there other confounding factors such as socioeconomic or genetic differences?"

Most agree that lupus presents a baffling riddle with hidden answers and no cure. But with the completion of the human genome, new treatments in trial, identification of new markers and earlier diagnosis, the lupus puzzle now has some promising pieces. "We certainly never want to give false hope, but we are at an all-time peak for lupus research. There is cause for great optimism on a variety of fronts," says Joseph Ahearn, MD, associate professor of medicine at the University of Pittsburgh School of Medicine and co-director of the Lupus Center of Excellence at the University of Pittsburgh Medical Center. "Ultimately a vaccine. ... Never getting the disease — that would be the Holy Grail here."

### Unraveling threads

**H**ERE'S A QUICK REVIEW OF WHAT IS KNOWN. Lupus is a chronic, multisystemic inflammatory autoimmune disease often affecting the skin, joints, blood and kidneys.

About 80% of patients are young women between 15 and 45. About 70% of lupus cases are SLE, the most severe and potentially fatal form of the disease. Other types include pediatric, discoid and drug-induced.

It's not clear how many people have lupus, but estimates range from 500,000 to 4 million. Women are five times more likely to die of the disease than are men. And according to the CDC, in the past 20 years, there has been a 70% increase in the number of African-American women dying from complications of lupus.

First identified by its characteristic raised red facial blotches, some say lupus got its name because the rash resembled a wolf bite. Doctors have known about lupus for centuries, but it was not until the 1950s that autoimmunity was associated with the disease.

For those with lupus, the immune system is not able to distinguish antigens from its own cells. As a result, the system begins making autoantibodies. There is speculation that environmental factors — viral or bacterial infections, UV light, prescription heart medication, antipsychotic drugs, some antibiotics, stress and certain hormones — may be the cause. Some researchers have even fingered the Epstein-Barr virus, mononucleosis, Lyme disease and anti-DNA antibodies. In August, researchers at the University of Florida, Gainesville, published findings in the *Journal of Arthritis and Rheumatism*, identifying pristane, a hydrocarbon oil, as an environmental trigger in mice.

Some investigators point to a genetic predisposition. Several areas of chromosome 1 and the Fas gene have been linked with lupus. "There are human families with a Fas mutation and autoimmune disease like lupus," says Ralph C. Budd, MD, a rheumatologist and director of the immunology program at the University of Vermont, College of Medicine in Burlington. How does that relate to lupus? "Cell death of autoreactive lymphocytes may not occur normally in the absence of one or more death receptors. In the case of Fas, in its absence or with a nonfunctional mutant, both humans and mice accumulate such autoreactive lymphocytes," he says. "Fas triggers a signal pathway that ultimately leads to degradation of many cell components, essentially autogestation."

Dozens of other genes are currently under investigation, but scientists still do not know which genes are associated with a greater likelihood of getting the disease.

### Clarifying a chameleon

**L**UPUS SYMPTOMS ARE OFTEN UNPREDICTABLE and transient, differing from patient to patient. They can change, mimic and confuse. Many patients endure chronic pain and fragile health for years before knowing why.

In a study by the Lupus Foundation of America, more than half of lupus patients went at least four years and saw three or more doctors before obtaining a correct diagnosis. For some it's worse: 12, 13 or 14 doctors before a diagnosis of lupus is made.

Misdiagnosis is less likely for patients with the classic rash and joint pain. Dr. Jaffe says. "The disease can hit any one of a number of organ systems, and that can determine how it presents," he says. "It is a complicated diagnosis."

Some common symptoms include persistent profound fatigue, joint pain and inflammation, skin rashes, extreme sensitivity to sunlight, mental confusion, chronic low-grade fever, Reynaud's-like extremities, mouth ulcers and hair loss. "Patients can be arthritic, psychotic, have low white blood cell count, low platelets. Sometimes they have profound malaise," Dr. Jaffe says.

There is no single test for lupus, although the FDA just approved a new screening tool projected to identify about 20% of those missed with other methods.

The color-coded test — anti-SR protein antibody assay — identifies SR proteins, a helpful biomarker for lupus, since a majority of patients produce antibodies to SR. According to the FDA, this test can identify 50% to 70% of lupus patients who react positively to SR proteins.

Scientists at the University of Pittsburgh are in the process of licensing a complement-based assay for diagnosis and monitoring. "In pilot testing, it performed significantly better than current gold standard tests such as ANA, serum C3, serum C4, and anti-double-stranded DNA," says Dr. Manzi. "In preliminary studies, the sensitivity, specificity, positive predictive value and negative predictive value of this assay ranged from 96% to 96% for a diagnosis of SLE versus healthy controls and patients with other autoimmune and inflammatory diseases."

According to the National Institutes of Health, initial screening includes a complete blood count, liver and kidney screening panels, laboratory tests for specific auto-antibodies — antinuclear antibodies, ANA — a syphilis test, urinalysis, blood chemistry and erythrocyte sedimentation rate.

But using the ANA alone is not adequate, says Terry Moore MD, director of the division of rheumatology at Saint Louis University School of Medicine. "It is nonspecific, and about 20% to 30% of healthy females are positive for ANA."

In addition to a medical history, lab work and a positive ANA, a high-titer anti-DNA antibody or anti-SN antibody are important indications of lupus.

"The anti-DNA, double-stranded nuclear protein is a more refined test," Dr. Jaffe says.

At times, biopsies of the skin or kidney can support a diagnosis of SLE.

### A sanguine future?

**R**IGHT NOW, TREATMENTS ARE NOT IDEAL. "Patients could die from the side effects," Dr. Moore says. Most common are NSAIDs, antimalarials such as Plaquenil (hydroxychloroquine sulfate) or chloroquine, steroids, or cytotoxic agents such as imatin (azathioprine) or Cytoxan (cyclophosphamide).

Until recently there has not been a specific drug for lupus. But a handful of pharmaceutical companies are beginning to file new drug applications with the FDA, says John Klippel, MD, scientific director of the Alliance for Lupus Research. "We're hopeful that within the next decade we'll see lupus drugs."

Some drugs in the pipeline include LJP 394, an investigational drug in phase III trials under development by La Jolla Pharmaceutical Co., San Diego. It is a selective B lymphocyte immunomodulator for the treatment of lupus renal disease.

Genelabs' Prestara, formerly Aslera, was approved in September by the FDA contingent on an additional clinical trial. Studies observed a positive effect on bone mineral density for women with mild to moderate SLE.

Alexion Pharmaceuticals Inc. is in phase II trials with the drug Eculizumab (5G1.1), a C5 inhibitor, for the treatment of lupus nephritis.

Human Genome Sciences is initiating a phase I clinical trial for LymphoStat-B, which works by binding to BlyS, a B Lymphocyte Stimulator that may be a sensitive marker of lupus disease activity. The drug will inhibit BlyS stimulation of B cell development and proliferation.

Although it's gotten some negative press, stem cell transplant shows great promise for lupus patients, says Ann E. Traynor, MD, associate professor of medicine at Northwestern Memorial University Hospital in Chicago. "I am really frustrated. The information is not getting to rheumatologists," she says. "There is a misunderstanding about its safety. ... There is no question of the natural incidence of death in the population we are treating. But no one has died, with the exception of one patient who relapsed."

Northwestern Memorial Hospital performed the country's first stem cell transplant for lupus about five years ago. Since then, it has performed more than 22. In the procedure, a patient's own stem cells are removed, and the immune system is deliberately destroyed with chemotherapy. Immediately after an escalated Cytoxan dose, patients are infused with stem cells, Dr. Traynor says. When the aberrant lupus lymphocytes are out of the picture, stem cells multiply and rebuild a healthy immune system.

Only available for patients who have failed other treatments, stem cell transplants are now entering phase III, multicenter trials. "Patients have gone from critically ill on 20 to 30 meds a day to nothing," Dr. Traynor says. "One point I would like to make — doctors who have had a patient die of lupus since the protocol was available need to strongly examine if they referred, and if not, why not. "My feeling now is there is no reason to die of lupus anymore." ♦

### DEATH TOLL

■ 1,406 deaths from lupus reported in 1996, up 61% from 1979.

■ 22,861 lupus deaths documented between 1979 and 1998.

■ 14.5% of arthritis deaths are from systemic lupus erythematosus.

■ 70% increase in death rates from SLE reported between 1979 and 1996 among black women 45 to 64.

■ 36.4% of SLE deaths are among people between 15 and 44.

■ 5 times higher death rate reported for women than men; three times higher for blacks than for whites.

SOURCE: CENTERS FOR DISEASE CONTROL AND PREVENTION, NATIONAL CENTER FOR CHRONIC DISEASE PREVENTION

### WEBLINKS

<http://www.lupus.org/>  
Lupus Foundation of America

<http://www.lupusny.org/>  
SLE (Lupus) Foundation Inc.